

**Coating of Pellets with
Aqueous Dispersions of Enteric Polymer by
using a Wurster-based Fluidized Bed
Apparatus**

A Dissertation submitted in Partial Fulfillment
of the Requirements for the
Degree of Doctor of Natural Science
(*Dr. rer. nat*)

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from Bangkok/Thailand

Hamburg 2002

**Überziehen von Pellets mit wässrigen,
magensaftresistenten Polymerdispersionen in
der Wirbelschichtanlage**

Dissertation

Zur Erlangung des Doktorgrades
des Fachbereiches Chemie
der Universität Hamburg

vorgelegt von

Mont Kumpugdee

aus Bangkok/Thailand

Hamburg 2002

ACKNOWLEDGEMENT

It is my particular desire to express my sincere gratitude and appreciation to my supervisor Prof. Dr. Jobst B. Mielck for all his encouraging support, guidance and suggestions for making every necessary facility during the time of my doctoral work.

I would also like to express my thanks to the Deutscher Akademischer Austauschdienst (DAAD) for the financial support and to all the companies i.e. Werner's Feine Dragees / Tornesch, Syntapharm / Mülheim-Ruhr, Seppic / France, Lehmann & Voss / Hamburg, Clariant / Frankfurt am Main, Hoechst / Burgkirchen, and BASF / Ludwigshafen for the substances used for the research work.

I also thank Dr. Kunick, Dr. Wieking, Mrs. Pies and Mrs. Wackendorff for the discussions and measurements of NMR and IR; Dr. Keyser and Mrs. Walter for the support of SEM-measurements.

I also express my particular appreciation for the kind assistance, encouragement and friendship granted to me by all my colleagues and special thanks to Mr. Schüler, Mr. Stockhusen, Mr. Struss, Mr. Ruth, Mrs. Borbe and Mrs. Belda for the laboratory and technical help.

I am also very thankful to all friends and persons who assisted me during the doctoral work although not mentioned in this acknowledgement.

Finally it is my great wish to express my cordial and deep thanks to my parents for their continuous and permanent love, support and care which was a great help to me during the time of my study and research work.

Mont Kumpugdee

2002

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Date of oral presentation and disputation: 12.07.2002

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BP	British Pharmacopoeia
µg	Microgram
µm	Micrometer
CAP	Cellulose acetate phthalate
CAP-E&P-Nico pellets	Pellets containing nicotinamide with a subcoat from a combination from ethyl cellulose and polyvinyl alcohol (100+30) then coated with cellulose acetate phthalate
CAP-EC-Nico pellets	Pellets containing nicotinamide with a subcoat from ethyl cellulose then coated with cellulose acetate phthalate
CAP-HPMC-Nico pellets	Pellets containing nicotinamide with a subcoat from hydroxypropyl methylcellulose then coated with cellulose acetate phthalate
CAP-MO pellets	Pellets containing methyl orange coated with cellulose acetate phthalate
CAP-Nico pellets	Pellets containing nicotinamide coated with cellulose acetate phthalate
CAP-P&E-Nico pellets	Pellets containing nicotinamide with a subcoat from a combination from polyvinyl alcohol and ethyl cellulose (100+30) then coated with cellulose acetate phthalate
CAT	Cellulose acetate trimellitate
cP	Centipoise (s)
DBS	Dibutyl sebacate
DEP	Diethyl phthalate
DSC	Differential scanning calorimetry
et al.	et alii
E&P	A combination of ethyl cellulose and polyvinyl alcohol (100 parts + 30 parts)
E&P-Nico pellets	Pellets containing nicotinamide coated with a subcoat from a combination of ethyl cellulose and polyvinyl alcohol (100 parts + 30 parts)
EC	Ethyl cellulose

EC-Nico pellets	Pellets containing nicotinamide coated with a subcoat from ethyl cellulose
EtOH	Ethanol
FTIR	Fourier transform infrared
g	Gram
GMPs	Good manufacturing practices
HCl	Hydrochloric acid
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
HPMCAS	Hydroxypropyl methylcellulose acetate succinate
HPMC-Nico pellets	Pellets containing nicotinamide coated with a subcoat from hydroxypropyl methylcellulose
HPMCP	Hydroxypropyl methylcellulose acetate phthalate
KBr	Calcium bromide
MeOH	Methanol
MFFT	Minimum film forming temperature (°C)
Mgst	Magnesium stearate
min	Minute (s)
ml	Milliliter
mmH ₂ O	Millimeter water (1 mmH ₂ O = 9.79 Pa)
mmole	Millimole
MO	Methyl orange
MP-1	Aeromatic MP-1, Fluidized bed apparatus
MW	Molecular weight
Nico	Nicotinamide
NMR	Nuclear magnetic resonance
No.	Number

P&E	A combination of polyvinyl alcohol and ethyl cellulose (100 parts + 30 parts)
P&E-Nico pellets	Pellets containing nicotinamide coated with a subcoat from a combination of polyvinyl alcohol and ethyl cellulose (100 parts + 30 parts)
Pa	Pascal
PEG	Polyethylene glycol
Ph.Eur.	European Pharmacopoeia
psi	Pounds per square inch (1 psi = 6895 Pa)
PVA	Polyvinyl alcohol
PVP	Polyvinyl pyrrolidone
q.s.	quantum satis
r.h.	Relative humidity
r.t.	Room temperature about 25 °C
rpm	round per minute
SEM	Scanning electron microscopy
Td	Dew point (°C)
TEC	Triethyl citrate
Tg	Glass transition temperature (°C)
TiO ₂	Titanium dioxide
Tm	Melting point
USA	United State of America
USP	The United State Pharmacopeia
UV	Ultraviolet
vol	Volume

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1. Introduction

The coating is an important process in the pharmaceutical industry. This technique has many benefits which include: improving esthetic qualities of the product, masking of unpleasant taste and odor, enabling the product to be easily swallowed by the patient, facilitating handling, improving product stability and modifying drug-release characteristics. In former times the coating processes were a kind of art which were hence developed to the compliance with good manufacturing practices (GMPs). The design of new equipment as well as the development of new coating materials have contributed to improve the products to today's standard <143,12>.

1.1 Literature review

1.1.1 Coating techniques

The differentiation of coating techniques is variable. Some experts classified the coating into three techniques. They are pan coating, top-spray fluid-bed coating and Wurster-based fluid-bed coating <206>. Other experts divided the coating by differentiating the spraying techniques. There are three techniques which can be used, i.e. the top-spraying using a conventional fluid-bed granulator, the bottom-spraying using a Wurster column and the tangential spraying using a rotor granulator. However, if all possible coating techniques are considered there will be five coating methods i.e. the fluidized-bed coating, the pan coating, the compression coating, the melting coating and the encapsulation <150>.

Fluidized-bed technology has been widely used for drying, granulating and coating of pharmaceutical products. Due to its highly efficient drying capacity this technique seems to be ideal for coating beads and particles which tend to agglomerate in a wet condition. It was reported that the coatings can be reproducibly performed by this technique with minimal defects of products. Therefore this technique was preferred for many formulations. The overview of the fluidized bed coating system was reported <150>.

Typical components of a fluid-bed processing system are an air conditioning unit, a ventilator, a product container, exhaust filters, a spray nozzle, a solution delivery unit, and a control panel. Nevertheless, fluidized-bed coating is a complicated process. Many

parameters will affect film formation, and are highly dependent on the characteristics of a given polymer. Therefore, it is necessary to investigate the processing conditions during product development. Because of the possibility to vary the coating parameters a special control of these parameters with a calibration is necessary. The combination of parameters should be carefully selected in order to optimize the process, as many factors can affect the fluidized bed process <65>.

The fundamental principle behind fluidized-bed coating in general and the Wurster-technique in particular is to suspend materials in an upward-moving column of warm air during the coating process. In summary the coating process consists of three phases: the start-up phase, the coating phase, and the drying/cooling phase. During the start-up phase, the heat supplied by the process air is used to heat the apparatus and the starting material, which is already in the fluidized state, to the desired temperature. During the coating phase, several processes take place simultaneously. These are: atomization of the film solution/suspension, transport of the film droplets to the substrate/core, adhesion of the droplets to the substrate, film formation, drying of film (at least partially) and the repetition of this cycle of the substrate. The final drying/cooling phase takes place without further spraying and is necessary for the development of the desired properties of the whole film.

The Wurster fluidized bed technique is different from the conventional technique. The basic Wurster fluidized-bed coating apparatus consists of four parts. The first part is a coating chamber which is essentially cylindrical in its shape with the axis of the cylinder in the vertical plane. The second part is the inner partition which is called the Wurster column. The coating step is performed only inside the Wurster column. The third part is the air-distribution plate which is designed to help loading the material such as particles, beads, or tablets to enter the coating zone. The fourth part is the spray nozzle which is located at the center of the air-distribution plate. During a normal operation the fluidizing air rapidly accelerates the particles or tablets up through the inner partition, where the coating takes place. The coated particles or tablets leave the cylinder upward and deceleration occurs in the region of the expansion chamber causing the product to drop back into the coating chamber in the region confined by the walls of the chamber and the Wurster column. The product moves down to the bottom of the coating chamber where the cycle begins again. The Wurster-based coating process is therefore very different from the top-spray coating process and optimization should be performed from a completely different angle of view <36,206>.

The fluidized-bed technology has also disadvantages in the way that it gives a porous product in comparison with a coating process in a coating pan or other equipment. The high air velocity will cause a fast drying process which sometimes can be too fast so that the polymer particles cannot fuse together to bring about a homogeneous film layer. Moreover, this high air velocity will cause a spray-drying effect which causes a high amount of fine dust. Most of it are polymer particles and only a small portion will be core component. Cores layered with drug with low binding force at the surface of the core will cause high friability. This causes a loss of drug content. The other disadvantage is the possibility of a dust explosion, whenever combustible powders in fine particle size are present in large volumes of air or oxygen. To avoid an explosion, the process air has to be exchanged by an inert gas. However, such a process is only economic by recirculation of the inert gases in a closed system. The use of such a system allows also the control of both the temperature and the humidity of the circulating gas. When discussing the coating process it is important to consider properties of the core e.g. the density and the diameter <36>.

Mehta, Valazza and Abele <98> reported about the effect of three techniques of fluid-bed coating (top-spraying, bottom-spraying or tangential-spraying) on the morphology of applied films and on drug release rates. They found that both caffeine pellets and aspirin granules can be successfully coated with an aqueous enteric coating system using any of the three fluid-bed processing methods.

1.1.2 Enteric coats

An enteric coat resists disintegration or dissolution in acidic gastric media but disintegrates or dissolves in intestinal fluids <143>. The definitions and the requirements in different Pharmacopoeia were different which has been discussed by Heckenmüller <69>.

One of the main reasons for using an enteric coat is to protect the stomach wall from the effect of the drug contents in a dosage form. Another main reason is to protect the drug contents in a dosage form from the harmful effect of gastric contents. Enteric coat can also be used to deliver the active ingredients to a particular region of the intestine such as the upper part of the small intestine or they can be incorporated into a tablet formulation for a direct compression process to form sustained release tablets or in a

wet granulation process to form particulates or beads which exhibit controlled-release characteristics in the gastrointestinal tract <143>.

Many factors can influence the preparation of enteric coated dosage forms e.g. the properties of the substrate such as the nature of drugs, additives or core. The properties of the polymer such as molecular weight, pH-dependent solubility, the pKa value, the total free carboxylic acid content or the degree of substitution of the polymer can also affect the preparation. The ionic strength of the dissolution fluid, the thickness of the coat, the permeability to gastric fluid and the presence or absence of plasticizers, other non-enteric components in the coat and defects can influence the dissolution of enteric coats <150,51>.

1.1.2.1 Enteric coating process differentiated by polymer formulations

The alcoholic enteric coating formulation was since long used in the pharmaceutical fields. The coating process using organic solvents was reported to have an advantage so far as it takes a shorter processing time because of the low heat of vaporization characteristic of the solvents. However, in the late 1960s, a drastic increase in the price of organic solvents and new strict limitations on the exposure of workers to toxic chemicals and on the discharge of such substances into the atmosphere created a renewed interest in the use of water as a solvent and vehicle for the coating process. Initially, aqueous systems were viewed with skepticism because of their lengthy processing times and because the appearance of products coated with aqueous films was inferior to that one of products coated using organic systems <65>.

1.1.2.1.1 Organic-based formulations

The mechanism of film formation from organic solution is completely different from the formation of film from a dispersion. When polymers are in solution they can exist as extended long chains or coils in the solvent depending on temperatures and shear. Chain extensions and partial immobilization of the solvated molecules make the solution highly viscous, even at low concentrations. At the beginning of the coating process the initial rapid evaporation of solvent from the atomized droplets of coating liquid occurred and caused an increase in polymer concentration and contraction in volume of the droplets. After that there was a further loss of solvent from the film at a slower rate

which is now controlled by the rate of diffusion of solvent through the polymer matrix. The following step was the immobilization of the polymer molecules at the solidification point. This process created shrinkage stresses that contributed to the internal stress within the coating and it will be related to some of the mechanical properties of the coated dosage form. The last step was the further gradual solvent loss from the film at a very much reduced rate. It was mentioned that the solvent loss from the film coat will be continuous but at an ever-decreasing rate. Solvent loss from the polymer matrix is governed by the amount of space between the polymer molecules which usually termed the free volume. As solvent loss progressed the glass transition temperature (T_g) of the polymer film increased and the free volume decreased. Ultimately, the free volume became so small that further removal of solvent from the coating became almost impossible. Indeed, total solvent removal requires the heating of films to a temperature significantly above the T_g of the solvent-free polymer. Since the T_g of some polymers such as HPMCP, CAP was very high (more than 150 °C), it was difficult to produce solvent-free film coating from these polymers.

Many factors can influence the quality of the finished coated product. For example: the interaction between the core material and the applied coat, the drying process and the uniformity of distribution of the coating material <143,65>.

In order to reduce the T_g of the pure polymer additives for example a plasticizer have been used. Some examples of such organic enteric formulations were discussed in this respect. Lovgren, et al. <91> have reported the use of an enteric organic coating formulation containing HPMCP and cetyl alcohol. They used this mixture for enteric coating of pellets containing omeprazole and alkaline compound. Cores, however, were first coated with a subcoat containing PVP and ethanol before the finishing enteric coating was performed. Chopra <35> used an aqueous ammonium alcoholic suspension consisting of CAP and TEC for coating of tablets. The coated tablets developed a rupture in the coat if they were in a simulated gastric fluid more than 60 min or in simulated intestinal fluid for 12 min.

1.1.2.1.2 Ammonia-based formulations

The ammonia-based formulations have been formulated to replace the organic based coating systems due to the safety, toxicity and environmental concerns. For example; Gordon, et al. <64> studied the possibility of different aqueous polymeric dispersion for

producing an enteric coated tablet. They manufactured the CAP aqueous dispersion by mixing two dispersions together. The first dispersion was prepared by dispersing CAP powder in water and then adding strong ammonia solution. The second dispersion was prepared by dispersing diethyl phthalate and polyvinyl alcohol in water. The naproxen sodium tablets cores were coated using a coating pan. The coated tablets demonstrated excellent physical resistance to acid medium with 0 % drug dissolved after 2 h. The tablets were also stored for 9 months at room temperature. Now these tablets bloated after 2 h in a gastric fluid. The dissolution test of aged tablets coated with CAP by using this ammonia-based formulation did not maintain their integrity in 0.1 N HCl medium. More studies concerning the ammonia-based formulations are mentioned in part 1.1.2.2.2.1.

1.1.2.1.3 Water-based formulations

The use of organic solvents in the coating of pharmaceutical dosage forms has become problematic due to regulatory requirements, flammability and limits on solvent residues in the coated product. The alternative aqueous coating systems can overcome these problems but suffer from certain limitations. The aqueous systems are susceptible to microbial contamination when preservatives were not added. The long processing time is caused by the higher energy of evaporation of water. Moisture-sensitive cores e.g. dry extracts, enzymes or substances prone to hydrolysis, can be damaged by the coating process. In addition, substances readily soluble in water can be incorporated into the film and problems of long-term stability can arise due to the inclusion of water. It is important to avoid sedimentation or coagulation of the film-former when dispersions are used. The incomplete film formation is the important problem. One of the factors that causes incomplete coalescence is the evaporation of the plasticizer <185>.

There are two aqueous based systems that are used in the pharmaceutical fields i.e. latex systems and the redispersed polymer. The latex systems have been used for coating for several years. The dried powder resulted by removing water from the aqueous polymeric dispersion. This dried powder can be redispersed again before use as an aqueous dispersion <65>.

In an aqueous dispersion system the polymer is dispersed as small particles rather than fully-entangled chains as it is in the solution. The mechanism of film formation of this system is different from the organic solution system. For example; the first step of the

mechanism of film formation from aqueous dispersions is the rapid evaporation of the aqueous medium, which brings the particles of dispersed polymer into close contact with one another. Then the individual polymer particles must be deformed and coalesce into a clear continuous film. The driving force for fusion comes from the capillary forces caused by high interfacial tension between water and the polymer and between water and air as water evaporates. Electrostatic charges must also be present but the capillary forces are the main force for overcoming the electrostatic repulsion. This more complex mechanism of film formation may lead to the differences in functional performance of aqueous based films compared to organic based films <10,65>.

This process of film formation is very sensitive to process conditions used during film coating. The coalescence of the latex particles will be very dependent on the free volume which influences the movement of polymer molecules between individual latex particles. Consequently, aqueous polymeric dispersions must be processed at temperatures in excess of the T_g of the polymer or plasticized polymer. However, incomplete coalescence occurred even at temperatures in excess of 20 °C above the T_g. Thus the optimum processing conditions for aqueous polymeric dispersions occur over a narrow range of temperatures <10,65>.

1.1.2.2 Enteric coating process differentiated by the type of polymers

The variation in pH that occurs, as an oral administered drug delivery system moves down the gastrointestinal tract has been very widely used as the trigger to cause the release of drug from enteric-coated drug delivery system. Polymers such as modified cellulosic polymers and synthetic acrylic polymers are commonly known as enteric coating polymers. These polymers contain ionizable carboxylic groups. In the low pH stomach environment the carboxylic groups remain un-ionized so that the polymeric coat remains insoluble but disintegrates or dissolves at the higher pH of the intestinal environment to allow the release of drug contents <12>.

The enteric coating polymers are divided into two groups i.e non-cellulosic and cellulosic polymers as listed below <12>.

1.1.2.2.1 Non-cellulosic polymers

- a) Methacrylic acid polymers
- b) Polyvinylacetate phthalate, PVAP
- c) Shellac

The non cellulosic polymer such as methacrylic acid polymers were investigated by many researchers. Eudragit L-30 D was widely used as aqueous dispersion for coating of products e.g. theophylline particles <5>, theophylline pellets <62>, caffeine tablets <19>. Dietrich and Ney <48, 49> have reported about the use of a dispersion of Eudragit L-30D and TEC for coating of pantoprazole and of omeprazole tablets.

1.1.2.2.2 Cellulose derivatives

- a) Cellulose acetate phthalate, CAP
- b) Hydroxypropylmethylcellulose acetate succinate, HPMC-AS
- c) Cellulose acetate trimellitate, CAT
- d) Hydroxypropylmethylcellulose phthalate, HPMCP

The cellulosic polymers <12> were used by many researchers but in the present work only two types of cellulosic polymers, i.e. CAP and HPMC-AS were used. Therefore their details are discussed in comparison with other enteric polymers.

1.1.2.2.2.1 Cellulose acetate phthalate (CAP)

The Table 1.1 to 1.5 summarized the research works concerned with CAP polymer. The evaluation of CAP powder, the free films of CAP from different media, the CAP coated tablets, capsules and pellets can be found in many reports mentioned in Table 1.1. The chemical stability of different CAP products such as powder, dispersion, free films, and of coated tablets/capsules and pellets was studied by many researchers as demonstrated in Table 1.2. Different types of plasticizers (Table 1.3) and the different coating techniques (Table 1.4) have been studied with CAP. Three types of coating formulations with CAP based on organic solvent, ammonia and water as dispersion medium were used (Table 1.5).

Evaluation of CAP products	No. of literature
powder	42,155,161,204
free films	147,148,70,177,176,178,83,161,145,191
organic solvent-based	
ammonia-based	14,70
water-based	147,164,117
coated tablets/capsules	144,164,186,18,34,131,170,65,82,130,70,64
coated pellets	200,31

Table 1.1: Summarization of some publications reporting on the evaluation of various CAP products such as powder, free films (prepared from organic solvent-based, ammonia-based or water-based system), coated tablets, capsules and pellets.

Chemical stability of CAP products	No. of literature
powder	155
dispersion	20,41
free films	191,43
coated tablets/capsules	185,82,190,188,189,187,170,65,130,186,34
coated pellets	185

Table 1.2: Summarization of some publications reporting on the chemical stability of various CAP products such as powder, dispersion, free films, and of coated tablets/capsules/pellets.

Type of a plasticizer used with CAP	No. of literature
Triethyl citrate (TEC)	185,117,14,41,186,83
Diethyl phthalate (DEP)	200,31,65,117,130,147,83,148,144,41,64,34, 131
Triacetin or other plasticizers	147,148,70,41,18

Table 1.3: Summarization of some publications reporting on the type of a plasticizer used in CAP formulations.

Type of coating process with CAP	No. of literature
fluidized-bed	200,130,70,34,131
pan coating or other techniques	115,14,64,82,144,65

Table 1.4: Summarization of some publications reporting on the type of coating process used to coat product by using the CAP formulations.

Coating formulation with CAP	No. of literature
organic-based	130,14,65,31,82,70,144
ammonium-based	31,64,130,70
aqueous-based	164,131,65,31,18,34

Table 1.5: Summarization of some publications reporting on the type of coating formulation prepared from CAP.

Evaluation of CAP products

Bauer, Lehmann and Osterwald <12> reported that the glass transition temperature (T_g) of CAP was about 100 °C. Roxin, Karlsson and Singh <155> have studied T_g of CAP powder by using DSC. They found that the T_g of fresh CAP powders was in the range of 172 - 174 °C, whilst the T_g of CAP after storage under climatic stress (40 °C, 89 % r.h.) was in the range of 155 – 175 °C. Karlsson and Singh <83> have also determined the T_g of free films prepared from CAP in acetone by using thermal mechanical analysis. They found that the T_g was in the range of 151-167 °C which may be due to residual solvent content in the film. Since it was reported that the T_g of pure CAP was very high, the addition of a suitable plasticizer was necessary to reduce the T_g to a temperature at which a coating process can be performed.

As reported by FMC <7>, plasticizers suitable for Aquacoat CPD were diethyl phthalate, triethyl citrate and triacetin at the amount of 20 to 24 % of the latex solids. The T_g of Aquacoat CPD could be reduced to 34 °C by a content of 25 % DEP. Higher amounts of DEP did not further reduce the T_g. With TEC as a plasticizer, however, 10 % and 30 % TEC to latex solids resulted in T_g of 38 °C and 32 °C, respectively.

Studies on the application of CAP polymer on coated enteric formulations with various active compounds have been reported <65,121>. Applications from organic solvent systems were used before and the use of aqueous dispersion of CAP were recently described <186>. Schmidt and Teuber <170> have critically discussed the problems of enteric dosage forms. They studied the differences between coating polymers such as HPMCP, PVAP, Eudragit L. They also mentioned that the type of the incorporated drug had an important affect on the stability of the CAP film coated products. For example; the CAP coated product contained sodium sulfathiazol. An ionic exchange happened between the protons of the acid groups of CAP and the sodium ions at the nitrogen atom of amide group of the drug. They used cobalt chloride as a model indicator for the determination of water diffusion through different polymer films, e.g. Eudragit L 100-55, Eudragit L 30 D and HPMCP coated onto pellets. The colour changed from blue to pink because the complex of cobalt-(II)-hexahydrate was formed. The coating amount on the pellets was about 4.2 mg/cm². The maximum time until the colour changed to pink was 12.5 min. They also studied the resistance against artificial gastric fluid (0.1 N HCl) by using methyl orange as an indicator. The results of aqueous dispersions of different polymers were also discussed. The worst result was shown by bisacodyl pellets coated with aqueous dispersion of polyvinyl acetate phthalate. Almost 90 % of bisacodyl were released from these pellets after one hour in 0.1 N HCl. The SEM pictures showed the lack of coalescence in the structure of films prepared from aqueous dispersion of HPMCP or carboxymethyl ethylcellulose. The film layers contained pores and canals. Films from an organic solution of Eudragit L showed very smooth structures without pores. Only the aqueous system from Eudragit L 30 D brings the result of the enteric coated pellets which resisted to 0.1 N HCl.

Obara and McGinity <116,117> studied the effect of processing conditions on the properties of free films prepared from polymers by the spray method. They reported that whilst the casting of CAP dispersion resulted in transparent films, poor film formation was observed with the spray method.

Chang <31> reported a non-enteric performance of CAP-coated theophylline beads prepared from Aquateric by a fluidized-bed process. The authors proposed that either the Pluronic F-68, a surfactant, in Aquateric may have had an adverse effect or the polymer was sensitive to the formulation variables, coating process and active substances.

Williams III and Liu <200> have studied the influence of fluidized-bed processing conditions as well as curing parameters with and without humidity on drug release from pellets. Theophylline pellets were prepared by extrusion-spheronization and then coated with diethyl phthalate-plasticized CAP dispersion (Aquacoat CPD) using a fluidized-bed coater. The parameters investigated were plasticizer level, outlet temperature, spray rate during coating application and fluidizing air velocities using a half-factorial design. They observed that the processing temperature during coating applications was a critical factor among the variables investigated. The release rate significantly decreased when the beads were coated at 36 °C compared to those coated at 48 °C. Higher coating efficiencies and better coalescence of films were obtained at the lower coating temperature. They mentioned that above the MFFT the drug release in acidic medium was decreased as the coating temperature was decreased. The curing at 60 °C can significantly reduce the drug release from pellets that were coated at 32 °C, but had no significant effect on the drug release from pellets which were coated at temperatures above 36 °C. The curing at 50 °C in an atmosphere containing 75 % r.h., irreversibly improved film formation by a better coalescence and improved the mechanical properties. The curing with heat and humidity for the film formation of CAP on the pellets was dependent on the curing temperature and on the moisture. The curing process with an addition of humidity was found to be more effective than without <200>.

Mr. Carlin <25> recommended that if the use of a plasticizer with a phthalate group was not wanted then triethyl citrate (TEC) can be used. The coating formulation containing 1 part of TEC and 4 parts of Aquacoat CPD was recommended. The T_g of the film prepared from this formulation will be below 35 °C. The product bed temperature should be kept low to avoid stickiness at temperatures above the T_g. The curing at a high temperature is not required, merely an additional 10 min drying at the recommended process temperature range of 32 – 36 °C. The dispersion of 15 % w/w solid content was recommended to be used as a starting concentration for the optimizations. The fluidized-bed apparatus as Aeromatic-MP1 will have a risk to create sticking due to overheating the bed (> 36 °C) or due to the overwetting (small drying rate). Therefore the low spraying rates were recommended and the product bed temperature should be held at 32 – 36 °C. Due to the large surface area of pellets a solid loading of 10 – 20 % Aquacoat CPD with a plasticizer on the pellets may be necessary to obtain a minimum thickness that resists a gastric fluid.

Many studies (Table 1.1) showed that CAP, in the form of an aqueous dispersion, provided adequate acid resistance on coated products at sufficient coating levels. Most of these coating studies were carried out on tablets or gelatin capsules, whereas only few studies reported on pellets. Pellets possess an advantage compared to tablets, such as low absorption variability and less propensity for dose dumping. Since they have a much larger surface area they required a higher amount of enteric polymer to achieve a desired property. However, they are of interest for controlling drug release.

Chemical stability of CAP products

CAP can be easily degraded by a hydrolysis. Roxin, Karlsson and Singh <155> have investigated different methods to observe the stability of CAP powder after storage at different temperatures and humidities (20 - 60 °C, 11 - 95 % r.h.). Especially the HPLC-method was suitable for determine the amount of free phthalic acid, which is one of the degradation products from CAP. Other methods, for example: infrared spectroscopy or gas chromatography can be used with acceptable results. Differential scanning calorimetry (DSC) is suitable for the determination of the Tg but not suitable to follow the stability of CAP. However, the water content can be well determined by this technique. They have found that the relative humidity has a greater effect on the storage stability of CAP powder than temperature. The authors have also found the new degradation product of CAP, formic acid, by using head-space gas chromatography-mass spectroscopy. The other known degradation products of CAP such as acetic acid, phthalic acid and phthalic anhydride can also be determined by the GC-method <155>.

The following examples show the stability of CAP-coated dosage forms under the stress test. Eshra <53> has reported on the stability of CAP film prepared from organic or aqueous formulations. In freshly prepared films of CAP from organic solution 3.2 % of free phthalic acid was measured, whereas films from an aqueous system 4.0 % free phthalic acid was found. After stress storage conditions at room temperature and 100 % r.h., the content of free phthalic acid in films from aqueous systems reached 8.0 %. Films from organic systems on the other hand had only 6.2 % free phthalic acid. Eshra also showed the effect of the pKa and the solubility in water of the drug incorporated in the free films on the hydrolysis of phthalyl groups of the polymer. The hydrolysis increased when the pH of the water-soluble drug increased. For example: the content of free phthalic acid after storage of the film containing nicotinamide (pH 6.3, pKa 3.35) or

procain HCl (pH 5.3, pKa 5.0) for 80 days at r.t. and 80 % r.h. was about 18 % and 14 %, respectively. These two drugs catalysed the hydrolytic reaction by the hydroxide ions (OH^-). However, this catalytic effect was different for the drug maleic acid (pH 1.25, pKa 1.92) because the reaction was induced by the hydrogen ions (H^+). However, hydrogen ions had less potential to the reaction compared to hydroxide ions. Therefore the content of free phthalic acid after 80 days at the same conditions was only 13 %. Eshra mentioned that the hydrolytic effect may be reduced if the extent of dissolved drug, caused by the absorbed water, was low. Therefore the contents of free phthalic acid of films containing insoluble drugs such as phenobarbital, tolbutamide and salicylic acid after storage were 8.0, 7.0, and 6.5 %, respectively, which means the content of free acid was significantly lower than that from soluble model drugs (nicotinamide, procain HCl and maleic acid) at the same storage condition. The result of CAP-coated tablets containing different drugs such as nicotinamide, phenobarbital maleic acid, etc. which were stored under r.t. and different humidities were also shown. For example, the content of free phthalic acid of tablets containing nicotinamide and coated with an organic or aqueous formulation of CAP was 16 % after storage for 180 days at r.t. and 80 % r.h.. Not only the chemical stability of these tablets was lost but also the physical properties such as the resistance against artificial gastric fluid and the disintegration time in a buffer medium. Eshra found that these tablets were not resistant to the acidic medium after storage. The reason for this result was the migration of the drug, especially the water soluble one, into the outer film layer containing CAP. The stability of enteric coated tablets was also studied by Thoma and Kräutle <187>. They have found that applying a barrier coat prior to the enteric coating consisting of aqueous dispersion of hydroxypropyl methylcellulose phthalate or CAP resulted in reduced swelling of the tablets.

1.1.2.2.2 Hydroxypropyl methylcellulose acetate succinate (HPMCAS)

Some researchers have reported about the use of HPMCAS <106>. The properties of free films prepared from aqueous dispersion containing HPMCAS were studied by Obara and McGinity and the results were also compared with films prepared from Eudragit L 30D and CAP <116>. The water soluble plasticizers such as TEC or triacetin showed greater compatibility to HPMCAS than the water insoluble as DBS <61>. The comparison of the results in form of isolated films and caffeine enteric coated tablets

from the aqueous dispersion of HPMCAS and other enteric polymers such as Aquateric, HP 55, Kollicoat MAE 30D was demonstrated <164>. The effect of some additives such as magnesium stearate and calcium stearate on the dissolution profiles of diltiazem hydrochloride from press-coated tablets with HPMCAS in the outer shell was studied by Fukui, Miyamura and Kobayashi <60>. Schmidt and Niemann <168,169> used HPMCAS for coating of bisacodyl pellets and compared the results with pellets coated with other enteric polymers such as CAT, and Eudragit L 30D. They also compared the results of aqueous based and the organic-solvent based formulations. The enteric coating process of pellets with an aqueous dispersion of HPMCAS in a fluidized bed was mentioned <87>.

The novel enteric coating method called **dry coating** by using HPMCAS was mentioned <115>. This method involves direct feeding of coating polymer powder and simultaneous spraying of a plasticizing agent without either organic solvent or water, using a centrifugal fluidized-bed apparatus. For film formation, a curing step was then necessary. The new method required a higher coating amount for gastric resistance compared with the conventional coating, but the processing time was dramatically reduced. The stability of HPMC-AS was determined in comparison with CAP in which the coating material Aqoat-AS-MF and CAP was stored at 60 °C and 100 % r.h. for many days. It was found that after 14 days the free acid content in form of succinic acid was about 1.8 % w/w. The enteric polymer CAP, on the other hand, produced free phthalic acid more than 5 % w/w after only 6 days at the same condition. That means HPMC-AS is more chemically stable than CAP <6>.

1.1.3 Some types of defects in enteric coated dosage forms

The defects that could be found in the enteric film coating were picking, twinning, orange peel roughness, edge erosion, film cracking, logo bridging and film splitting or peeling <143,10,154>. The picking defect resulted when for example the coating on two adjacent cores is not sufficiently dry before contact occurs between them. Some process conditions included low spray rates coupled with excessive drying conditions and the use of excessive atomizing air pressure, which accentuate premature drying of the droplets of coating liquid and this can cause the orange peel roughness. This problem may also be compounded by attempting to spray coating liquids with excessively high viscosities. The cores especially tablets whose edges were often

exposed to the attritional effects had the fracture at this point what was not uncommon and resulted in edge erosion. Cracking or peeling of film coatings occurred when the internal stress developed within the coating and drying exceeded the tensile strength of that coating.

If one of these defects occurred then the properties of the enteric coated products will be altered. Down and Booth <51> reported on the effect of pinholes on the dissolution behaviour of enteric coated tablets.

1.1.4 Interaction between a drug and enteric polymers

Eshra <53> showed that the hydrolytic process of phthalyl groups of CAP was increased after storage when the coated tablets contained some drugs such as nicotinamide, maleic acid and phenobarbital compared to tablets without any drug. This occurrence was due to the diffusion of the drug into the film layer and the drug acted as a catalyst for the hydrolytic process. He has also mentioned that the salt bonding between nicotinamide and the free phthalic acid of tablets coated with CAP formulations may be responsible for the longer disintegration time of more than 60 min.

Some publications <3,4,75> showed that the tertiary amine drugs such as naltrexone and morphine will form hydrogen bonds with Eudragit L, whereas the secondary amine drugs such as carteolol hydrochloride, phenylephrine and pseudoephedrine will form salt bonds.

The interactions between erythromycin and enteric polymers such as CAP using different techniques such as IR-spectroscopy, X-ray diffraction analysis and NMR-spectroscopy were reported <163>. The amine salt interaction between the carboxyl group of the acid polymer and the nitrogen atom of erythromycin was demonstrated by this former work.

Gordon, et al. <64> studied the properties of naproxen sodium tablets coated with the CAP aqueous dispersion and found that there was an inability of these tablets to maintain their integrity during dissolution testing. This may be due to an interaction between the enteric coat (CAP) and the drug (naproxen sodium) since this drug is a weak base. Incompatibilities with acid-sensitive drugs (e.g. omeprazole) are possible because CAP has free carboxylic acid <12,88>.

1.1.5 Coating formulation with different additives

The primary coating materials, usually polymeric, will often require the addition of other excipients, such as plasticizers, pore formers, or antiaggregation agents, in order that the product is conveniently manufactured in the desired quality. It is therefore appropriate to give attention to some of these types of excipients.

Most of the polymers that are used in pharmaceutical film coating procedures are amorphous to partially crystalline in nature. One characteristic of these polymers is that as the temperature is lowered the T_g is reached, below which a critical cessation of molecular motion on the local scale appears. Under these temperature conditions, the polymer exhibits many of the properties of inorganic glasses, including toughness, hardness, stiffness and brittleness. For this reason the T_g is described as one below which a polymer is brittle and above which it is flexible. Normally the T_g of typical polymers used in the film coating process was high, therefore the modification of the polymer to achieve a reasonable T_g was necessary. The addition of a plasticizer into the coating formulations seemed to be suitable. The plasticizer when chosen correctly and employed in the right level alters the physical properties of polymers and enhances their film-forming characteristics. When a plasticizer interacts with a polymer it is believed to interpose itself between the polymer chains to neutralize the forces holding the chains together to increase the free volume or intramolecular space and eventually to soften the polymer matrix. The T_g of the polymer will be reduced and impart more flexibility. The basic requirements to be met by a plasticizer are permanence and compatibility. The permanence dictates that the plasticizer should have a low vapor pressure and low diffusion rate within the polymeric film. The high molecular weight plasticizers were then favourite. The compatibility demands that the plasticizer should be miscible with the polymer and exhibit similar intermolecular forces to those present within the polymer.

Plasticizers used with pseudolatex dispersions dissolved in the colloidal or near colloidal particles soften them and thereby promote their coalescence during film formation. Although some authors have conducted intensive research to correlate plasticizer efficiency in film formation with physical properties such as molecular weight of the plasticizer or the T_g and intrinsic viscosity of the polymer dissolved in the plasticizer, the fact remains that the polymer and plasticizer must have mutual solubility in order to interact effectively and provide continuous flexible films. Thus plasticizers must be

chosen from materials that have been shown to be useful for a particular polymer. Plasticizers commonly used in the pharmaceutical fields are triethyl citrate, diethyl phthalate, dibutyl sebacate, triacetin, glycerol, and polyethylene glycol, etc. <143,150>.

The non-traditional plasticizers such as methyl paraben, ibuprofen, chlorpheniramine maleate and theophylline were studied to find out the influence of these substances on the thermal and mechanical properties of the polymeric films <202,203>

Some excipients may be used in coated pharmaceuticals for one purpose and be used in other pharmaceuticals to fulfill a different function. Thus, magnesium stearate (Mgst), most commonly used in pharmaceutical technology as a lubricant <11> has been used to prevent agglomeration of coated particles <150>. Some research works reported about the unconventional way of adding additives in the coating formulations e.g. magnesium stearate <151>, talc <195>, colloidal silicon dioxide <195> and titanium dioxide <17>.

1.1.6 Coating with non-ionic polymers

Basic actives such as sodium salicylate may interact with CAP and create a micro pH greater than 5.5. A suitable subcoat layer was then required <65>. The subcoat or isolating layer was usually used to separate the core material from the enteric coating polymers. This layer should hinder or reduce the effect from the core, as pH values, to the enteric layer.

Thoma and Kräutle <187> have used HPMC as a barrier coat prior to the enteric coating consisting of aqueous dispersion of coating agent HPMCP or CAP. TEC was used as a plasticizer. The result showed that the swelling of CAP enteric coated tablets can be reduced, whereas the HPMCP coated pellets were not influenced by this subcoat. The subcoat from an aqueous system of HPMC was often used, though the effect from the subcoat on the stability of the enteric dosage form was not well studied.

The following polymers were generally used as subcoats because of non-ionic property and the authors have investigated their effect on the dosage form.

1.1.6.1 Hydroxypropyl methylcellulose (HPMC)

HPMC was used by many researchers, for example: as a film forming agent <10,97,89,106>, a matrix for producing tablets <13,196> or for layering of drug <149>. The use of HPMC was reviewed in the literature <1,162>. The physical properties of

free films from HPMC such as crystallinity, T_g, intrinsic viscosity were investigated <71,107,95>.

Mc Philips, Craig, Royall and Hill <95> have shown that the glass transition temperature (T_g) of HPMC powder measured by modulated temperature differential scanning calorimetry (MTDSC) was about 162 °C and the T_g of HPMC films was about 164 °C – 167 °C. Lehtola et al. <88> studied the T_g of free films prepared from aqueous based HPMC plasticized with different types of polyethylene glycol (PEG 400, 1500 and 4000). By using the DSC technique they have found that the T_g of free film from HPMC alone was 119 °C. The T_g of HPMC with PEG 400 was between 119 - 138 °C depending on the concentration of PEG which was varied from 10 to 30 % w/w. If the concentration of PEG was increased then the T_g was reduced. The T_g of HPMC plasticized with PEG was higher than that of HPMC without plasticizer. This may be due to the higher moisture content of unplasticized HPMC film. The T_g of HPMC and PEG 1500 or PEG 4000 surprisingly kept almost constant at 130 and 136 °C, respectively though the concentration of PEGs was varied from 10 to 30 % w/w. The free film from HPMC plasticized with 20 % w/w PEG 400 and 20 % w/w TiO₂ showed the T_g of 134 °C which was higher than the T_g of the same film without TiO₂. This appearance seems to be due to the hindering of mobility of polymer chains in the presence of pigment particles.

1.1.6.2 Ethyl cellulose (EC)

Physical properties such as crystallinity, T_g or swelling of ethyl cellulose have been reported <167,58,124>. Ethyl cellulose generates very hard or tough films and needs a plasticizer to soften the film, i.e., to improve flexibility and reduce brittleness. The T_g of EC is 120 °C which is defined as the temperature above which EC is in a rubbery state. Thus an unplasticized EC film would be in the glassy state at temperatures at which products are manufactured and stored and would not perform its intended function. The plasticizer must be able to dissolve the polymer to promote chain mobility and flexibility. Thus a comparison of the solubility parameters of plasticizers with that of EC is predictive of effectiveness. Alternatively free films can be prepared with various plasticizers at different levels and examined thermomechanically to investigate effectiveness <67>. For example; the softening temperature of Aquacoat ECD and 24 % w/w DBS was reported to be 54 °C. A number of plasticizers were reported to be

compatible with Aquacoat ECD e.g. DEP and DBS because of the value of the solubility parameter <67>.

It is reported that the T_g of Aquacoat ECD is lowered as the concentration of a plasticizer such as DBS, DEP or TEC is increased. This appearance will promote coalescence of polymer particles. The T_g of unplasticized Aquacoat ECD was 129 °C, whereas the T_g of Aquacoat ECD film plasticized with 20 % w/w DBS, DEP or TEC was 44 °C, 44 °C and 36 °C, respectively. The optimum plasticizer level was reported to be 20 – 24 % w/w <179>. Another report showed that the Aquacoat ECD dispersions plasticized with DBS at 15 %, 25 % and 30 % gave intact clear films above 34 °C, 28 °C and 27 °C, respectively. TEC at the same concentrations exhibited a MFFT of 32 °C, 30 °C and less than 23 °C, respectively <117>. The solubility parameter of EC, DEP and DBS was reported to be 21.1, 20.5 and 18.8 (J/m³)^{1/2} × 10⁻³, respectively. Therefore, DEP and DBS seemed to be more efficient as a plasticizer for Aquacoat ECD than TEC. Pellets coated with aqueous based systems using Aquacoat ECD were widely studied <118,205,21>. The curing was an important factor for a good coalescence of EC. The combination of EC and other polymers such as HPMC was also studied <59,67,116,117,118,149,179,205>.

1.1.6.3 Polyvinyl alcohol (PVA)

PVA is available in different viscosity grades. It was used as excipient in many fields e.g. production of paper, polymerisation, textile, foils and ceramic <142>. In the pharmaceutical field it can be used as stabilizer in dispersion <85,105>, filler in tableting <146>, in pelletisation <142>, in microencapsulation <142>, for microparticles <24,173> or sponges <142> but PVA alone as a film forming agent is not published. Therefore it is of interest to study the possibility to use PVA for coating of pellets.

The possibility to incorporate PVA instead of gelatine in the sugar coating formulations was studied and the authors mentioned that PVA was a good stabilizer for the sugar coating suspensions <105>. It was also reported that PVA can be used as a stabilizer in the aqueous phase for preparation of microencapsulation using cellulose acetate butyrate <85>. Microspheres of PVA containing diclofenac sodium can be prepared by an emulsion-chemical cross-linking method <33>. The cross-linked PVA was reported to be used for preparing microparticles for the controlled-release oral solid dosage form <173>. In the tableting process PVA can be used as a matrix for producing the

compressed tablets containing a water soluble drug <146>. The release- and swelling-behaviour of these tablets were studied.

The possibility of using PVA for the ocular drug delivery was studied in form of liposomes and nanoparticles <24> and the delivery of protein was also studied <68>. The incorporation of bovine serum albumin into PVA hydrogel films was successfully performed and the effect of the freezing and thawing process and its subsequent release behaviour were reported.

It was reported that PVA can be used to produce the complex containing phenobarbital using spray drying technique <81>. The crystallization of the drug in the polymer PVA shown under a light microscope, by SEM, DSC or X-ray diffraction depended on the concentration of the incorporated drug.

The chemical stability of PVA was studied <2,96>. As PVAs contain residual acetate groups they can therefore be degraded by the hydrolytic process. The elastic behaviour, the internal stress and the swelling of PVA were also studied <174,175>.

The mixture of PVA and HPMC was reported to be used as film forming agents applying PEG 6000 as a plasticizer <160>. The moisture permeation properties of HPMC containing PVA and filled with talc or titanium dioxide have been evaluated using the sorption-desorption technique <119>.

1.2 Statement of the problem

The stability of cellulose acetate phthalate (CAP)-coated dosage forms <86,121> especially when the dosage forms contained a basic drug was reported <53>. Therefore the possibility to increase the stability of the dosage form and to avoid the hydrolysis of the CAP polymer was of interest.

A suitable model for this intention was therefore a model which provided a direct contact between a basic drug and the enteric polymer (CAP). In order to produce such a model sugar spheres in the size range of 800 - 1000 μm or 1000 - 1180 μm were used as cores. These cores shall be coated with a layer of solid basic drug and finally coated with CAP.

The desirable observation of chemical or physical interaction between a model drug and the outer enteric layer (CAP) may be well performed with this arrangement. That means, only the effect of the contact between drug and polymer can be observed and additional effects of other excipients will be avoided as they may occur in form of tablets <53>.

In this present work the spherical model will have a thin layer of a water soluble, weak basic drug (nicotinamide). This thin layer will represent the effect of an interaction which may have occurred because of a direct contact with the enteric polymer (CAP). When the drug diffuses to the outer layer it will change the properties of CAP. This diffusion can be avoided by using a seal coat (subcoat). Moreover, the subcoat may hinder the interaction between the basic drug and the enteric polymer (CAP). Different non-ionic polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC) and polyvinyl alcohol (PVA) shall be tested to find out the possibility to use one of them as a subcoat. HPMC was used as a subcoat in some recent studies <15,86,109>. In this present work HPMC will be used to compare the result with EC and PVA. The effect of each subcoat on the CAP-coated pellets containing nicotinamide shall be tested.

However, before the stability of the enteric coated pellets can be investigated the physical properties of the coated pellets should be acceptable. The important physical property is the resistance against artificial gastric fluid (0.1 N HCl). If the enteric coated pellets have passed this test the chemical stability test by storage of the coated pellets under different combinations of temperatures and humidities can then be performed.

Therefore first of all a coating process and a suitable formulation of an aqueous dispersion of CAP to produce enteric coated pellets have to be developed. The coating

processes will be performed by using a Wurster-based fluidized bed apparatus (Aeromatic-MP1). The two commercial CAP products in the form of the spray dried powder (Aquateric) and a ready-to-use aqueous dispersion (Aquacoat CPD) will be investigated. Different types of plasticizers are added into the aqueous dispersions of CAP. One plasticizer is a water soluble i.e. triethyl citrate (TEC). The other two plasticizers are water insoluble i.e. diethyl phthalate (DEP) and dibutyl sebacate (DBS). For the coating processes using Aquacoat CPD and TEC as a plasticizer the coating formulations and parameters shall be developed based on the combination of the publications by Williams and Liu <200>, Carlin <25> and the product information of Aquacoat CPD <7>. Model pellets containing methyl orange shall be used to develop the coating process using Aquacoat CPD and TEC <170>. The pellets containing nicotinamide will be coated with the formulation containing Aquacoat CPD and TEC as well. On the other hand, for the coating processes using Aquateric or Aquacoat CPD and DEP or DBS as a plasticizer the coating formulations and parameters will be developed on the basis of the studies by Chang <31>, the product information of Aquateric <9> and Aquacoat CPD <7>.

The products with different subcoats will be combined and applied as a loading material for a common coating process using an aqueous dispersion of CAP and a plasticizer. This assures the same coating conditions and reduces the number of trials. Therefore the differentiation of products with different subcoats after finishing the process must be possible. The different colours (red, green, orange and blue) are therefore used as a marker for each product for the identification.

The effect of post-drying at different temperatures and humidities outside the coating apparatus were studied with some CAP-coated pellets.

The determination of different properties of the products such as morphology, thickness, diameter, swelling and the resistance against artificial gastric fluid was performed.

As the water content in the dosage form is the important factor that can affect the hydrolytic process of the polymer especially CAP, the determination of the water content will therefore be investigated by Karl-Fischer Titration.

The chromatographic method as HPLC will be used to determine the content of free phthalic acid, which is the indicator for the chemical stability of CAP. Some CAP-coated pellets will be optically observed after storage under different temperatures and humidities. The long time stability test can be done only after the CAP-coated pellets have passed the enteric resistance test.

2. Experimental part

2.1 Materials

2.1.1 Core materials: Sugar spheres

Sugar spheres defined by the USP XXIV <181> should contain not less than 62.5 % and not more than 91.5 % of sucrose ($C_{12}H_{22}O_{11}$), calculated on the dried basis, the remainder consisting chiefly of starch. They consist of approximately spherical particles of a labeled nominal size range. The loss on drying at 105 °C for 4 h should not be more than 4 % w/w. The particle size test is in accordance with the procedure for coarse powders. Not less than 90 % of it should pass the coarse sieve size and not more than 10 % should pass the finer sieve size stated in the labeling.

Sugar spheres are solid drug excipients of spherical size. They are characterized by their geometry, whereas the process of manufacture and the composition are variable according to special uses. In contrast to the well-known granulates the pellets have nearly ideal spherical form. Normally, the diameter of pellets is below one millimeter <198>.

Materials used in this work:

Sugar spheres used in this work were manufactured by Werner's Feine Dragees, Hanns G. Werner GmbH+Co., Tornesch.

They contained 62.5 - 91.5 % saccharose, 8.5 - 37.5 % corn starch and up to 4 % purified water. The values from the certificate of analysis of different batches used in this work are shown in the following table.

Batch number	Nominal size fraction (μm)	Actual content in size fraction (% w/w)	Loss on drying at 4 h, 105 °C (% w/w)
08430427	850-1000	91.5	1.58
08430993	850-1000	94.5	1.51
08530984	1000-1180	92.7	1.91
08530099	1000-1180	96.2	1.13

Table 2.1: Batches and properties of sugar spheres used as cores.

2.1.2 Neutral polymer: Hydroxypropyl methylcellulose (HPMC)

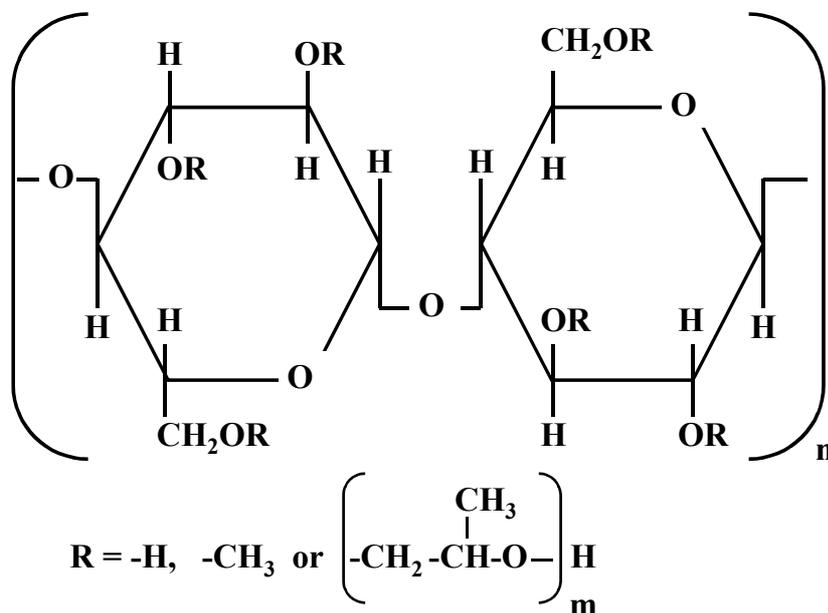


Figure 2.1: Structural formula of HPMC

Hydroxypropyl methylcellulose is cellulose 2-hydroxypropyl methyl ether and is known as Hypromellose, Hydroxypropylcellulosum, hypromellosum. HPMC is a propylene glycol ether of methylcellulose. It is characterized by different mean substitution degrees: $-OCH_3$ 1.12 - 2.0 and $-OCH_2 - CHOH - CH_3$ 0.1 - 0.34, this means in the number of methoxy groups (16.5 – 30 %) and hydroxypropoxy groups (4 – 32 %) per glucose unit <77,78,79>.

HPMC is an odorless, tasteless, white or creamy-white fibrous or granular powder and has no ionic charge. It dissolves in cold water in all proportions and binary organic solvents systems such as methylene chloride with methanol, ethanol or isopropanol offer a good solubility <79>. HPMC has the glass transition temperature (T_g) at 40 °C - 45 °C and the melting point (T_m) of HPMC is 190 - 305 °C <77>.

Low viscosity grades of HPMC such as Pharmacoat 603 are used in aqueous film coating, while high viscosity grades are used in organic solvent film coating. For film coating, concentrations reaching 80 - 100 cP are optimum. These viscosities correspond to the concentrations of 6 - 10 % w/w. Films prepared from HPMC are not brittle but to obtain a highly flexible film an addition of a plasticizer such as polyethylene glycol (PEG 6000) is required. Sometimes titanium dioxide or talc was recommended to

be added in a large amount to HPMC e.g. 20 % w/w. However, addition of inorganic substances such as TiO_2 may cause a marked decrease in the tensile strength, often leading to occurrence of cracking and detachment. Therefore, it should be added when a relative high viscosity grade (high molecular weight) of HPMC was used such as Pharmacoat 645W or Pharmacoat 606. The addition of a water-insoluble polymer such as ethylcellulose to HPMC may delay the dissolution of the film or drug. The examples of the mixed film prepared from HPMC and EC showed that the mixing ratio of HPMC:EC at 5:5 caused a film that was nearly insoluble in simulated gastric fluid, whereas the mixing ratio at 7:3 caused a film soluble in this fluid.

Materials used in this work:

The products of Pharmacoat were manufactured by Shin-Etsu Chemical Co., Ltd., Pharmaceutical Materials Department, Tokyo, Japan and they are distributed by Syntapharm GmbH, Mülheim-Ruhr.

The following batches of HPMC were used in this work;

Pharmacoat 645W, Lot No. 605231. This batch contained, as mentioned in the certificate of analysis, 28.8 % methoxy content and 9.5 % hydroxypropoxyl content. The pH of it was 6.7 and the apparent viscosity measured after EP was 4.46 mPa.s.

Pharmacoat 603W, Lot No. 612646. This batch contained, as mentioned in the certificate of analysis, 29 % methoxy content and 9.5 % hydroxypropoxyl content. The pH of it was 7.2 and the apparent viscosity measured after EP was 3.28 mPa.s.

2.1.3 Neutral polymer: Sepifilm LP 010

Sepifilm LP is a ready to use product. It is composed of hydroxypropyl methylcellulose, microcrystalline cellulose and stearic acid.

Sepifilm LP is in granular form and because of the presence of cellulose it is almost fast and easy to make a dispersion of Sepifilm. The size of grains is 0.2 to 2 mm, which allows a good flow and is dust-free with an easy handling. It is easy to be wetted and because of the porosity of the grains it allows a fast dispersion within 30 min at room temperature. The manufacturer indicated a good adhesion and a good quality with homogeneous film. Therefore it can be used as a film forming composition intended for gastro-soluble film coating of tablets and microgranules sensitive to moisture. The dissolution profile and the disintegration were not different between tablet coated with

Sepifilm LP and non film-coated tablets both at pH = 1 and pH = 5.5. Comparing the property of protection against moisture of film prepared from Sepifilm LP and HPMC, it was found that the moisture intake of fumitory tablets under stressfull condition (40 °C, 90 % r.h.) was halved when the tablets were coated with Sepifilm LP in comparison with HPMC <171,172>.

Material used in this work:

Sepifilm LP 010, Lot No. 64211 was manufactured and distributed by Seppic, Paris, France.

As mentioned in the certificate of analysis, the batch used in this work contained 4.3 % volatile matter and 8 % stearic acid. The viscosity of 12 % dispersion was 678 cP.

2.1.4 Neutral polymer: Ethyl cellulose (EC)

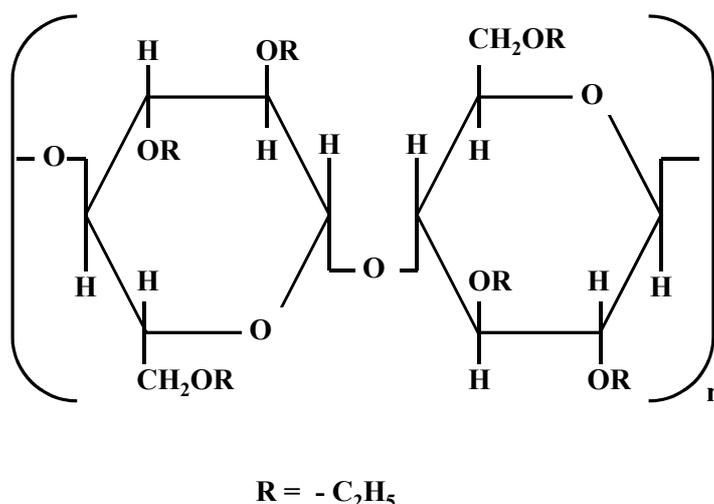


Figure 2.2: Structural formula of EC

Ethyl cellulose is stated in many pharmacopoeia such as EP 1997, BP and USP. EC is an ethyl ether of cellulose. When EC was dried at 105 °C for 2 h, it should contain not less than 44 percent and not more than 51 percent of ethoxy ($-OC_2H_5$) groups <55,56>. EC is an odorless, tasteless, white or creamy-white granular powder and has no ionic charge. It is insoluble in water but soluble in organic solvent such as methanol, ethanol, ethyl acetate, acetone or chlorinated hydrocarbon. Molecular weight of EC varied from 150,000 to 300,000 <54>. The glass transition temperature (T_g) of EC is 129 °C. The

degradation temperature of EC is $> 200\text{ }^{\circ}\text{C}$ and minimum film forming temperature (MFFT) of EC and 20 % DEP is $75\text{ }^{\circ}\text{C}$.

Ethyl cellulose has a nonionic and moisture barrier properties, therefore EC can be used as a coating material. The reason why EC can be used as a moisture barrier may be due to the fact that EC itself is insoluble and does not absorb moisture. In addition, a latex film of any polymer seems to be more dense than a solution cast film. This property may improve the barrier property of the latex film from EC. Therefore EC may be better than HPMC as a subcoat for hindering the moisture or the diffusion of the substance or water. HPMC is a water soluble polymer and therefore may absorb moisture into or through its film. This may be the result that HPMC is not a good polymer film used for hindering the moisture <8>.

The ethyl cellulose aqueous dispersion was also mentioned in USP XXIV <55>. It is a colloidal dispersion of ethyl cellulose in water. It should contain not less than 90 percent and not more than 110 percent of the labeled amount of ethyl cellulose. It can contain suitable amounts of cetyl alcohol and sodium lauryl sulfate, which assist in the formation and stabilization of the dispersion. It may contain suitable antifoaming and antimicrobial agents. The pH of the EC dispersion is between 4 and 7. The commercial available EC dispersion are for examples Aquacoat ECD and Surelease. The detail of Aquacoat ECD will be discussed further on because it will be used for this work.

Material used in this work:

Aquacoat ECD-30 was manufactured by FMC Corporation, Pharmaceutical Division, Philadelphia, USA and distributed by Lehmann & Voss & Co., Hamburg.

The following batch of ethylcellulose dispersion was used in this work;

Aquacoat ECD 30, Lot No. J8381. This product contained cellulose ethyl ether [CAS.No. 9004-57-3], hexadecan-1-ol [CAS.No. 36653-82-4] and sodium dodecyl sulphate [CAS.No. 151-21-3]. As mentioned in the certificate of analysis it contained 26.2 % ethylcellulose, 1.3 % sodium lauryl sulfate and 2.5 % cetyl alcohol. The viscosity of this dispersion was 11 cP and pH was 6.3.

2.1.5 Neutral polymer: Polyvinyl alcohol (PVA)

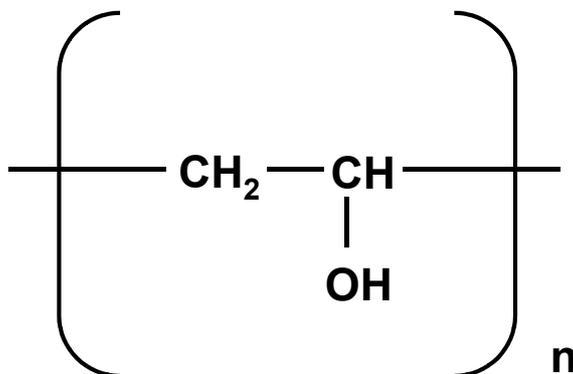


Figure 2.3: Structural formula of PVA

Polyvinyl alcohol defined in USPXXIV is a polymer in which the average value of n lies between 500 - 5000. Various grades with different viscosities and molecular weights are commercially available such as products from Mowiol or Poval, etc <140,141>.

A commercial product Mowiol is obtained by hydrolysis of polyvinyl acetate in methanol using sodium hydroxide as catalyst. The difference in concentration of catalyst, reaction temperature, and reaction time will result in various residual amounts of acetyl groups, i.e. fully hydrolysed or partially hydrolysed. The distribution of acetyl groups in partially hydrolysed polyvinyl alcohol will be controlled by the catalyst and solvent. That is why the alkaline alcoholysis results in a block-type distribution of acetyl groups, while the acidic reaction gives mostly statistically distributed acetyl groups. Most of these types contain about 11 % acetyl, that means the degree of hydrolysis is 88 mol %. The fully hydrolysed polyvinyl alcohol has a degree of hydrolysis of about 97 to 100 mol %. It has a high crystallization tendency and crystallinity. This is the main reason for a reduction in the cold-water solubility of the polyvinyl alcohol.

Mowiol has different grades and was classified by the degree of polymerization and hydrolysis. They are supplied in the form of fine granules, some grades are available in a fine particle size. The nomenclature of Mowiol is that the first position means the viscosity (mPa.s) of 4 % w/w of the substance in water at 20 °C and the second position means the degree of hydrolysis of the polyvinyl acetate (mol %) on which it is based (partially and fully hydrolysed Mowiol grades). For example: Mowiol 4-88 is a partially hydrolysed type, this grade has a viscosity of 4 ± 0.5 mPa.s, the degree of hydrolysis is

87.7 ± 1 mol % and the residual content of acetyl group is 10.8 ± 0.8 % w/w, whereas Mowiol 4-98 is a fully hydrolysed type <142>.

Apart from water there are other solvents for Mowiol e.g. dimethyl sulphoxide, formamide, dimethyl formamide and phosphoric acid. Mono- and multivalent alcohol such as methanol, ethanol, glycerine or ethylene glycol may cause certain Mowiol grades to swell but will not dissolve them. The glass transition temperature of Mowiol is about 40 to 80 °C depending on the type. The melting point range of the crystall is 180 to 240 °C.

Mowiols can be used as emulsifier, protective colloid, plasticizer, filler in pelletization or coating material. The microencapsulation, sponges or emulsion can be also prepared from Mowiols. The low molecular, partially hydrolysed grades such as Mowiols 3-83, 4-88 and 5-88 are preferred as binders for pelletizing because they cause no problems for the production of sprayable solutions with variable solids content. The partially hydrolysed Mowiols grades are from the low and medium viscosity range and they are preferably used as co-binder for microencapsulation. For coating purposes Mowiols 3-98, 4-98, 6-98 and also 5-88 are preferably used. As it was reported from the company Clariant, although Mowiols is not hygroscopic, films from Mowiols absorb some moisture. The amount of moisture absorbed depends on the partial pressure of the water vapour. In order to measure water absorption, they used 0.3 mm films which were cast from 10 % aqueous solution from Mowiol solution and then dried in air at 23 °C and 50 % r.h. These films were afterwards stored for 7 days at 23 °C and at various relative humidities between 15 and 92 %. The water absorption was measured by gravimetric weight analysis under comparable conditions. The result showed that films prepared from partially hydrolysed Mowiol such as 4-88, 8-88, 18-88, 26-88 or 40-88 had a water content of about 6 % w/w, whereas films prepared from fully hydrolysed Mowiol such as 4-98, 10-98, 20-98 or 28-99 had a water content of about 7.5 % w/w. That means in general the fully hydrolysed films absorb slightly more water at low humidities than the partially hydrolysed ones. The water resistance of dried Mowiol films rises with increasing molar mass and the degree of hydrolysis <142>.

Materials used in this work:

Mowiol products were manufactured by the company Clariant GmbH, Frankfurt am Main and distributed by Hermann Ter Hell & Co. GmbH, Hamburg.

The following batches in a granulate form were used in this work.

Mowiol 3-83, Lot No. 601B25192

Mowiol 3-98, Lot No. DEBC009711

Mowiol 4-88, Lot No. 601B29217

Mowiol 4-98, Lot No. DEBC003522

Mowiol 8-88, Lot No. 601BE0352

Mowiol 10-98, Lot No. DEBC006732

Mowiol 18-88, Lot No. DEBC003543

Mowiol 20-98, Lot No. 601BH0081

Mowiol 26-88, Lot No. DEBC006525

2.1.6 Enteric polymer: Cellulose acetate phthalate (CAP)

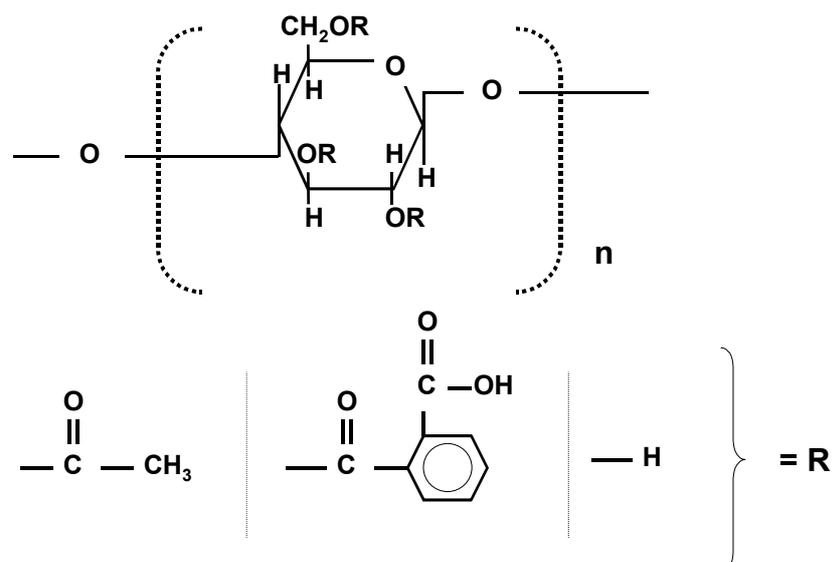


Figure 2.4: Structural formula of CAP

Cellulose acetate phthalate (CAP) known as *cellulosi acetas phthalus* in the Ph.Eur. 1997, *cellacefate* in the USP XXIV, and *cellacephate* in the BP 1993. Other synonyms such as cellulose acetate hydrogen 1,2 - benzenedicarboxylate, cellulose acetate monophthalate or cellulose acetylphthalate are mentioned <29>. CAP is a reaction product of phthalic anhydride and a partial acetate ester of cellulose. It contains not less than 21.5 percent and not more than 26 percent of acetyl (C₂H₃O) groups and not less

than 30 percent and not more than 36 percent of phthalyl (o-carboxyl-benzoyl, $C_8H_5O_3$) groups, calculated on the anhydrous, acid free basis <26>. The limit of phthalyl content stated in EP1997 and BP 1993 however is different from the USP that is 30 - 40 %. The limit of free acid of CAP in USP XXIV, EP 1997 and BP 1993 is the same that means no more than 3 %, whereas the limit in USPXXIII is higher namely not more than 6 %, calculated as free phthalic acid. The free acid was determined by the titration method using dilute methanol as solvent, 0.1 N sodium hydroxide as titrant and phenolphthalein as an indicator <27,28,30>.

CAP is a white, free-flowing powder or colourless flakes, tasteless, odourless or may have a slight odor of acetic acid. It is a hygroscopic substance, practically insoluble in water, alcohols, hydrocarbons and chlorinated hydrocarbons but soluble in dilute solutions of alkalis, a number of ketones, esters, ether alcohols, cyclic ethers and in certain solvent mixtures such as acetone : ethanol, acetone : methanol or ethyl acetate : isopropanol. The relative molecular weight of CAP is ca. 30,000. The glass transition temperature (T_g), melting point (T_m) and minimum film forming temperature (MFFT) of CAP is 160 – 170 °C, 192 °C and 56 °C, respectively <29>. The pKa value of CAP is 4.4 - 4.7 depends on phthalyl content <29>.

There are two commercially available CAP products to be used as a coating dispersion <7,9>. One is in form of redispersing powder called Aquateric CD, the other one is in form of a ready-to-used dispersion called Aquacoat CPD. Both these two products will be discussed in details in the following part because they will be used in this work.

2.1.6.1 Aquateric CD-910

Aquateric is composed of solid or semi-solid polymer spheres of cellulose acetate phthalate ranging in size from 0.05 to 3 μm with average particles of 0.2 μm . Aquateric was accomplished by a special mechanical emulsion technique to produce the submicron size particles and subsequent spray drying after addition of suitable physical barrier materials. In its initial form Aquateric is a dry, white water-insoluble powder. It is then dispersed in water to create the reconstituted latex film coating system. A typical dispersion may consist of 10 - 30 % solids, yet have a viscosity in the 50 - 100 cP range. Aquateric consisted of 70 % CAP, the remainder comprises polyoxypropylene-polyoxyethylene block co-polymer and acetylated monoglycerides for stabilizing the physical property of the product. Diethyl phthalate (DEP) has been found to be an

effective plasticizer for use in Aquateric because of its effective interaction with CAP polymer. It was also reported that propylene glycol showed a good plasticization effect. Mixed plasticizer systems including DEP, polyethylene glycol (PEG) 400 have been reported to provide fully continuous films for enteric performance as well. PEG 400, on the other hand, tended to over soften the film and resulted in twinning or sticking. In summary the following plasticizers were recommended to be used with Aquateric: the water insoluble plasticizer DEP, the water soluble triacetin, triacetin citrate or propylene glycol and the combination of DEP and triacetin at 1:1 ratio.

Materials used in this work:

The following batches of Aquateric, which was produced by FMC Corporation, Pharmaceutical Division, Philadelphia, USA and distributed by Lehmann & Voss & Co., Hamburg, were used in this work.

Lot. No. L6271, This batch according to the certificate of analysis contained 70 % cellulose acetate phthalate and 2.1 % free phthalic acid.

Lot. No. L9242, This batch as mentioned in the certificate of analysis contained 70 % cellulose acetate phthalate and 1.3 % free phthalic acid.

2.1.6.2 Aquacoat CPD- 30

Aquacoat CPD contained 23 % cellulose acetate phthalate [CAS.No. 9004-38-0], 7 % poloxamer [CAS.No. 9003-11-6] and 70 % water [CAS.No. 7732-18-5]. It is commercially available as a 30 percent by weight dispersion. The typical coating level for enteric coated beads using Aquacoat CPD is 10-15 %. Because of a high surface area of dosage form beads need more coating substances than tablets which need only 6-10 % coating level. Recommended plasticizers for use with Aquacoat CPD include diethyl phthalate (DEP), triethyl citrate (TEC) and triacetin. The amount of 20-24 % plasticizers to Aquacoat CPD latex solids was recommended for the most applications. For example; if DEP was used at 20 % to solid content of latex, the glass transition temperature (T_g) of Aquacoat CPD was reduced to 34 °C, but using TEC at the same concentration, the T_g was reduced to 35 °C.

Materials used in this work:

The following batches of Aquacoat CPD, which was manufactured by FMC Corporation, Pharmaceutical Division, Philadelphia, USA and distributed by Lehmann & Voss & Co., Hamburg, were used in this work.

Lot No. K9261, This batch as mentioned in the certificate of analysis contained total solid content of 30.2 %. The content of cellulose acetate phthalate was 24 % and of free phthalic acid was 0.4 %. The pH of this dispersion was 2.7 and the viscosity was 12 cP.

Lot No. K0061, This batch as mentioned in the certificate of analysis contained total solid content of 29.5 %. The content of cellulose acetate phthalate was 22 % and of free phthalic acid was 0.5 %. The pH of this dispersion was 2.6 and the viscosity was 13 cP.

Lot No. K9441, This batch as mentioned in the certificate of analysis contained total solid content of 29.6 %. The content of cellulose acetate phthalate was 22 % and of free phthalic acid was 0.5 %. The pH of this dispersion was 2.7 and the viscosity was 12 cP.

Lot No. K9251, This batch as mentioned in the certificate of analysis contained total solid content of 30.2 %. The content of cellulose acetate phthalate was 24 % and of free phthalic acid was 0.7 %. The pH of this dispersion was 2.8 and the viscosity was 12 cP.

2.1.7 Enteric polymer: Hydroxypropyl methylcellulose acetate succinate (HPMCAS)

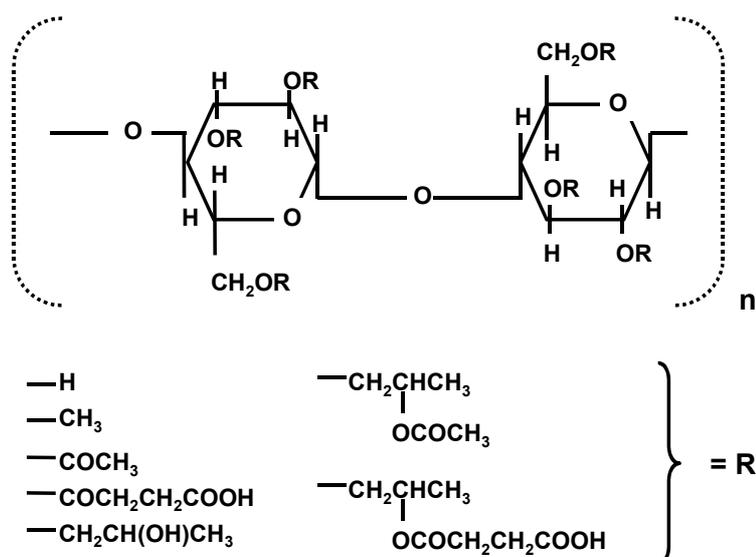


Figure 2.5: Structural formula of HPMCAS

Hydroxypropyl methylcellulose acetate succinate (HPMCAS) was not mentioned in any Pharmacopoeia but was mentioned in the Japanese Pharmaceutical Excipients 1998.

There are different grades of HPMCAS available depending on the molecular weight distribution as mentioned from the Company ShinEtsu, Japan. The commercial available product is Aqoat in the form of dried powder. Aqoat type AS-LF has the highest molecular weight, type AS-HF has the lowest molecular weight, and type AS-MF has the middle molecular weight. Only the properties of Aqoat type AS-MF will be discussed in details because it will be used in this work.

Aqoat type AS-MF should contain 21 - 25 % methoxyl content, 5 - 9 % hydroxypropylxyl content, 7 - 11 % acetyl content and 11 - 14 % succinoyl content. The free succinic should not be more than 1 %. The average particle size should not be more than 10 μm , the size through 75 μm should not be less than 99 % and the size retained on 53 μm should not be more than 10 % <6>. It is a white powder without odour. It is not soluble in water but it is soluble in acetone, buffer solutions of pH more than 6, a mixture of some solvent such as a mixture of methylene chloride and ethanol (1:1) or a mixture of ethanol and water (8:2). The recommended plasticizers are TEC, triacetin and propylene carbonate. The pKa of HPMCAS is 4.8-5.0, therefore it is less acidic than CAP.

Material used in this work:

Aqoat AS-MF, Lot No. 910049, distributed by Syntapharm GmbH, Mülheim an der Ruhr, was used for this work. The content of different groups in this batch is 23.4 % methoxyl, 7 % hydroxypropylxyl, 9 % acetyl, and 11.2 % succinoyl. The free succinic acid content is 0.03 %. The average particle size is 4.6 μm and the 90 % cumulative of the particle size is 10.2 μm .

2.1.8 Model indicator: Methyl orange (MO)

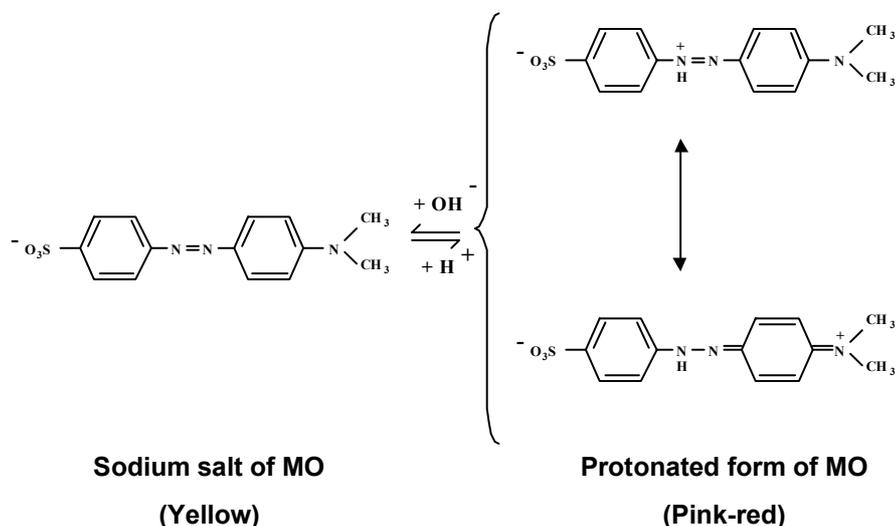


Figure 2.6: Colour changing of methyl orange in acidic or basic medium

Methyl orange has many synonyms such as 4-[[4-Dimethylamino) phenyl]-azo] benzenesulfonic acid sodium salt, sodium p-dimethylaminoazobenzene-sulfonate, helianthine B, acid orange 52, orange III, gold orange or tropaeolin D. The chemical formula is $\text{C}_{14}\text{H}_{14}\text{N}_3\text{NaO}_3\text{S}$ with the molecular weight of 327.33 g/mol. It was prepared from sulfanilic acid sodium nitrite and dimethylaniline <99 - 104>.

Methyl orange is a yellow powder or crystalline scales. It is soluble in 500 parts of cold water and more soluble in hot water but practically insoluble in alcohol. At pH 3.1, methyl orange has the maximum absorption at wavelength range of 501 - 504 nm (λ_1), whereas at pH 4.4, methyl orange has the maximum absorption at wavelength range of 467 - 471 nm (λ_2). The specific absorption A (1%, 1 cm) at λ_1 is 1050 - 1150, whereas the specific absorption A (1%, 1 cm) at λ_2 is 750 - 850.

It was normally used as indicator in 0.1% aqueous solution. The colour of methyl orange at pH of 4.4 is yellow and at pH of 3.1 is red. That means it produces a red colour in moderately acidic solutions and a yellow colour in weakly acidic and alkaline solutions <99 - 104>

Material used in this work:

Methyl orange, Art. No. 1322, Lot No. 003 L687522, E.Merck, Darmstadt

2.1.9 Model drug: Nicotinamide

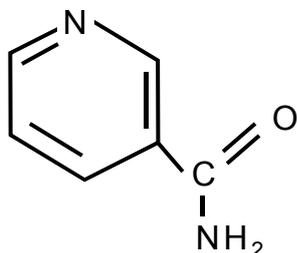


Figure 2.7: Structural formula of nicotinamide

Nicotinamide has many synonyms such as Nicotinamidum, Niacinamide, Nicotinic acid amide, Nicotylamide, vitamine B₃, vitamine PP and Pyridine-3-carboxamide. The chemical structure is C₆H₆N₂O, with the molecular weight of 122.1 g/mol.

Nicotinamide has the actions described under nicotinic acid but it has no vasodilator action. Nicotinamide is therefore used as an alternative to nicotinic acid for the prevention and treatment of pellagra. Pellagra is characterised by loss of appetite, lethargy, weakness, diarrhoea, dermatitis and mental changes.

It is a white crystalline powder or colourless crystals with a faint characteristic odour and a salty and bitter taste. The melting point is 128 to 131 °C. It absorbs insignificant amounts of moisture at relative humidities up to about 90 % at 25 °C. It is soluble in water (1:1), in alcohol (1:1.5) and in glycerol (1:10). It is slightly soluble in chloroform and ether. A 5 % w/v solution in water has a pH of 6 to 8. The pKa is 3.3 at 20 °C. The solution of nicotinamide 1 part in 50,000 part of water has a ratio of ultraviolet absorption of $A_{245\text{nm}}/A_{262\text{nm}}$ between 0.63 and 0.67. The values of specific absorption of nicotinamide in different media are $A(1\%, 1\text{ cm}) = 410$ at 260 nm in 0.1 M HCl, $A(1\%, 1\text{ cm}) = 221$ at 262 nm in MeOH, $A(1\%, 1\text{ cm}) = 231$ at 262 nm in 0.1 M NaOH. The IR spectrum of nicotinamide in KBr shows bands in the following regions; 3360, 3140, 1660, 1590, 1400, 1370, 1185, 1010, and 660 cm⁻¹ <110 - 113>.

Materials used in this work:

Nicotinamide, Art. No. 183830, Batch No. 96010810, Synopharm GmbH, Hamburg

Nicotinsäureamid Testsubstanz, Art. No. 6828, Batch No. K 16823528, Merck KGaA, Darmstadt

2.1.10 Colour

Four different colours used as markers will be discussed in details in the following part <39,57>.

2.1.10.1 Blue colour

The blue colour was achieved from Indigotin blue. The synonyms of indigotin blue are such as indigo carmin, indigo-Karmin, L-Blau 2, E 132, food blue 1, acid blue 74. It is a synthetical organic substance.

2.1.10.2 Red colour

The red colour was achieved from L-Rot Z 3020, extra conc bes.rein, G.Siegle & Co.GmbH, Stuttgart. This colour has many synonyms such as erythrosin BS, LB-Rot 1, L-Rot 11, E127, food red 14, acid red 51. It is a synthetical organic substance.

2.1.10.3 Orange colour

The orange colour was achieved from L-Orange Z 2010, extra conc bes.rein, G.Siegle & Co.GmbH, Stuttgart. This colour has many synonyms such as Gelborange S, jaune orange S, jaune soleil, sunset yellow FCF, L-Orange 2, E 110. It is a synthetical organic substance.

2.1.10.4 Green colour

The green colour was achieved from L-Grün Z 6130, extra conc bes.rein, G.Siegle & Co.GmbH, Stuttgart. This colour is the mixture of E 102 and E 132. E102 is known as tartrazine and E 132 is indigotin which was mentioned before.

2.1.11 Plasticizers

2.1.11.1 Polyethylene glycol (PEG)

Empirical formula:



when **m** represents the average number of oxyethylene groups.

Polyethylene glycol is an addition polymer of ethylene oxide and water. PEG has many synonym such as Carbowax, Macrogol, Macrogolum and Lutrol. The CAS registry number is 25322-68-3 <135,136>.

Polyethylene glycol is available in different grades. PEG grades 200 - 600 are liquids whilst grades 100 and above are solids at ambient temperatures. Liquid grades occur as clear, colorless or slightly yellow-coloured, viscous liquids. They have a slight but characteristic odor and bitter, slightly burning taste. The liquid form is very hygroscopic, although hygroscopicity decreases with increasing molecular weight. The example of the liquid form is PEG 400 which has an average molecular weight of 380 - 420, its value of hydroxy is 264 - 300. Solid grades are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. The solid form is not hygroscopic. The example of the solid form is PEG 4000 which has an average molecular weight of 3000 - 4800, its value of hydroxy is 30 - 36. The pH of 5 % w/v solution of PEG 4000 is 4.5 - 7.5. All grades of PEG are soluble in water and miscible in all proportions with other PEGs. The liquid form is soluble in acetone, alcohol, benzene, glycerin and glycols. The solid form is soluble in acetone, dichloromethane, ethanol and methanol. They are slightly soluble in aliphatic hydrocarbons and ether but insoluble in fats, fixed oils and mineral oil.

Polyethylene glycols are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations. They function as an ointment base, a plasticizer, a solvent or a lubricant in tablet or capsule formulations.

Materials used in this work:

Polyglykol 400, Product No. IOPC10, Lot No.E06396218, Hoechst AG, Burgkirchen. From the certificate of analysis this batch has an average molecular weight of 380 - 420, its value of hydroxy is 267 - 295. The pH of 10 % solution is 6.9.

Polyglykol 4000S, Product No. IOPI20, Lot No.E06395713, Hoechst AG, Burgkirchen. From the certificate of analysis this charge has an average molecular weight of 3700 - 4500, its value of hydroxy is 25 - 30. The pH of 10 % solution is 6.4.

2.1.11.2 Dibutyl sebacate (DBS)

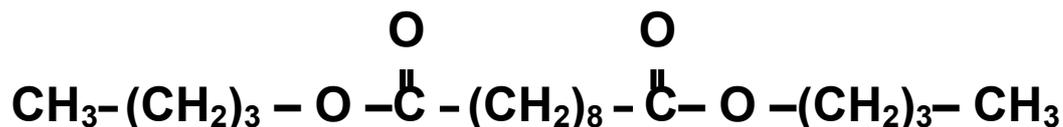


Figure 2.8: Structural formula of DBS

Dibutyl sebacate consists of the ester of n-butanol and saturated dibasic acids, principally sebacic acid. DBS has many synonyms such as butyl sebacate, decanedioic acid dibutyl ester, dibutyl decanedioate, dibutyl 1,8-octanedicarboxylate or sebacic acid dibutyl ester. The chemical name is di-n-butyl sebacate. The CAS registry number is 109-43-3. The empirical formula is C₁₈H₃₄O₄ with a molecular weight of 314.47.

DBS is a clear, colourless, oily liquid with a bland to slight butyl odor. It is soluble in ethanol, propan-2-ol and mineral oil but practically insoluble in water.

DBS can be used in oral formulations as a plasticizer for film coatings. It can also be used as a synthetic flavor and flavor adjuvant in food products e.g. ice cream and nonalcoholic beverages <44,45>.

Material used in this work:

Dibutyl sebacate, Lot No. 374235/1 13998 and 384343/1 33399, Fluka Chemie AG, Buchs, Switzerland

2.1.11.3 Diethyl phthalate (DEP)

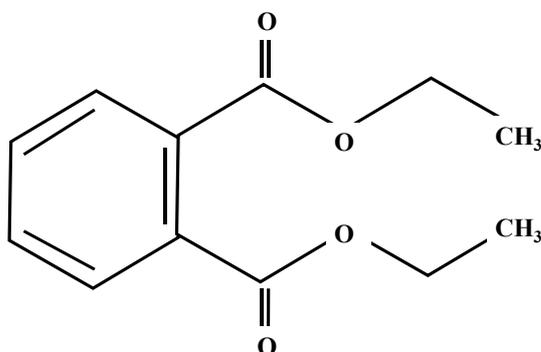


Figure 2.9: Structural formula of DEP

Diethyl phthalate has many synonyms such as ethyl phthalate, palatinol A, phthalic acid ethyl ester or ethyl benzene-1,2-dicarboxylate. The chemical structure of DEP is $C_{12}H_{14}O_4$ with a molecular weight of 222.24. The chemical name is 1,2-benzene-dicarboxylic acid, diethyl ester. The CAS registry number of DEP is 84-66-2. DEP should contain not less than 98 percent and not more than 102 percent of $C_{12}H_{14}O_4$, calculated on the anhydrous basis.

DEP is a clear, colourless, oily liquid. It is practically odorless, or with a very slight aromatic odor and a bitter, disagreeable taste. The solubility of DEP is 1 g in 1 L water. It is miscible with ethanol, acetone, dichloromethane or isopropanol. DEP can be used as a plasticizer for film coating on tablets, beads and granules. It is also used as an alcohol denaturant or as a perfume fixative in the perfumery <46,47>.

Material used in this work:

Diethyl phthalate, Lot No. 8223231000, S 24263749, Merck-Schuchardt, Hohenbrunn

2.1.11.4 Triethyl citrate (TEC)

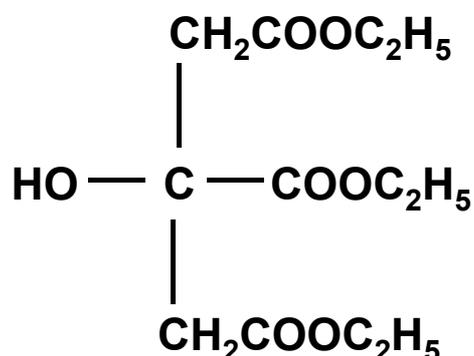


Figure 2.10: Structural formula of TEC

Triethyl citrate has many synonyms such as citric acid ethyl ester, ethyl citrate and Citroflex 2. The chemical name is 2-Hydroxy-1,2,3-propanetricarboxylic acid, triethyl ester. The CAS registry number is 77-93-0. The empirical formula is $\text{C}_{12}\text{H}_{20}\text{O}_7$ with a molecular weight of 276.29.

TEC occurs as a bitter tasting, odorless, practically colorless, oily liquid. The solubility of TEC is 1 part in 125 parts of peanut oil, 1 part in 15 parts of water. It is miscible with 95% ethanol or ether. The viscosity at 25 °C is 35.2 mPa.s. TEC can be used as a plasticizer for aqueous based coatings in oral formulations. Moreover, in the food products it can be used as sequestrant and in cosmetics as a deodorizing agent <193,194>.

Material used in this work:

Triethyl citrate, p.a., Lot No. S24374806, Merck-Schuchardt, Hohenbrunn

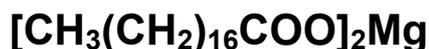
Plasticizer	Boiling point (°C)	Vapor density (air = 1)	Vapor pressure (mmHg)	Water solubility (% w/w)
DEP	295	7.66	100 at 220 °C	0.15
DBS	349	10.80	10 at 200 °C	0.01
TEC	294	9.7	1 at 107 °C	6.5

Table 2.2: Properties of three types of plasticizers <179,205>.

2.1.12 Additives

2.1.12.1 Magnesium stearate

Empirical formula:



Magnesium stearate is a compound of magnesium with a mixture of solid organic acids obtained from fats and consists chiefly of variable proportions of magnesium stearate, magnesium palmitate and magnesium oleate. Magnesium stearate has many synonyms such as magnesium octadecanoate, magnesii stearas, stearic acid magnesium salt. The chemical name is octadecanoic acid magnesium salt. The CAS registry number is 557-04-0. The empirical formula is $\text{C}_{36}\text{H}_{70}\text{MgO}_4$ with a molecular weight of 591.27.

Magnesium stearate is a fine, white, precipitates or milled, impalpable powder of low bulk density, having a faint, characteristic odor and taste. The powder is greasy to the touch and readily adheres to the skin. It is practically insoluble in ethanol, ether and water but slightly soluble in warm benzene and warm ethanol.

Magnesium stearate is primarily used as a lubricant in capsule and tablet formulations at the concentration between 0.25 - 5 %. Because of its hydrophobicity it may retard the dissolution of a drug from a solid dosage form, therefore the lowest possible concentration is preferred to be use <94>.

Material used in this work:

Magnesium stearate, Lot No. 91320, Riedel-de Haen, Seelze

2.1.12.2 Talc

Empirical formula:



The synonyms of talc are such as French chalk, purified talc, talcum, soapstone or steatite. It is a purified, hydrated, magnesium silicate which may contain a small variable amounts of aluminium silicate and iron. The CAS registry number is 14807-96-6 <182,183>.

Talc is a fine, white to grayish white, impalpable, odorless, crystalline powder. It is unctuous, adheres readily to skin, soft to touch and free from grittiness. It is insoluble in water, organic solvents, cold acids and dilute alkalis. The particle size distribution varies with the source and grade of talc but normally 73 - 90 % were less than 2 μm . The concentration of 1 - 10 % w/w can be used as lubricant or glidant in tablet and capsule manufacture, whereas at the concentration of 5 - 30 % w/w, it is used as filler for tablets and capsules. It was used as a dust powder at the concentration of 90 - 99 % w/w.

Material used in this work

Talc, asbest-free, Batch No. 97030190, Synopharm GmbH, Barsbüttel

2.1.12.3 Colloidal silicon dioxide

Colloidal silicon dioxide has many synonyms such as colloidal anhydrous silica, high dispersed silicium dioxide, silica colloidalis anhydrica, silicium dioxydatum dispersum. The CAS registry number is 7631-86-9. Colloidal silicon dioxide is a submicroscopic fumed silica prepared by the vapor-phase hydrolysis of a silicon compound. It contains not less than 99 percent and not more than 100.5 percent of SiO_2 .

Colloidal silicon dioxide is a light, fine and white amorphous powder. It is odourless and has a particle size of about 15 nm. It is practically insoluble in water and in mineral acids with the exception of hydrofluoric acid. It dissolves in hot solutions of alkali hydroxides.

Colloidal silicon dioxide can be used as a glidant in oral formulations such as tablets and capsule. Sometimes it is used as a stabilizer in a suspension or as an adsorbance for drying of hygroscopic powder or granules <37,38>.

Material used in this work:

Aerosil 200, Lot No. 28002, Degussa, Frankfurt

2.1.12.4 Polysorbate 80

The synonym of polysorbate 80 is polyoxyethylene 20 sorbitan monooleate. The chemical name is sorbitan, mono-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives. The CAS registry number is 9005-65-6. Polysorbate 80 is an oleate ester of sorbitol and its anhydrides copolymerized with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides. It is a yellow to amber coloured oily liquid with a mild odour and a bitter taste. It is soluble in water, ethanol but not soluble in mineral oil. Normally it is used as a surfactant <137-139>.

Material used in this work:

Tween 80, Lot No. 394974/1, 20599, Sigma-Aldrich Chemie GmbH, Steinheim

2.1.12.5 Poloxamer 407

General formula:



Poloxamer 407 is a polyoxyethylene – polyoxypropylene – blockcopolymer. Poloxamer has many synonyms such as Pluronic, poloxalkol, polyethylene - propylene glycol copolymer, or Supronic. The content of polyoxyethylene in Poloxamer 407 is about 70 %. The CAS registry number is 9003-11-6.

Poloxamer 407 is white, coarse-grained powder. The molecular weight (MW) is 9840-14600 g/mol. The pH of a 2.5 % solution in water is 5 - 7.5. It is soluble in water, ethanol 95 % and iso-propanol but it is not soluble in ether, paraffin and fatty oil. Poloxamer 407 can be used as a thickening agent, a gel formation agent or a co-emulsifier. It can also be used as a stabilizer for topical or oral suspensions because it has an effect to the viscosity of the formulation <132-134>.

Material used in this work:

Lutrol F127, Batch No. 380184, BASF Aktiengesellschaft, Ludwigshafen

All substances were received from the companies in Germany with the exception of those substances where the other countries have been indicated.

2.2 Analytical Methods

2.2.1 Determination of thickness and morphology of pellets by scanning electron microscope (SEM)

The thickness and the morphology of pellets has been determined by using the scanning electron microscope {55,56}. Both the whole and the cut pellets were investigated under SEM. Three coated or layered pellets can be well divided into two parts by using a surgical blade {57} and then the samples of 6 half pellets or three of the whole pellets ($n = 3$) from different products were fixed onto the aluminium plate which was covered with double-sided carbon tape. The mounted samples were coated with gold under vacuum before investigation at 10 - 12 kV under SEM. The best suited magnifications for revealing the film thickness and morphology were selected. One picture was taken from each of half a pellet so that at the end 6 pictures were resulted. The mean thickness of each product was calculated from 6 values ($n = 6$).

2.2.2 Determination of diameter of pellets

The size of pellets in form of a diameter before and after each coating process was determined in order to follow up the running process.

2.2.2.1 Calibration and validation

Calibration

The image analysis system {35,36} coupled with a digital camera {37} connected to a Nikon-camera {9} using an adapter was calibrated before use by utilizing a standard glass-plate {49}, which gave the value of pixel per micrometer. The following data show values of the calibration for this condition of the image analysis.

Scale X = 16.15 ± 0.02 $\mu\text{m}/\text{pixel}$ ($n = 3$, $p < 0.05$), Total picture size = 48 μm

Scale Y = 16.23 ± 0.02 $\mu\text{m}/\text{pixel}$ ($n = 3$, $p < 0.05$), Total picture size = 35 μm

Validation

The validation to prove the accuracy of the system was performed by using metallic spherical balls {59} in three sizes. These metallic balls have exactly defined diameters

with a known standard deviation as shown in Table 2.3 and therefore they are an ideal object for the validation. Ten balls ($n = 10$) at each size were used for the validation. The balls were arranged on a lustreless black surface of velour-type paper. A top light [42] was used to light up the pellets. The colour pictures of pellets were taken. These pictures were converted with a help of software [S3] into grey pictures, which afterwards have been converted again into binary pictures. The binary pictures have been analysed by the software integrated in the image analyser. The diameter (D), equivalent to the sphere which had the same projected area as the object, was automatically calculated by the computer [35]. Data of the validation of this combination were shown in Table 2.3.

Theoretical diameter (μm) ($n = 10$)	Experiential diameter (μm) ($n = 10$)
2002 ± 1	2020 ± 20
1500 ± 1	1520 ± 20
1001 ± 1	1020 ± 20

Table 2.3: Validation data as diameter of the spherical balls with the purpose of determination of diameters of pellets.

2.2.2.2 Measurement of diameters of pellets

The number of 100 - 150 pellets of each product were measured by using the image analyser combined with a camera as described above. Pellets were arranged so that they did not touch each other on a lustreless black surface of velour-type paper [No. 024750/2, Herlitz PBS AG, Berlin]. The pictures of these pellets were taken and converted in the same way as mentioned in 2.2.2.1. Finally, the mean diameter with standard deviation for each product was calculated and reported.

2.2.3 Sieve analysis of pellets

In order to know the size distribution of the pellets before and after the coating process, the sieve analysis was performed. This test in the combination with the test from 2.2.2 will give more details about size and size distribution of coated pellets or cores. For this

test the amount of about 20 g per product were fractioned by applying a sieve set of 6 sieve sizes i.e. 800, 1000, 1120, 1250, 1400 and 1600 μm {4} and these sieves were fixed at the two dimensional vibrating sieve machine {58} at the medium vibrating level and shaking for 5 min. After finishing the vibration the product laying on each sieve size was collected and weighed using an analytical balance {1}.

2.2.4 Weighing of pellets

The weight of each product was measured in order to know the real mass of coating materials layered on the surfaces of cores. The weighing process was carried on with all products such as sugar spheres, HPMC coated pellets, nicotinamide layered pellets and enteric coated pellets. Up to 100 pellets of each product have been weighed on an analytical balance {2}: Portions of 10 pellets were counted and then weighed up to a total number of 100 pellets. The weight of 10 pellets was noted and the mean weight and the standard deviation of these 10 measurements calculated. The weight of one pellet can be calculated from these 10 values.

2.2.5 Determination of form and size of particles

The form and size of some particles such as additives or polymer used in the coating formulation was important. Normally the particle size of substances used in this formulation should be as small as possible in order to avoid the blockage of the spraying nozzle. The simple method to observe form and size was the use of the microscopic method which, however, gave only the two dimensional information. This method was simplified by combination with a video camera and imaging system integrated with a software program.

2.2.5.1 Calibration

The image analysis system {35,36}, coupled with a digital camera {37} connected to a light microscope {40} with an objective of 10x using an adapter and a top light {41}, was calibrated before use by utilizing a standard glass-plate {50}, which gave the value of pixel per micrometer. Data below show values of the calibration of this combination.

Scale X = $1.3296 \pm 0.0017 \mu\text{m}/\text{pixel}$ (n = 3, p < 0.05), Total picture size = 1021 μm

Scale Y = $1.3362 \pm 0.0017 \mu\text{m}/\text{pixel}$ (n = 3, p < 0.05), Total picture size = 758 μm

2.2.5.2 Measurement of form and size of particles

Particle size and form of substances that are not water soluble such as talc or magnesium stearate were determined in order to use the data for supporting the decision whether these substances can be incorporated into the coating dispersion or not. Talc or magnesium stearate may hinder the twins formation during or after finishing the coating process but their size should be fine enough to avoid a blockage of the nozzle during spraying. For this test the substance was first dispersed in glycerol 85 % {Glycerin, Lot No. 933 K 12503393, E.Merck, Darmstadt} in a dilute dispersion on the glass plate {Microscope slides, 76 x 26 mm, ready to use, Lot No. 1243380, Carl Roth, Karlsruhe} before pictures of them were taken. Only the big particle size that can be seen under the microscope was considered. Fine particles that were in the high portion were not considered as they may not cause problems of blockage. Moreover, two types of talc i.e. before and after grinding with a jet mill {38}, were determined to observe the effect of the milling process.

The formulations containing CAP, TEC and HPMC-AS were also investigated by the microscopic method before using as a coating dispersion in the process in order to determine the big particles or aggregates that may happen after the mixing process or during processing time.

2.2.6 Determination of swelling

Enteric coated products should not swell after contact with an acidic medium. However, if this process occurs, this will cause a failure of resistance against artificial gastric fluid. Some works <185,187> had mentioned a problem of swelling of enteric coated polymers especially cellulose derivatives. Mostly the weighing method was used in this case to determine the swelling property. In this work, however, the diameter of the products under a light microscope was used to calculate the percentage of swelling. This method allows to follow up the swelling or dissolving of coated products against time and therefore problems by eliminating a medium were not involved.

2.2.6.1 Calibration and validation

Calibration

The image analysis system {35,36}, coupled with a digital camera {37} connected to a light microscope {41} with the objective of 16x using an adapter and a ring-light from the top, was calibrated before use by utilizing a standard glass-plate {50}, which gave the value of pixel per micrometer. Data below show values of the calibration.

Scale X = $6.0288 \pm 0.0096 \mu\text{m}/\text{pixel}$ ($n = 3$, $p < 0.05$), Total picture size = 4630 μm

Scale Y = $6.0350 \pm 0.0086 \mu\text{m}/\text{pixel}$ ($n = 3$, $p < 0.05$), Total picture size = 3422 μm

Validation

Validation was performed with the metal balls as mentioned before. The validation data using metallic balls {59} are show in Table 2.4.

Theoretical diameter (μm) (n = 10)	Experiential diameter (μm) (n = 10)
2002 \pm 1	2020 \pm 10
1500 \pm 1	1515 \pm 9
1001 \pm 1	1015 \pm 6

Table 2.4: Validation data as diameter of the spherical balls with the purpose of determination of swelling of pellets.

2.2.6.2 Measurement of swelling of pellets

To observe the swelling process the pellets have been fixed onto a glass plate and laid into the glass petridish. The acid medium 0.1 N HCl was poured into the petridish. The first colour picture of pellet was taken by using the image analyser coupled with a light microscope (as described before in 2.2.6.1) after the image was focused as soon as possible, normally after less than 30 sec. The second colour picture was taken after the diameter reached a maximum swelling level or after 2 h. The comparison between the diameters at the beginning and the end gives the information about the swelling or

dissolving of coated pellets. The percentage of the swelling can be calculated as shown below;

$$\% \text{ swelling} = \frac{(D2 - D1) \times 100}{D1}$$

D1 = Diameter (μm) of the pellet at the starting time in 0.1 N HCl after adjusting the sharpness of an image

D2 = Diameter (μm) of the pellet after 2 h or at the highest swelling in 0.1 N HCl

2.2.7 Determination of colour change of methyl orange of CAP coated pellets

As the colour of methyl orange can change from yellow (basic medium) to pink (acidic medium) as mentioned before in the part 2.1.8, it can be used as an indicator for a fast test of a resistance against artificial gastric fluid. The use of methyl orange in the preformulation of enteric coated products was also mentioned in the work of Schmidt and Teuber <170>, therefore the use of methyl orange was also carried out in this work. The observation of colour change of methyl orange can be easily done by using a light microscope coupled with a video camera and an image system as mentioned in the part 2.2.6. This system allowed the follow-up of the process of colour changing. If the enteric coated products were resistant against acidic medium their colour did not change. If the colour changed from yellow to pink after a certain time this indicated that the enteric coated layer cannot hinder the diffusion of acidic medium into the core.

This test was therefore carried out by using 6 pellets per product. They were fixed onto a glass plate by double-sided tape, which laid in a glass petridish. The acidic medium (0.1 N HCl) was poured into the petridish. The colour picture of each pellet was recorded by the image analyser, coupled with a light microscope {41} and the objective of 16x, as fast as possible after the pellet contacted the acid medium. Normally it took less than 30 sec. After this, one picture was taken every minute with an automatic software programm up to 30 min for each product. The time at which the colour of the pellet changed to pink and had constant intensity was recorded as judged by the experienced eye. This time period demonstrated the diffusion of 0.1 N HCl into the inner HPMC-MO layer.

2.2.8 Determination of the content of methyl orange in coated pellets

It was important to determine the content of methyl orange incorporated in coated pellets because this value will reveal the amount of coated pellets that should be used for release studies in the part 2.2.16. Moreover, the ratio of methyl orange and phthalyl groups in the CAP-polymer can be calculated as mentioned in the part 2.2.9. The simple method for determination of the content is to make use of ultraviolet-spectrophotometer. As methyl orange can absorb UV light at different wavelengths as mentioned in the part 2.1.8, this property will therefore allow the determination of the content both in an acidic or a basic medium.

2.2.8.1 Calibration and validation

Calibration

First of all the wavelength at which the maximum absorption occurred should be found. The solution of methyl orange in 0.1 N HCl should be prepared. The absorption curve versus wavelength of this solution was determined by the UV-spectrophotometer {68} using a 1 cm quartz-cuvette {11} scanned from 300 to 600 nm. The example of the UV-spectrum was shown in Figure 2.11. It shows that the maximum absorption occurred at the wavelength of 508 nm. The absorbance at 508 nm is 0.4736 in this figure and the concentration of methyl orange is 0.4871 mg/100 ml. This wavelength of 508 nm was used later on to determine the concentration of known solutions to create the calibration curve of methyl orange in 0.1 N HCl.

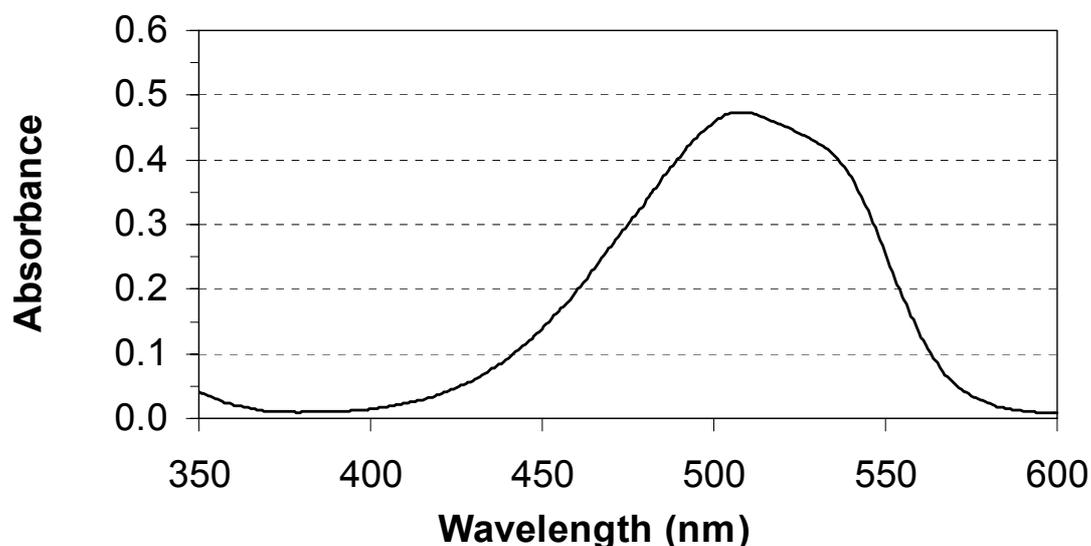


Figure 2.11: UV-spectrum of methyl orange (0.4871 mg/100 ml) in 0.1 N HCl.

To create the calibration curve, three stock solutions were prepared by accurately weighing {2} methyl orange of about 0.006 g. This amount of methyl orange was then placed into a 100 ml-volumetric flask {Volumetric flask 100 ml, tolerance ± 0.1 ml, Brand, Wertheim}, 0.1 N HCl {Hydrochloric acid 0.1 N, Merck KGaA, Darnstadt} was added to have an acquired volume of 100 ml. To increase the solubility of methyl orange in 0.1 HCl, this flask was placed in the ultrasound bath for 30 min. Each of the stock solutions was diluted into 5 concentrations by pipetting 1.00, 1.50, 2.00, 2.50 and 3.00 ml, respectively {Volumetric pipettes 1, 2, 3 ml, tolerance ± 0.01 ml, measuring pipettes 5 ml, tolerance ± 0.02 ml, Brand, Wertheim} and filling to 25.00 ml {Volumetric flask 25 ml, tolerance ± 0.04 ml, Brand, Wertheim} with 0.1 N HCl. The absorbances of these solutions were measured at 508 nm in triplicate. Therefore from each stock solution there were 15 values of absorbance. At the end there were 45 values for use to calculate the regression line by using the statistic programm Toccata {S4}. The result of 45 values showed the linearity and the homogeneity at the confidential level of 95 %. The equation (Eq-1) was used for calculating the concentration of the unknown solution of methyl orange in 0.1 N HCl. The residual plot of absorbances versus concentrations was shown in Figure 2.12.

$$Y = 0.9727 X \quad \dots\dots\dots (Eq-1)$$

Y was absorbance at 508 nm

X was concentration of methyl orange (mg/100 ml) in 0.1 HCl

The standard deviation of the slope was 5.0×10^{-5} . Therefore the specific absorption A (1 %, 1 cm) of methyl orange in 0.1 N HCl from this work was 973. The limits of detection and determination were 3.3047×10^{-4} and 6.6094×10^{-4} mg/100 ml, respectively.

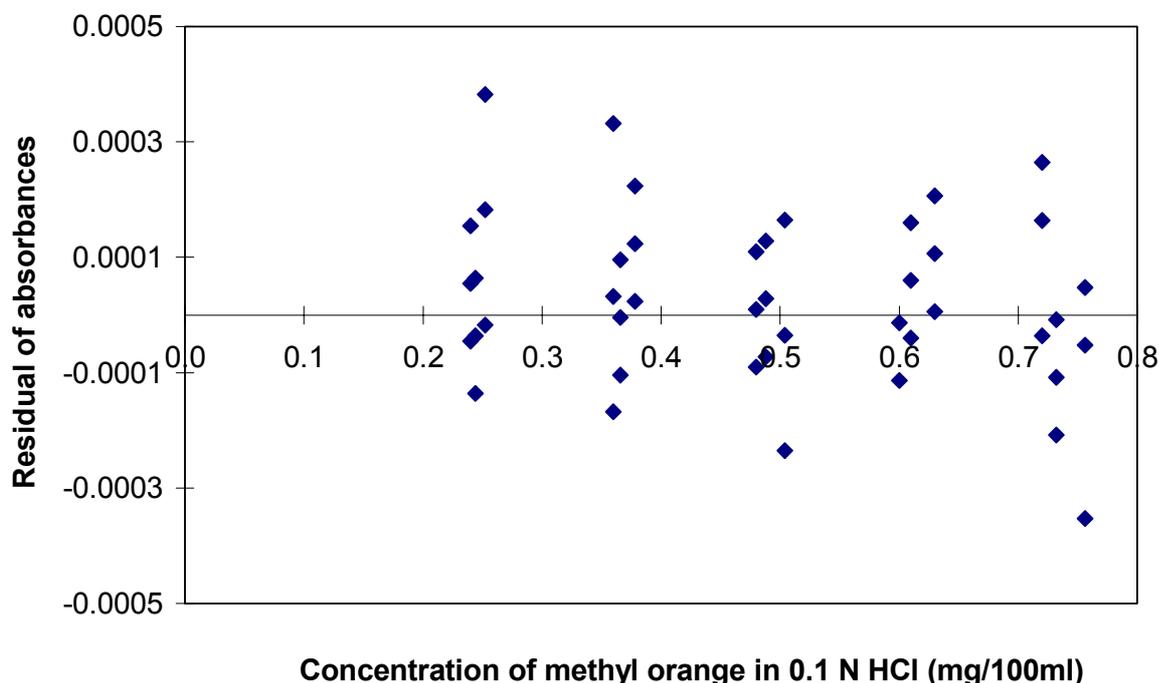


Figure 2.12: Residual plot of 45 values of the calibration curve of methyl orange in 0.1 N HCl, using UV-method.

Validation

The validation was carried out by using the known solution at the concentration of 0.5 mg/100 ml. This is notified as a theoretical concentration. This solution was pumped using a peristaltic pump {51} at the pump rate of 5 g/min through the tubing set which contained two types of tubes i.e., the flexible tube {Tygon-Schlauch D, 1.6 x 0.8 mm, Art. No. 132050, Lot No. 9903251, R3603, Desaga, Heidelberg} for a peristaltic pump and the non-adhesion tube {PTFE, 1.6 x 3.2 mm, Art. No. 2717300090 VE1, Otto Steiner, Hamburg} for transportation of solution into the 1 cm-quartz flow-through cuvettes {12}. The absorption at 508 nm was noted and the real concentration of the

solution was calculated by using the calibration curve. The result showed that the real concentration was not significantly different from the theoretical concentration.

2.2.8.2 Measurement of content of methyl orange in one pellet

The amount of methyl orange in one pellet was determined by using the equation „Eq-1“ from 2.2.8.1, at a maximum absorption of methyl orange at 508 nm in 0.1 N HCl. About 71 mg or 68 pellets of methyl orange-loaded pellets were accurately weighed {5} and dissolved in a 10 ml-volumetric flask {Volumetric flask 10 ml, tolerance ± 0.04 ml, Brand, Wertheim}. The volume was adjusted to 10 ml by adding 0.1 N HCl. This flask was put into an ultrasound bath {67} for 30 min to dissolve methyl orange from the pellets. The dispersion was filtered through 0.45 μm pore size filter {Rotilabo Spritzenfilter, Art No. P8161, PTFE, Carl Roth, Karlsruhe} to have a clear solution before measuring the absorbance at 508 nm in a UV-spectrophotometer {68}. For example if this solution has the absorption of 0.5, the concentration of methyl orange in 100 ml is 0.51 mg. Five samples from each batch were measured after this procedure. The results are shown together with the standard deviation of the content in absolute weight (mg) and % w/w which was calculated on the basis of the mean weight of one methyl orange-loaded pellet.

2.2.9 Calculation of phthalyl content in coated pellets

It was important to know the content of phthalyl in coated pellets in order to calculate the ratio between methyl orange and phthalyl groups in CAP polymer. This ratio may indicate the possible salt formation between hydrogen atom of phthalic acid group of CAP and nitrogen atom of methyl orange, as indicated in the part 2.2.11. The calculation will be done only with the product containing methyl orange in order to have an idea about possible salt formation.

As mentioned in Ph.Eur. <30> or BP <27>, CAP should contain not less than 30 % and not more than 40 % of phthalyl groups, whereas the limit in USP XXIV <26> is 30 % - 36 %. Therefore for this work the mean content of 35 %, based on Ph.Eur. 1997 <30>, will be used for calculation. As mentioned in the certificate of analysis of Aquacoat CPD, the dispersion of Aquacoat CPD contained 29 - 32 % of solid content and therefore the

mean value of 30 % will be used for the calculation. This amount of solid content had 19 - 27 % of CAP, so that the mean value of 23 % will be used for the calculation.

The increase of coated solid amount on the cores will surely increase the amount of phthalyl content. Therefore the calculation was done on basis of different products. The result of calculated phthalyl content (μg or mmole) and its ratio to methyl orange will be demonstrated.

Hereafter an example of the result from the calculation is given:

Product B has a weight gain of 4.5 % w/w from the coating formula R 11, Table 2.25, the mean weight of one pellet is 1.07 mg, part 3.1.1

The amount of solid content of coating materials in one pellet ($A_1 = \text{mg}$) can be calculated as follows;

$$A_1 = (\% \text{ weight gain} \times \text{weight of one pellet}) / 100 \quad \dots\dots\dots \text{Eq-2}$$

The amount of Aquacoat in one pellet ($A_2 = \text{mg}$) can be calculated as follows;

$$A_2 = (100 \times A_1) / 125 \quad \dots\dots\dots \text{Eq-3}$$

The amount of CAP in one pellet ($A_3 = \mu\text{g}$) can be calculated as follows;

$$A_3 = (23 \times 1000 \times A_2) / 100 \quad \dots\dots\dots \text{Eq-4}$$

The experiential amount of phthalyl in one pellet ($A_4 = \mu\text{g}$) can be calculated as follows;

$$A_4 = (A_3 \times 35) / 100 \quad \dots\dots\dots \text{Eq-5}$$

The ratio of methyl orange and content of phthalyl in one pellet ($A_5 = \mu\text{g}$) can be calculated as equation Eq-6. The molar content of phthalyl ($A_6 = \text{mmole}$) can be calculated by dividing A_5 by the molecular weight of phthalyl groups i.e. 149.

$$A_5 = (\text{amount of methyl orange in } \mu\text{g}) / A_4 \quad \dots\dots\dots \text{Eq-6}$$

$$A_6 = A_5 / 149 \quad \dots\dots\dots \text{Eq-7}$$

2.2.10 Determination of the content of nicotinamide in coated pellets

It was necessary to determine the content of nicotinamide incorporated in coated pellets because this value will reveal the amount of coated pellets that should be used for release studies in the part 2.2.15. The simple method for determining the content is to use UV-spectrophotometer {68}. Nicotinamide can absorb UV light at different wavelengths as mentioned in the part 2.1.9. This property will therefore allow the determination of content whether in 0.1 N HCl, buffer pH 6.8 <126>, 1.5 NaCl or a mixture of MeOH and water (50 + 50 ml). This work showed the values of the specific

absorption of nicotinamide in different media as follows; $A(1\%, 1\text{ cm}) = 420$ at 261 nm in 0.1 N HCl, $A(1\%, 1\text{ cm}) = 255$ at 262 nm in buffer pH 6.8, $A(1\%, 1\text{ cm}) = 254$ at 262 nm in 1.5 NaCl, and $A(1\%, 1\text{ cm}) = 263$ at 262 nm in a mixture of MeOH and water.

2.2.10.1 Calibration and validation

Calibration

First of all the wavelength at which the maximum absorption occurred should be found. The solution of nicotinamide in two media e.g. 0.1 N HCl or buffer pH 6.8 should be prepared. The absorption curve versus wavelength of this solution was determined by the spectrophotometer using a 1 cm quartz-cuvette scanned from 240 nm to 290 nm. The example of the UV-spectrum was shown in Figure 2.13, which shows the maximum absorption of nicotinamide in buffer pH 6.8 at the wavelength of 262 nm, whereas the maximum absorption in 0.1 N HCl occurred at 261 nm (data not shown). In Figure 2.13 the absorbance at 262 nm is 0.4776 and the concentration of the known concentration of nicotinamide is 1.8702 mg/100 ml. The ratio between absorption at 245 nm and 262 nm was 0.663. This was in agreement with the reference. One of these two wavelengths i.e., 261 and 262 nm was used for detection of nicotinamide later on in the medium of 0.1 N HCl or buffer pH 6.8, respectively.

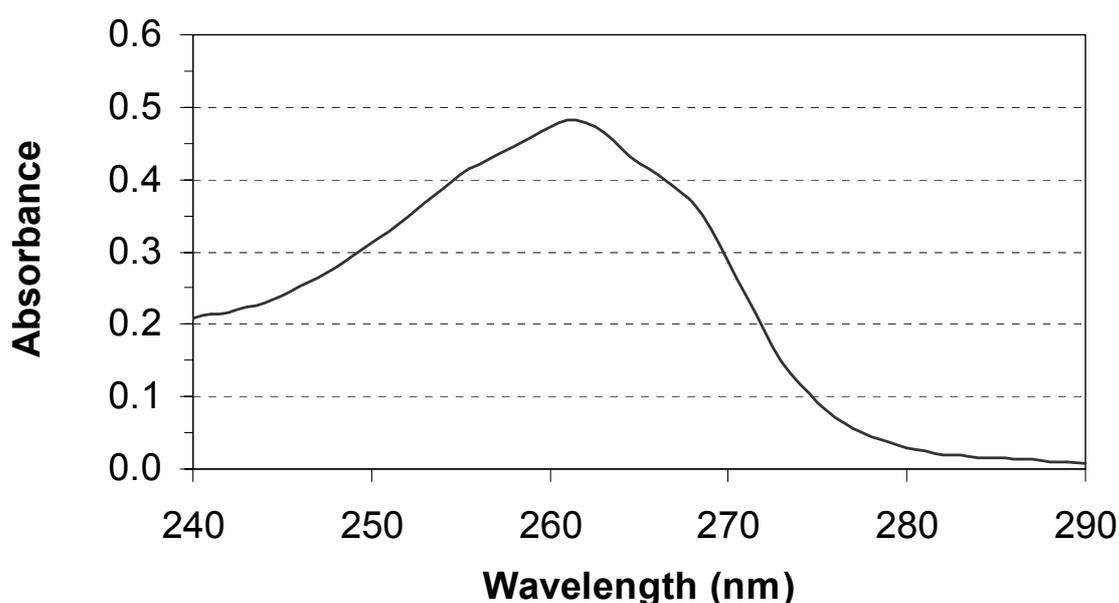


Figure 2.13: UV-spectrum of nicotinamide (1.8702 mg/100 ml) in buffer pH 6.8.

To create the calibration curve for each medium (0.1 N HCl or buffer pH 6.8), two stock solutions were prepared by accurately weighing {3} nicotinamide of about 0.01 g in a 250 ml-volumetric flask {Volumetric flask 250 ml, tolerance ± 0.15 ml, Brand, Wertheim}. 0.1 N HCl or buffer was then added to have an acquired volume of 250 ml. Each stock solution was diluted in 7 concentrations by pipetting 2.00, 3.00, 3.50, 4.00, 4.50, 5.00, and 6.00 ml, respectively {Volumetric pipettes 2, 3, 4, 5, 6 ml with tolerance ± 0.01 ml, measuring pipettes 5 ml tolerance ± 0.02 ml, Brand, Wertheim} and filling to 10.00 ml with 0.1 N HCl or buffer. The absorbance at 261 nm for 0.1 N HCl or at 262 nm for buffer pH 6.8 of these solutions were measured in triplicate. Therefore from each stock solution there are 24 values of absorbances. At the end there are 48 values for use to calculate the regression line by using the statistic program Toccata {S4}. The result of 48 values showed the linearity and the homogeneity at the confidential level of 95 %. The two equations, i.e. Eq-7 or Eq-8 were used for calculating the concentration of the unknown solution of nicotinamide in 0.1 N HCl or buffer. The residual plots of nicotinamide in 0.1 N HCl or buffer were in Figure 2.14 or Figure 2.15, respectively.

$$Y = 0.4197 X \quad \dots\dots\dots \quad (\text{Eq-7})$$

Y was absorbance at 261 nm

X was concentration of nicotinamide in 0.1 HCl (mg/100 ml)

The standard deviation of the slope was $\pm 5.7 \cdot 10^{-5}$. The limits of detection and determination were 2.9638×10^{-3} and 5.9276×10^{-3} mg/100 ml, respectively.

$$Y = 0.2554 X \quad \dots\dots\dots \quad (\text{Eq-8})$$

Y was absorbance at 262 nm

X was concentration of nicotinamide in buffer pH 6.8 (mg/100 ml)

The standard deviation of the slope was $\pm 1.7 \cdot 10^{-5}$. The limits of detection and determination were 1.8404×10^{-3} and 3.6808×10^{-3} mg/100 ml, respectively.

Validation

The validation was carried out by using the known solution at the concentration of 2.0 mg/100 ml. This is notified as a theoretical concentration. This solution was pump using peristaltic pump at the pump rate of 5 g/min through the tubing set into the 1 cm quartz

flow-through cuvettes. The absorption at 261 nm was noted and the real concentration of the solution was calculated by using the calibration curve. The result showed that the real concentration was not significantly different from the theoretical concentration.

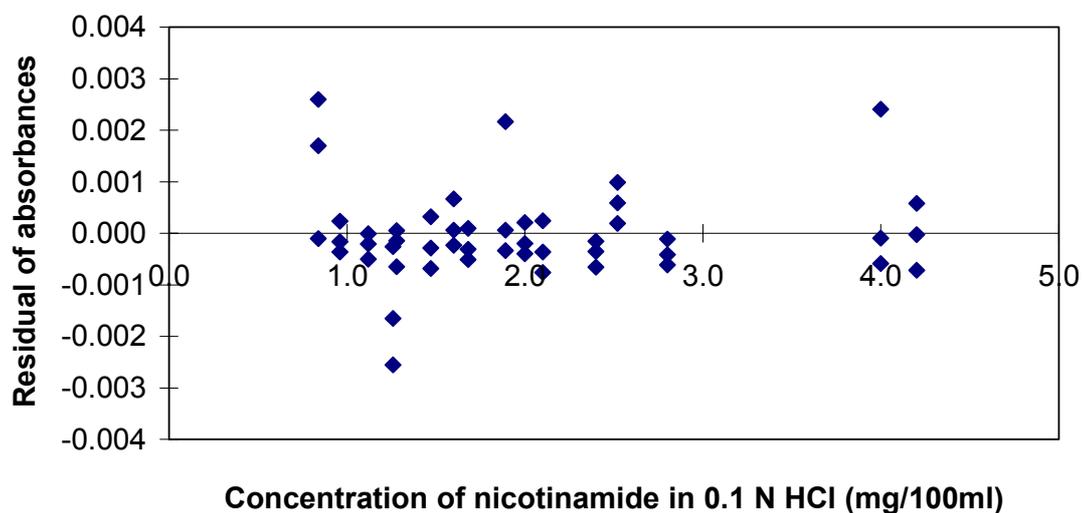


Figure 2.14: Residual plot of 48 values of the calibration curve of nicotinamide in 0.1 N HCl, using the UV-method.

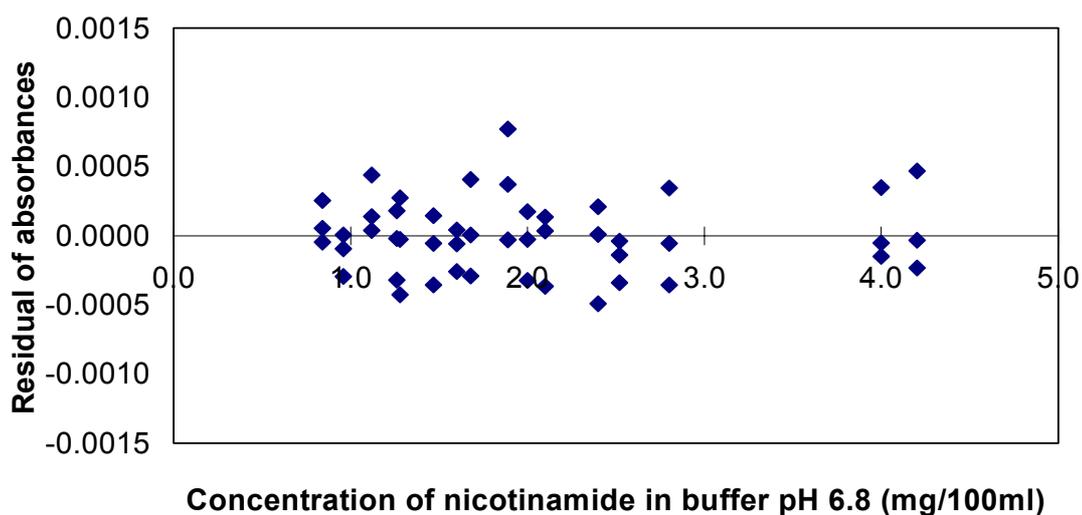


Figure 2.15: Residual plot of 48 values of the calibration curve of nicotinamide in buffer pH 6.8, using the UV-method.

2.2.10.2 Measurement of content of nicotinamide in one pellet

The amount of nicotinamide in one pellet was determined by using the equation from 2.2.8.1, at a maximum absorption of nicotinamide at 262 nm in buffer pH 6.8. About 0.01 g or 15 pellets of loaded pellets or equivalent to about 1 mg of nicotinamide were used. The pellets were accurately weighed {2} and dissolved in a 100 ml-volumetric flask. The volume was adjusted to 100 ml by adding buffer pH 6.8. Flasks containing nicotinamide loaded pellets were put into an ultrasound bath for 30 min to dissolve nicotinamide from the pellets. The dispersion was filtered through 0.45 µm pore size filter {Rotilabo Spritzenfilter, Art No. P8161, PTFE 0.45 µm, Carl Roth, Karlsruhe} to have a clear solution before measuring the absorbance under UV-spectrophotometer {68} at 262 nm. This test was done in triplicate for each batch. The mean value of the three values will be shown together with the standard deviation of the content in absolute weight (mg) and % w/w which was calculated on the basis of the mean weight of one nicotinamide loaded pellet with or without subcoats.

2.2.11 Determination of salt formation by FTIR and NMR

First of all four products should be prepared for the test using FTIR or NMR. The first product was a coprecipitate of 5.0 g of solid Aquacoat CPD or about 17.0 g of the dispersion, 1.25 g of TEC and 5.0 g of methyl orange powder in 1 N HCl {Hydrochloric acid 1 N, Ref. No. 00287/87, Carl Roth, Karsruhe}, which was prepared by dispersing all materials together. The solvent was removed in a glass petridish under ambient temperature in order to avoid chemical degradation of the substances. The second product was a film from 5.0 g of solid Aquacoat CPD or about 17.0 g of the dispersion and 1.25 g of TEC. They were prepared by removing water from the dispersion of Aquacoat CPD and TEC in a glass petridish at ambient temperature. The third product was methyl orange in a recrystallized form. It can be recrystallized from HCl and was used as a reference substance for methyl orange in its protonated form of a pink colour. The fourth product was methyl orange in the sodium salt form as a powder which was used as received from the company. This product has a yellow colour.

2.2.11.1 FTIR-technique

For recording FTIR spectra about 1 mg of each product was mixed together with potassium bromide {Potassium bromide for spectroscopy, Uvusul, Lot No. 015B222007, E.Merck, Darmstadt} and then compressed to a tablet of 8 mm diameter on a hand-operated press {32} at 8 tons for 2 min. The film resulted from CAP and TEC was dissolved in dichloromethane {LiChrosolv, Lot No. K 18537344, E-Merck, Darmstadt} and the solution was spread on a sodium chloride disc {Sodium chloride disc for IR spectroscopy, size 22 x 38.5 x 4, Korth Kristalle GmbH, Altenholz-Kiel}. This tablet or disk was then placed in a FTIR chamber {24} and was scanned from 400 to 4000 cm^{-1} . FTIR spectra {S5} were recorded and compared to find out a shifting of bands or new ones.

2.2.11.2 NMR-technique

Both ^1H and ^{13}C were measured by using NMR-spectroscopy {47}. TMS {Tetramethylsilane 99.9 %, NMR grade, Lot No. 26907029, Sigma-Aldrich Chemie, Steinheim} was taken as an internal standard, whereas DMSO {Dimethyl sulfoxide- d_6 99.8 %, Lot No. B 4950, Deutero, Kastellaum} as a solvent. The four above mentioned products were measured and the resulted NMR spectra {S6} were compared to find out the difference or shift of bands.

2.2.12 Postdrying (curing) studies of enteric coated pellets

As it was mentioned <380,151> that postdrying of coated pellets may improve the film properties. These trials were therefore carried out. Enteric coated pellets using CAP and DEP or CAP and DBS were put in glass vials or porcelain bowl without cover and then placed into a hot air oven {26} controlling the temperature (condition 1 and 2) or put into the control temperature and humidity by using hygrostatic glass container containing saturated salt and put in hot air ovens {25,26} at different temperatures (conditions 3 - 6). NaCl {Sodium chloride, Lot No. K 10352600, E.Merck, Darmstadt} used for creating the desired humidity was analytical grade.

Number of condition	Salt	Temperature(°C)	Humidity (% r.h.)
1	without salt	70	-
2	without salt	80	-
3	NaCl	40	75
4	NaCl	50	75
5	NaCl	60	75
6	NaCl	70	75

Table 2.5: *Postdrying conditions using a hot air oven and/or saturated salt <114>.*

2.2.13 Optical characterization of pellets after storage

HPMC coated pellets without nicotinamide (Product P, part 2.4.2), which were used as comparison products, and enteric coated pellets were determined. Only enteric coated pellets using CAP and DEP with different subcoats, i.e. HPMC (Product EE, Table 2.26) and a combination of PVA and EC (Product cc, Table 2.29), were put in glass vials {Glass vials 5 ml, Lot No. B101095, Soffieria Bertolini, Torino, Italy} without cover and then placed into the hygrostatic glass container containing different saturated salts. The temperature of these containers were controlled by using hot air ovens {25} or a cabinet {10} at different temperatures. The combination of salt and temperature gave the required humidity, which was well demonstrated in Table 2.6. The products were optically investigated in order to observe the change in colour, shiny, stickiness, etc. over a period of time over 30 days. All substances used to create different humidities such as NaBr {Sodium bromide, Lot No. 90310, Riedel-de Haen, Seelze}, KI {Potassium iodide, Lot No. B 438440, E.Merck, Darmstadt}, NaNO₃ {Sodium nitrate, Lot No. A 254937, E.Merck, Darmstadt}, NaCl {Sodium chloride, Lot No. K 10352600, E.Merck, Darmstadt}, KBr {Potassium bromide, Art No. 4907, E.Merck, Darmstadt}, and MgBr₂.6H₂O {Magnesium bromide-6-hydrate pure, Lot. No. 42650, Riedel-de-Haen, Seelze} were analytical grade.

Number of condition	Temperature (°C)	Humidity (% r.h.)	Salt
1	25 {10}	57.5	NaBr
2		68.9	KI
3		74.2	NaNO ₃
4		75.3	NaCl
5		80.9	KBr
6	30 {25}	30.4	MgBr ₂ .6H ₂ O
7		56.0	NaBr
8		67.8	KI
9		73.1	NaNO ₃
10		75.1	NaCl
11		80.3	KBr
12	35 {25}	30.2	MgBr ₂ .6H ₂ O
13		54.0	NaBr
14		67.0	KI
15		79.8	KBr
16	40 {25}	30.0	MgBr ₂ .6H ₂ O
17		53.1	NaBr
18		66.1	KI
19		79.5	KBr
20	45 {25}	29.8	MgBr ₂ .6H ₂ O
21		52.0	NaBr
22		70.0	NaNO ₃
23		74.7	NaCl
24		79.2	KBr
25	50 {25}	29.7	MgBr ₂ .6H ₂ O
26		50.9	NaBr
27		79.0	KBr

Table 2.6: Storage conditions of coated pellets after Nyqvist <114> for optical characterization.

2.2.14 Determination of water content by Karl-Fischer-Titration

Water content was determined by using Karl-Fischer Titration apparatus {39}. The method was modified from Werner <199>. The dispersing medium for pellets was the combination of 20 ml Hydranal Solvent {Hydranal-Solvent, Art No. 34800, Lot No. 70270, Riedel-de-Haen, Seelze} and 10 ml formamide {Formamide p.a. grade, Art No. 96841000, Lot No. 250K18921184, E-Merck, Darmstadt}. The Hydranal Titrant-5 {Hydranal Titrant 5, Art No. 34801, Lot No. 72180, Riedel-de-Haen, Seelze} was used as titrant. The dry titration of the system was first done and then the titration with samples. These samples were prepared as follows; a standard substance or pellets were put into the glass container containing the dispersing medium while constantly stirring. The dispersion time for each sample was 5 min and the titration was done from 100 mV to 0 mV which was an endpoint. The titration rate in the first period was at the high rate (about 2 ml/min) and near to the endpoint the rate was reduced to about 0.5 ml/min.

2.2.14.1 Calibration and validation

Calibration

The calibration of the method was done by using non-hygroscopic standard substance for volumetric Karl-Fischer Titration. The standard substance is Hydranal Eichstandard 5, Art No. 34813, Lot No. 90330, Riedel-de-Haen, Seelze. This substance 1 ml consists of 5.02 mg of water or 1 g consists of 5.91 mg of water. Normally the drift was not more than 0.007 ml/min and the titer of the Titrant-5 was 4.9305 mg of water/1 ml. The result from the determination by using this substance and the above described method showed homogeneity and linearity after Toccata {S4}. The equation used for calculating the content of water in coated pellets was therefore as follows;

$$Y = 1.2118 X \quad \dots\dots\dots \quad (\text{Eq-10})$$

Y was volume of Titrant-5 used (ml)

X was the weight of the standard substance (g)

The standard deviation of the slope was ± 0.0073 (ml). The limit of detection was 0.02745 g of standard substance or equivalent to water of 0.1622 mg. The limit of

determination was 0.05490 g of standard substance or equivalent to water of 0.3244 mg. The residual plot showed also the well performed method for determining the content of water in the samples because the residuals were not more than ± 0.04 ml.

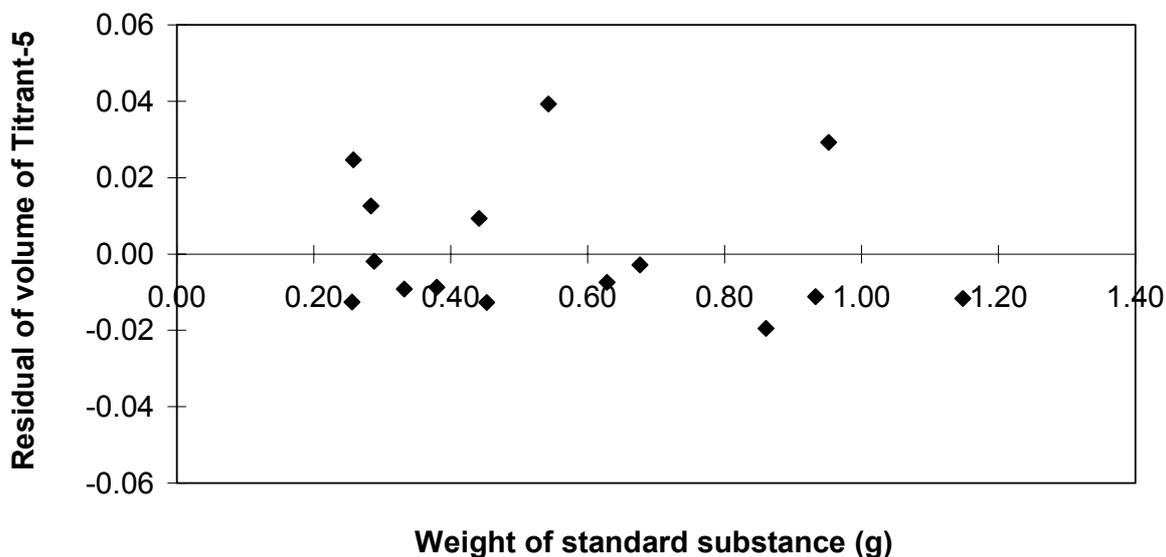


Figure 2.16: Residual plot of 15 values of the calibration curve of the standard substance, using Karl-Fischer titration.

Validation

The validation was performed by using standard substances {Hydranal Eichstandard 5, Art No. 34813, Lot No. 90330, Riedel-de-Haen, Seelze}. The result showed that there was no significant difference between the theoretical value of water content and the experimental one. Consequently, this is the suitable method for determining water in the product.

2.2.14.2 Measurement of water content in pellets

Samples of 10 - 15 mg of pellets were analyzed by dispersing them in the mixture of the above mentioned solvent for 5 min and then the titration by using Titrant-5 was performed.

2.2.15 Determination of free phthalic acid by HPLC

The simple spectroscopic method such as UV-spectroscopy {68} was first used to see whether it was possible to separate the two reference substances i.e. phthalic acid and nicotinamide or not. First of all the UV-spectra of phthalic acid in different media such as 0.1 N HCl, MeOH {Methanol, LiChrosolv, Lot No. K 25904418849, Merck KGaA, Darmstadt}, THF {Tetrahydrofuran, LiChrosolv, Lot No. I 912101949, Merck KGaA, Darmstadt}, water, NaOH {Sodium hydroxide granules, p.a. grade, EWG No. 2151855, Lot No. B828069618, Merck KGaA, Darmstadt} and a mixture of MeOH and water were done by using the standard substance {Phthalic acid, Lot No. 42130, Riedel-de-Haen, Seelze}. The values of specific absorption of phthalic acid in different media are $A(1\%, 1\text{ cm}) = 77$ at 275 nm in 0.1 N HCl, $A(1\%, 1\text{ cm}) = 75$ at 275 nm in MeOH, $A(1\%, 1\text{ cm}) = 85$ at 275 nm in THF, $A(1\%, 1\text{ cm}) = 85$ at 280 nm in water and $A(1\%, 1\text{ cm}) = 52$ at 272 nm in NaOH. The example of UV-spectrum of phthalic acid solution was shown in Figure 2.17. The spectrum showed the maximum absorption at 283 nm with a specific absorption $A(1\%, 1\text{ cm}) = 87$. The concentration of phthalic acid in a mixture of MeOH and water (50 + 50 ml) was 5.96 mg/100ml.

The next step was to determine the mixture of phthalic acid and nicotinamide by using UV-spectrophotometer. Therefore the solution of the standard mixture in a mixture of MeOH and water (50 + 50 ml) was prepared. The concentration of phthalic acid was 4.864 mg/100ml and nicotinamide was 0.752 mg/100ml. The UV-spectrum of this mixture was shown in Figure 2.18. It was found that the maximum absorption peaks of phthalic acid (~ 283 nm) and nicotinamide (~ 262 nm) were not well separated and therefore it was not possible to use UV-technique to determine the content of free phthalic acid in the combination with nicotinamide.

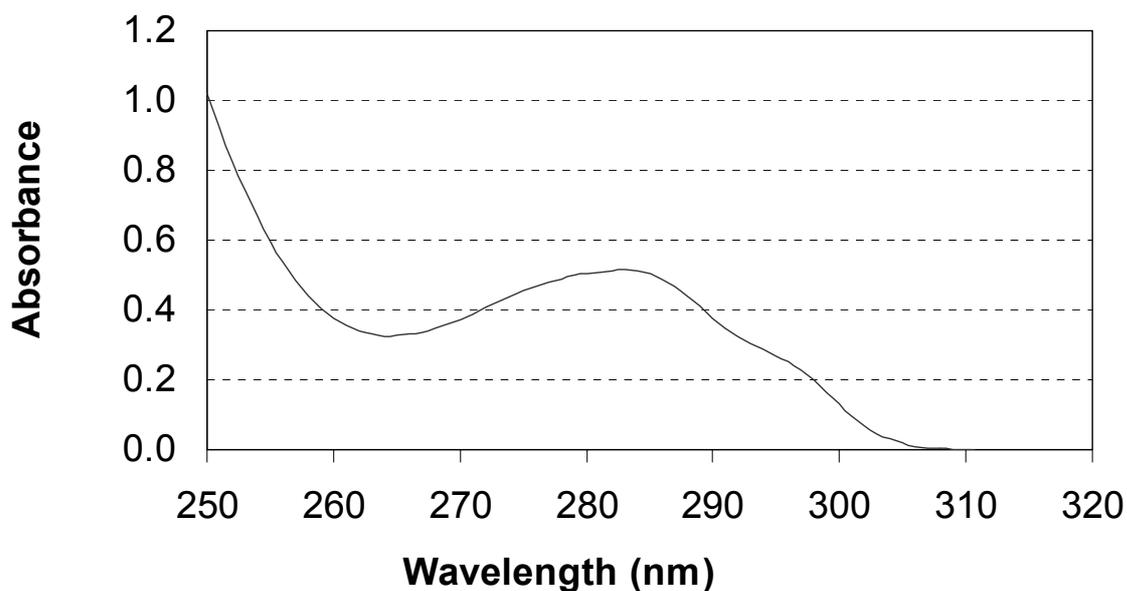


Figure 2.17: UV-spectrum of phthalic acid (5.96 mg/100 ml) in a mixture of MeOH and water (50+50 ml).

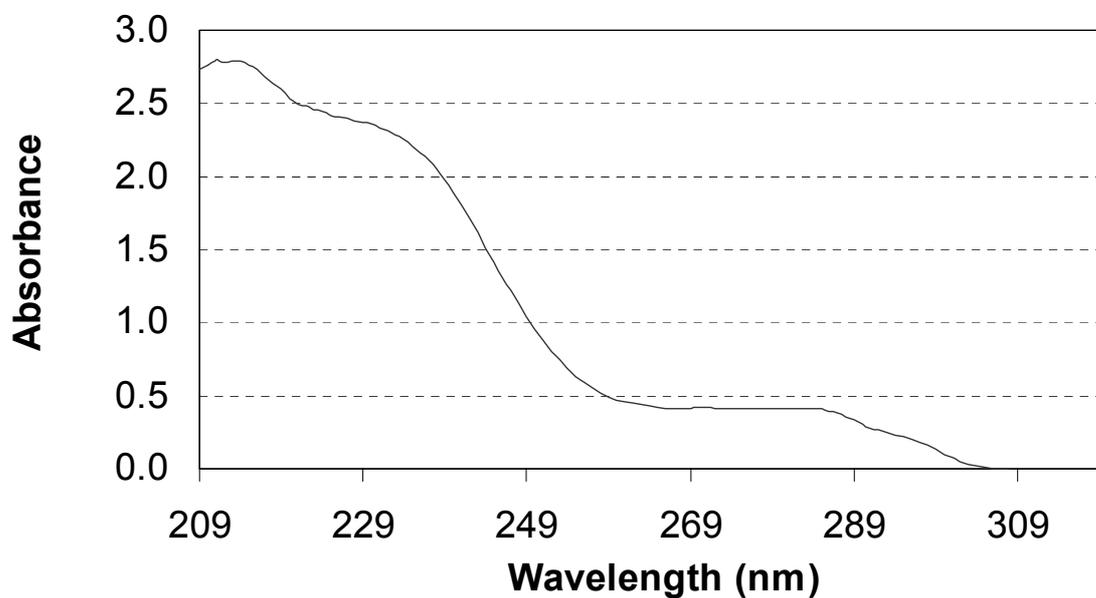


Figure 2.18: UV-spectrum of a standard mixture of phthalic acid (4.864 mg/100 ml) and nicotinamide (0.752 mg/100 ml) in a mixture of MeOH and water (50+50 ml).

Some authors <155,20> have reported about the determination of free phthalic acid by using HPLC-method. Therefore in this work the modified method based on the former reports was used. The 0.025 M phosphate buffer <125> in mixture with MeOH in different ratio was used as eluent. Different flow rates were applied as trials in order to reduce the retention time of the substances. However, the conditions should not be performed with a high pressure to maintain the life of the column and other parts of the system. Three samples, i.e. phthalic acid (1.12 mg/100ml), nicotinamide (1.06 mg/100ml) and their mixture were prepared. If necessary the pH {53} was adjusted below 3 using ortho-phosphoric acid {Ortho-phosphoric acid 85 0%, p.a. grade, Lot No. 83560, Riedel-de-Haen, Seelze}. Each solution was filled in HPLC vials with caps {Vials N11-1, Art No. 70214, Amber glass 1 ml, Macherey-Nagel, Düren} then measured by different conditions demonstrated in Table 2.7. The best suitable condition was then selected basing on the presented low pressure and the well separated peaks of nicotinamide and phthalic acid with an acceptable retention time. The example of the HPLC-chromatogram was shown in Figure 2.19. At the region of 3.0 min (O) were peaks of the injection, at 4.4 min (I) was a peak of nicotinamide and at 10.8 min (II) was a peak of phthalic acid.

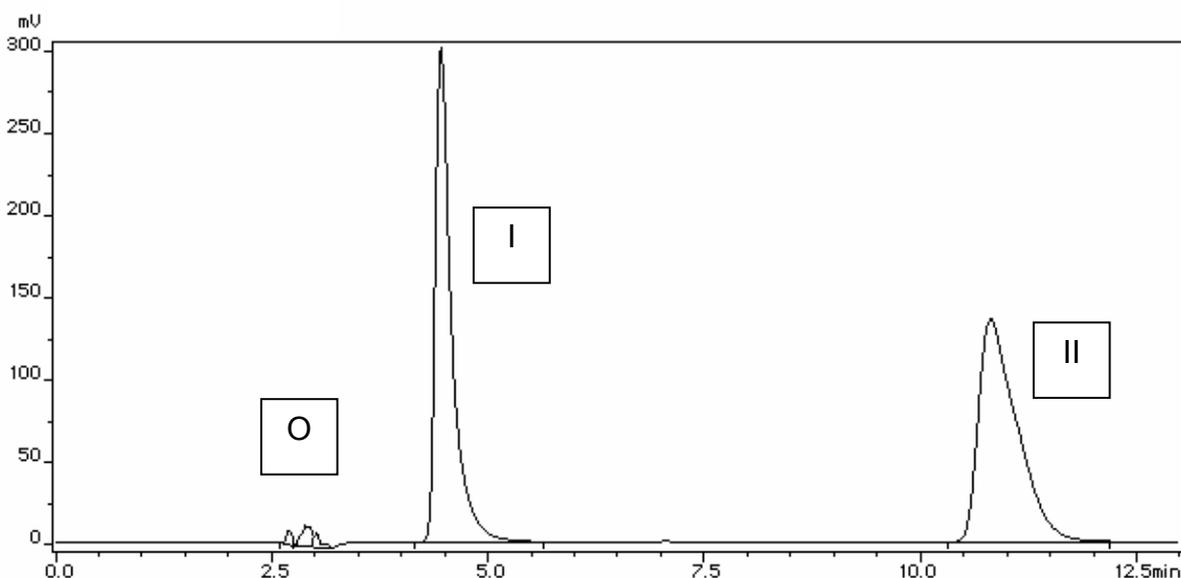


Figure 2.19: HPLC chromatogram of a standard mixture containing nicotinamide 2.15 mg/100ml (I) and phthalic acid 1.92 mg/100ml (II) at a flow rate of 0.8 ml/min and a mixture of 0.025 M phosphate buffer and MeOH (80+20 ml) as an eluent.

Substance	Mobile phase (ml+ml) buffer * + MeOH	Flow rate (ml/min)	Pressure (bar)	Retention time (min)	
				nicotinamide	phthalic acid
nicotinamide	80 + 20	1.2	270	2.9	-
		1.0	230	3.5	-
		0.8	187	4.4	-
phthalic acid	80 + 20	1.2	270	-	7.1
		1.0	230	-	8.6
		0.8	187	-	10.8
std mixture	80 + 20	1.2	270	2.9	7.1
		1.0	230	3.5	8.6
		0.8	187	4.4	10.8
nicotinamide	70 + 30	0.8	-	3.6	-
phthalic acid		0.8	-	-	7.2
std mixture		0.8	-	3.6	7.2
nicotinamide	50 + 50	0.8	-	3.2	-
phthalic acid		0.8	-	-	4.1
std mixture		0.8	-	3.2	4.1

*Table 2.7: Conditions of HPLC in the preliminary trials; nicotinamide (1.06 mg/100 ml), phthalic acid (1.12 mg/100ml), std mixture contained nicotinamide (2.15 mg/100 ml) and phthalic acid (1.92 mg/100ml), buffer * = 0.025 M phosphate buffer <125>, and - means not measured*

The following conditions will therefore be used for characterization of free phthalic acid in coated pellets containing nicotinamide.

HPLC conditions:

Column {28}: Nucleosil 5 μ C18, 100 °A

Dimensions: 250 x 4.6 mm

Mobile Phase: 0.025 M Phosphate Buffer-Methanol (80 + 20 ml, pH 3)

Flow rate {31}: 0.8 ml/min

Detection {30}: UV @ 210 nm

Temperature: ambient

Injection {27}: 20 μ L

2.2.15.1 Calibration and validation

Calibration

The conditions as mentioned above were applied to create a calibration curve of phthalic acid in water. The mobile phase containing 0.025 M phosphate buffer and methanol was first filtered through the filter set containing a cellulose nitrate filter paper {Lot No. 0899113079901503, 0.2 μm , Sartorius, Göttingen} and then the solution was degassed by putting the volumetric flask into the ultrasound bath {67} for 15 min. This solution of mobile phase was pumped {31} through the degas unit {29} into the HPLC-column {28}.

The solution of the standard substance {Phthalic acid, $\text{C}_8\text{H}_6\text{O}_4$, Lot No. 42130, Riedel-de-Haen, Seelze} was prepared by dissolving free phthalic acid in CO_2 -free water and the pH was adjusted below 3 using ortho-phosphoric acid {Ortho-phosphoric acid 85 %, p.a. grade, Lot No. 83560, Riedel-de-Haen, Seelze}. The solutions of 8 different concentrations of 0.34, 0.51, 0.68, 1.02, 1.53, 5.00, 10.00, 17.00 mg/100 ml were prepared in triplicate and each concentration was measured three times. At the end there were 72 values for calculation of the regression line. After the test of linearity and homogeneity at the confidential level of 95 % using the statistical program Toccata {S4}, the regression line using the area under the curve of HPLC-chromatogram showed a slope of 1114782 with a standard deviation of ± 2153 . The limits of detection and determination were 0.02309 mg/100ml and 0.14064 mg/100ml, respectively. On the other hand the regression line using the height of the curve of HPLC-chromatogram showed a slope of 69.77 with a standard deviation of ± 0.144 . The limits of detection and determination were 0.02899 mg/100ml and 0.15723 mg/100ml, respectively. The example of the residual plot using the area of 72 values was shown in Figure 2.20.

Validation

The validation was performed by measuring the known standard solution of phthalic acid (2.0 mg/100ml) and nicotinamide (2.0 mg/100ml) in CO_2 -free water for three days. Each solution was freshly prepared at every day of the measurement in triplicate and every solution was measured three times. The measured values of the area under the curve or the height were calculated to receive the concentration. The data calculated by using regression line based on the area under the curve gave the values of recovery of 99.0 ± 0.1 %, whereas the values using the regression line based on the height of the

peak gave the values of recovery of $98.0 \pm 0.5 \%$. This means this method is suitable for detecting of free phthalic acid in a mixture with nicotinamide.

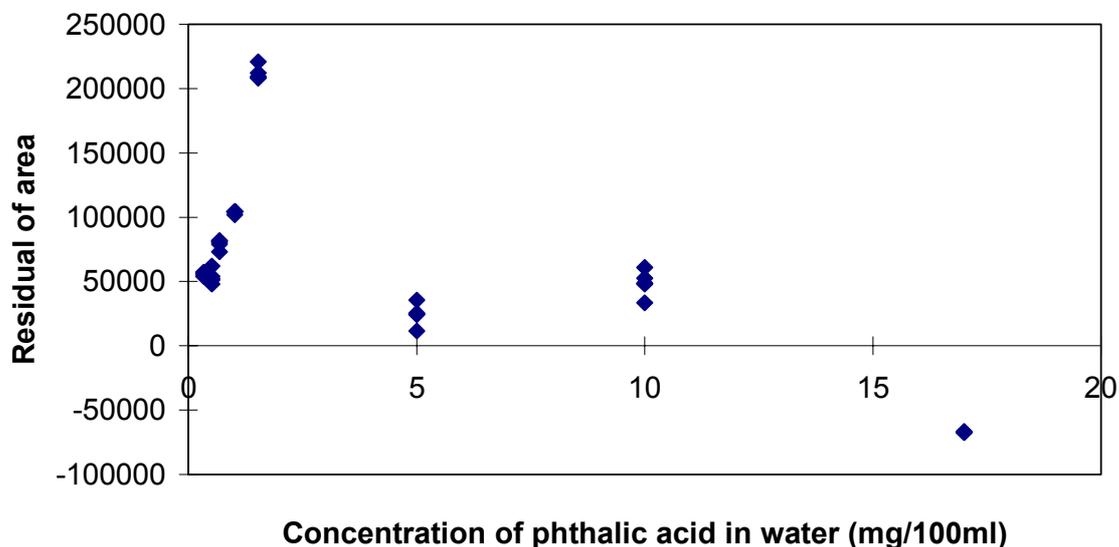


Figure 2.20: Residual plot of 72 values of the calibration curve of the solution of phthalic acid in water, using HPLC-method.

2.2.15.2 Measurement of free phthalic acid in coated pellets

The exact amount of about 2.50 g of enteric coated pellets (Product Ff, Table 2.27) was weighed {2} and then they were put in a 100 ml-volumetric flask, 10 ml of tetrahydrofuran {Tetrahydrofuran, LiChrosolv, Lot No. I 912101949, Merck KGaA, Darmstadt} was added, followed by about 70 ml of distilled water. The samples were vibrated in the ultrasound bath for 30 min. The pH of the dispersion was adjusted to lower than 3 by adding ortho-phosphoric acid {Ortho-phosphoric acid 85%, p.a. grade, Lot No. 83560, Riedel-de-Haen, Seelze} and then the total volume of 100 ml was adjusted by distilled water. After well mixing the dispersion was filtered through 0.45 μm PTFE-filter {Rotilabo Spritzenfilter, Art No. P8161, 0.45 μm , Carl Roth, Karlsruhe} before analysis by HPLC at the condition as mentioned before. Five samples were prepared after the above mentioned method. Every sample was measured three times and therefore at the end there were 9 values for one product. The mean value of free

phthalic acid in the samples was calculated using both the regression lines based on the area and the height of the HPLC-chromatograms.

2.2.16 Release studies

The resistance against artificial gastric fluid can be tested by the release studies. If enteric coated products were totally resistant to the artificial gastric fluid there will not be any amount of the model indicator or drug in the release test medium (0.1 N HCl). The concentration of the model indicator or drug can be calculated by using UV-spectroscopy and the regression line of model indicator or drug from the part 2.2.8.1 or 2.2.10.1, respectively. However the release profile was mostly demonstrated in the percentage of release of the model indicator or drug. That means the cumulative percentage of drug at a certain time was compared to the total incorporated amount in the coated product that was used in each test.

Moreover, the release of some products containing nicotinamide which were coated with ethyl cellulose or with a combination of ethyl cellulose and polyvinyl alcohol in the buffer pH 6.8 <126> were tested because the subcoat should not have any sustained release effect both in 0.1 N HCl and buffer pH 6.8 <126>.

2.2.16.1 Calibration and validation

Calibration for methyl orange

The regression line was taken from part 2.2.8.1. That means the equation used for calculating the concentration of methyl orange in the coated pellets was as follows;

$$X = \frac{Y}{0.9727}$$

Y was absorbance at 508 nm

X was a concentration of methyl orange (mg/100 ml) in 0.1 N HCl

Calibration for nicotinamide

The regression line was taken from part 2.2.10.1. That means the equation used for calculating the concentration of nicotinamide in the coated pellets was as follows;

$$X = \frac{Y}{0.4197}$$

Y was absorbance at 261 nm

X was a concentration of nicotinamide (mg/100 ml) in 0.1 N HCl

The other equation for calculating the concentration of nicotinamide in buffer pH 6.8 <126> was as follows;

$$X = \frac{Y}{0.2554}$$

Y was absorbance at 262 nm

X was a concentration of nicotinamide (mg/100 ml) in buffer pH 6.8 <126>

Validation

The dissolution test was performed in a 6 - vessel dissolution test apparatus with the paddle method as described in the USP XXIII. The dissolution apparatus consisted of a UV-spectrophotometer {68} with a computer, a peristaltic pump {51}, a water bath {18} fitted with variable-speed stirring unit and a heater in order to have an automatic construction assembly. The six cylindrical curved-bottomed glass vessels were filled with 400 ml of acid medium (0.1N HCl) or buffer pH 6.8 <126> which were warmed to 37 °C ± 0.5 °C and temperature was kept constant during the dissolution test.

Solutions of the known concentration of methyl orange (0.5 mg/100 ml) or nicotinamide (2.0 mg/100 ml) was used. The results showed that this method gave the recovery of 98 ± 0.5 % for both the substances.

2.2.16.2 Release studies of coated pellets

Pellets containing methyl orange

CAP coated pellets equivalent to about 0.8 mg of methyl orange (MO) were accurately weighed {2} and then placed into one glass vessel containing 400 ml of 0.1 N HCl. The rotational speed of paddle was adjusted to 100 rpm. The sampling was performed

automatically every 5 min by using a peristaltic pump with six flow-through cuvettes {12}. Ultraviolet detection was at λ maximum of methyl orange i.e. 508 nm at a time period of every five minutes. The percentage of MO dissolved in an artificial gastric fluid (0.1 N HCl) medium was observed until the steady level was obtained or for 2 h. All the experiments were performed in duplicate. The results will be shown in form of dissolution profiles and percentages of MO released during the first five minutes. These values were compared between different products.

Pellets containing nicotinamide

CAP coated pellets equivalent to about 8 mg of nicotinamide were accurately weighed {2} and then placed into one glass vessel containing 400 ml of 0.1 N HCl or buffer pH 6.8 <126>. The rotational speed of paddle the sampling method and the detection time period were the same as mentioned above. Only the ultraviolet detection was at λ maximum of nicotinamide i.e. 261 nm in 0.1 N HCl and 262 nm in buffer pH 6.8. All the experiments were performed in duplicate and the results will be shown in form of dissolution profiles and percentages of nicotinamide released during the first five minutes as well.

2.2.17 Optical appearance after the release study

This test was done in the dissolution test apparatus (as described in 2.2.16) in order to demonstrate the same conditions as in the release study. About 200 pellets were put into each glass vessel containing 400 ml of 0.1 N HCl or buffer pH 6.8 <126>. About 10 pellets were taken at an interval of 15 minutes over 2 h and were observed under an image analyser coupled to a light microscope {41}, as mentioned in the part 2.2.6. Pictures of these pellets have been taken and the time that pellets stayed in the medium and they began to break was recorded.

2.3 Coating apparatus

The fluidized bed apparatus, Aeromatic MP-1 {20}, is a pilot scale machine which can be used for coating of fine particles, pellets, granules or tablets <120>. Two combinations of Aeromatic MP-1 served for this present work. The first combination is MP-1 with inserted filters. The second one is MP-1 connected with a cyclone. The details of these two combinations will be discussed.

2.3.1 Coating apparatus (MP-1) with inserted filters

Figure 2.21 shows its component which consists of a conical product container (no. 14) made from acrylic glass, perforated bottom with different percentage of free holes (no. 11), the Wurster column (no. 13) with a diameter of 6 cm and a height of 18 cm. The spraying unit (no. 15) was in a position in between the Wurster column. The partition part (no. 12) between the end of the Wurster column and the perforated plate can be varied. However, normally 0.8 cm was used in this work. Products inside the container will be fluidized from the process air from the bottom to the upper part and at the same time they will be coated with the fluid that was atomized by the air. In the region outside the Wurster column the product will flow downward and flow into the center through the partition part. The product will be blown upward again from this center with continuous coating cycles. During the upward flow of the product the drying phase was carried out by the heated process air. Because of the interchange of water content between the process air and products the process air carried more water content. Consequently, there was a temperature decrease of the process air. This process air flows through the filters and the outlet air tube by the sucking process from the ventilator (no. 19).

The important variables during a coating process were measured inside the coating apparatus. Different sensors were installed at different positions i.e. three positions for temperature (no. 1 to 3), one position for temperature and humidity using dew point (no. 4), two positions for air flow (no. 5 and 6) and one position for mass flow of coating liquid (no. 7). The signals from these 7 channels were collected at the data recording device {14} at the same time. These signals were both demonstrated on the display of the data recording device and automatically saved on a disc. This process facilitates to observe changes of process conditions which may happen during the coating process. This permits a fast manual regulation.

As mentioned before the product container is made from acrylic glass and therefore very suitable for the visual observation of the coating process. A free downward flow of the product at the sight of the acrylic glass product container is one of the indications of a good fluidization but such limited observation could be misleading. In addition it is possible to supervise this situation by monitoring the outlet air temperature. Every product has an unique constant drying period in which the bed temperature remains relatively constant for a significant length of time. Therefore, if the outlet air temperature rises more rapidly than expected, it is an indication that fluidization is incomplete <122>. In our work the temperature profiles of temperatures at four positions were demonstrated on the display of the data recording device. These four temperatures were measured using thermocouples {63}. These sensors should be calibrated before used, see part 2.3.3.1. Therefore values of inlet air temperature before heating, inlet air temperature after heating, product bed temperature and outlet air temperature can be observed and shown in degree celcius ($^{\circ}\text{C}$). These temperature profiles will allow better control of the coating process. The effective drying and coating phases can be monitored. Guidelines and exemplary values are given and discussed in the literature and therefore can be used as a guideline for the preliminary experiments. After suitable temperatures for a process were chosen the control of these temperatures could easily be done.

As heated air was used to dry the product during the coating process, the drying capacity of the air must be carefully monitored. The drying capacity of the air depends upon the relative humidity (r.h.) of the incoming air. At 100 % r.h. the air is holding the maximum amount of water but if the temperature of the air is raised the relative humidity drops and the air can hold more moisture. If air is saturated with water vapor at a given temperature, a drop in temperature will force the air mass to release some of its moisture through condensation. The temperature at which moisture condenses is the dew point temperature. Dew point and vapor pressure are directly related. Thus, the drying capacity of the air varies significantly during processing. By dehumidifying the air to a pre-set dew point, one can maintain constant drying capacity and, hence, a constant process time. If absolute humidity varies during the year, changes in the relative humidity of the heated, fluidizing air will result. For this reason the air humidity may actually be lower than desirable during cold and dry seasons and a rehumidification or a wetting process may be necessary <122>.

In this present work the relative humidity of the outlet air was measured using the Hygrolog-hygrometer {33}. This was also calibrated before use, see part 2.3.3.2. This relative humidity can be calculated by using the outlet air temperature and its dew point. This value showed the water content inside the coating column during coating process. It can be affected by the content of water in the inlet air as mentioned before and therefore the water content of the inlet air should be controlled by using a dehumidifying unit {15}. The inlet air of room temperature was cooled down to about 5 °C by a condensing process. This air then has a humidity of about 98 % r.h., which means that this cool air contains 5 g of water in one kg of air. This cool air will then be used as inlet air into the Aeromatic MP-1 before heating. After heating this air will have a lower relative humidity whereas the absolute water content of the air remains the same as before heating. For example, if the process air was heated to 65 °C then the relative humidity of this air will be 3.5 % r.h. However, it was problematic when the process was carried out in the winter season because the relative humidity of the inlet air for the dehumidifying unit was already low. The water from the air could not be further removed and after heating in the coating apparatus, the relative humidity was extremely low. If a high relative humidity is needed for the coating process this inlet air should be wetted before use. The wetting process, however, was not possible in our laboratory because no humidifier was available. Therefore the coating process had to be carried out in the season with high relative humidity so that the dehumidifying process could be performed. The profile of the relative humidity of the outlet air shows the range which must be controlled to maintain the same coating conditions.

The spraying rate can be observed by using a mass flow rate. That means the decreasing of mass or weight (g) over the time was recorded. A digital balance {17} connected with a digital/analog converter served for the observation. The analog (mA) values were collected in the data recording device and they were converted into digital values again. These digital values were the base for the calculation of the spraying rate over the time.

The air flow in the Wurster fluidized bed system is a combined air flow of the fluidization air and the atomizing air at the nozzle. Air and substrate velocities are not uniform across the upper part of the product bed. The velocities at the center are significantly higher than those along the walls. There is a risk that the substrate might fall down along the wall of the Wurster column, and that clusters of particles might be formed at certain process conditions in the upper part of the product bed. The terminal velocity of

particles in the upper part is limited by the height of the expansion chamber. Unfortunately, the terminal velocity of the particles cannot be calculated. The product concentration in the mist region of the upper part must be high enough to secure adherence of all spray droplets to substrate particles. The region where the product flows down outside the Wurster column is a slightly expanded bed where the air rate is below the minimum fluidization velocity. This is the region where sticking mostly occurs, since the movement is gentle and the particles are in close contact to each other <36>. As the velocity of the process air during the coating process is an important factor which affects the flow pattern of the product, the control of this velocity allows to regulate a desired process. In this present work the mass flow of the atomizing air and the volume stream of the process air were measured using flowmeters {21,22} and their values were shown in the form of volume of air over time (m^3h^{-1}). These two values were separately measured at the positions demonstrated in Figure 2.21.

Moreover, the flow pattern can be affected by the perforated air distributor plate. This plate is defined by its percentage of open area. In this present work there were five different openings available i.e. 6 %, 8 %, 11 %, 13 % and 20 % {52}. These interchangeable plates provide a range of loading capacities so that batches of various sizes can be produced efficiently and with a uniform quality. To prevent channeling a plate that provides the optimum lift properties should be selected. This plate was afterwards covered with a finer screen (e.g. screen size 100 μm) which provides appropriate means of supplying air to the bed.

To move air in a fluidized bed apparatus, an exhaust ventilator mounted outside of the processing area imparted the motion and the pressure to the air by action of a turbine-wheel. The moving air acquires a force or pressure component in its direction of motion because of its weight and inertia. Thus, a negative static pressure will exist on the inlet side of the ventilator. The pressure drops (ΔP) can be determined by all the components of the complete system. As filters can cause a significant pressure drop, many process failures result from the selection of filter media with a wrong pore size. The process failure can also occur when the filter clogs because of excessive fluidization of fine powder or when filters are improperly cleaned after finishing the process. A too fine filter will impede fluidization, causing excessive ΔP , and a too coarse filter will cause loss of valuable product carried by the process air <122>. In our coating apparatus the pressure difference between inside the product container and behind the filters was demonstrated in millimeter of water ($\text{mm H}_2\text{O}$) on the pressure gauge at the

control panel of the coating apparatus. The value of about 250 mm H₂O or 2450 Pa shows the critical point, that means filters were blocked with fine dust or particles and the coating process had to be stopped.

2.3.2 Coating apparatus (MP-1) in connection with a cyclone

A Wurster fluidized bed apparatus as mentioned before connected with a cyclone instead of inserting filters was used to coat the products as shown in Figure 2.21. All sensors were positioned and recorded on the data recording device as mentioned in part 2.3.1.

Before the coating process was carried out using this setup, the coating apparatus was tested under different process conditions, especially the flow pattern of different types of products and the loading weight at different air flow regulating positions (0 - 10). The absolute pressure and the pressure differences (ΔP) at 3 different positions, were measured. The first position was the pressure difference between air inside the product container and air inside the exhaust air tube after having passed the cyclone (ΔP_1). This value (mm H₂O) was shown on the pressure gauge, Magnehelic-Barometer {7}, at the control panel of the coating apparatus. The second point was the pressure difference between air in the product container and room air (ΔP_2). This value was shown on the display of a Baratron-Barometer {6} in Torr. The last position was the pressure difference between air above and below the perforated bottom plate. This value was shown also on the pressure gauge, Magnehelic-Barometer {7}, at the control panel in mm H₂O. However, before the values from these two gauges on the control panel were used in the experiment they were compared to the respective values measured by using the Baratron-Barometer. It was found that there was a deviation of only ± 2 mm H₂O between the value shown on the gauges on the control panel and that from the Baratron-Barometer. This evidence was judged as sufficient for the accuracy as of the Magnehelic-Barometer and the values were then directly taken from these two gauges.

The air flow rate was also measured by the sensor integrated inside the coating apparatus (No. 23 in Figure 2.21) and the value was shown in percentage on the control panel. This value of percentage did not show the physical values. Therefore another measurement using a flowmeter as mentioned before 2.3.1 was used. This measurement

results in values with the desired physical dimension of m^3h^{-1} on the display of the data recording device {14}.

In order to study the affect of the cyclone compared to the originally inserted filters, the preliminary test was performed. Air in the laboratory at room temperature was used as a reference {5}. The absolute pressure of it was 100508 Pa. Conditions of all trials (Table 2.8 to 2.10) were as follows: diameter of nozzle 1.2 mm, atomizing pressure 2.5 - 2.6 m^3h^{-1} , perforated plate 8 %, room temperature and relative humidity 23 - 25 °C, 50 - 52 % r.h.. First the test with a fluidized bed with inserted filters and varying air flows (about 70 to 150 m^3h^{-1}) with or without pellets was carried out. The pressure difference between air inside product container (MP-1) and room air ($\Delta P2$) was measured by a Baratron-Barometer, in Torr. These values were converted into Pascal by multiplying with 133.3. The pressure difference between air inside MP-1 and air inside exhaust air tube behind the filters or the cyclone was shown on the control panel in mm H_2O , the data were converted into Pascal by multiplying by 9.8.

The result as seen in Table 2.8 showed that without cyclone and loading product the air flow can be increased to the maximum of about 150 m^3h^{-1} . The resistance from filters ($\Delta P1$) increased when the air flow was increased by adjusting the regulator. However, the highest resistance from the filters was about 176 Pa. The same behavior can be found with the resistance from the perforated bottom plate ($\Delta P3$) by increasing the air flow. Absolute pressures were calculated at two different positions i.e. air inside the product container (Pii) and air inside the exhaust air tube (Piii) because the pressure of air in the laboratory room (Pi) was known. The data show that the absolute pressure of air inside MP-1 (Pii) and the absolute pressure of air in the exhaust air tube (Piii) were decreased by increasing air flow.

After loading the fluidized apparatus with 100 g of coated pellets (Table 2.9) and 250 g, respectively, the resistance from filters at the same air flow of about 90 m^3h^{-1} was not significantly different, i.e. $\Delta P1$ was about 80 Pa (data not shown). The comparison between different loading amounts at the same air flow of about 90 m^3h^{-1} for the combination of a fluidized bed apparatus with inserted filters or with a cyclone instead shown in Table 2.10. By using a cyclone, the air flow at the maximum position of the regulator was about 90 m^3h^{-1} . The resistance of the cyclone was about 2400 Pa ($\Delta P1$) and almost the same for all three loading amounts (0 g, 100 g and 250 g). This pressure difference was almost the same as that seen after performing a fluidized bed process with inserted filters which then were covered with fine dust which caused the highest

filter-resistance (2450 Pa) as mentioned before. However, under this condition of the highest process air flow the product flow cannot be increased further if required. Therefore further trials by spraying the polymer dispersion to the product to increase the weight were carried out. The product flow was monitored during the coating process to see whether it needed the regulation of the air flow or not. The result was that after spraying the pellets with the polymer dispersion there was an increase of weight but further increase of the air flow was not necessary. This means the further coating trial by using a fluidized bed apparatus in connection with a cyclone can be well carried out.

Details of the installation of accessories and equipments <120> for Figure 2.21.

1. Sensor for inlet air temperature before heating {66}
2. Sensor for inlet air temperature after heating {63}
3. Sensor for product bed temperature {63}
4. Sensor for outlet air temperature and humidity {33}
5. Sensor for volume stream of process air {22}
6. Sensor for mass flow of atomizing air {21}
7. Digital balance with digital output for mass flow of coating liquid coupled with a digital/analog converter {17}
8. Dehumidifying unit {15}
9. Filter for inlet air
10. Heater for inlet air
11. Perforated bottom plate {52}
12. Partition part between a Wurster column and perforated bottom plate
13. Wurster column
14. Product container
15. Spraying unit
16. Peristaltic pump {51}
17. Container for spraying solution or dispersion
- 18a. Filters
- 18b. Cyclone with a glass flask {13}
19. Ventilator
20. Sound absorber
21. Data recording device {14} for sensors no. 1 to 7
22. Printer {54}
23. Flowmeter integrated inside Aeromatic MP-1 {23}

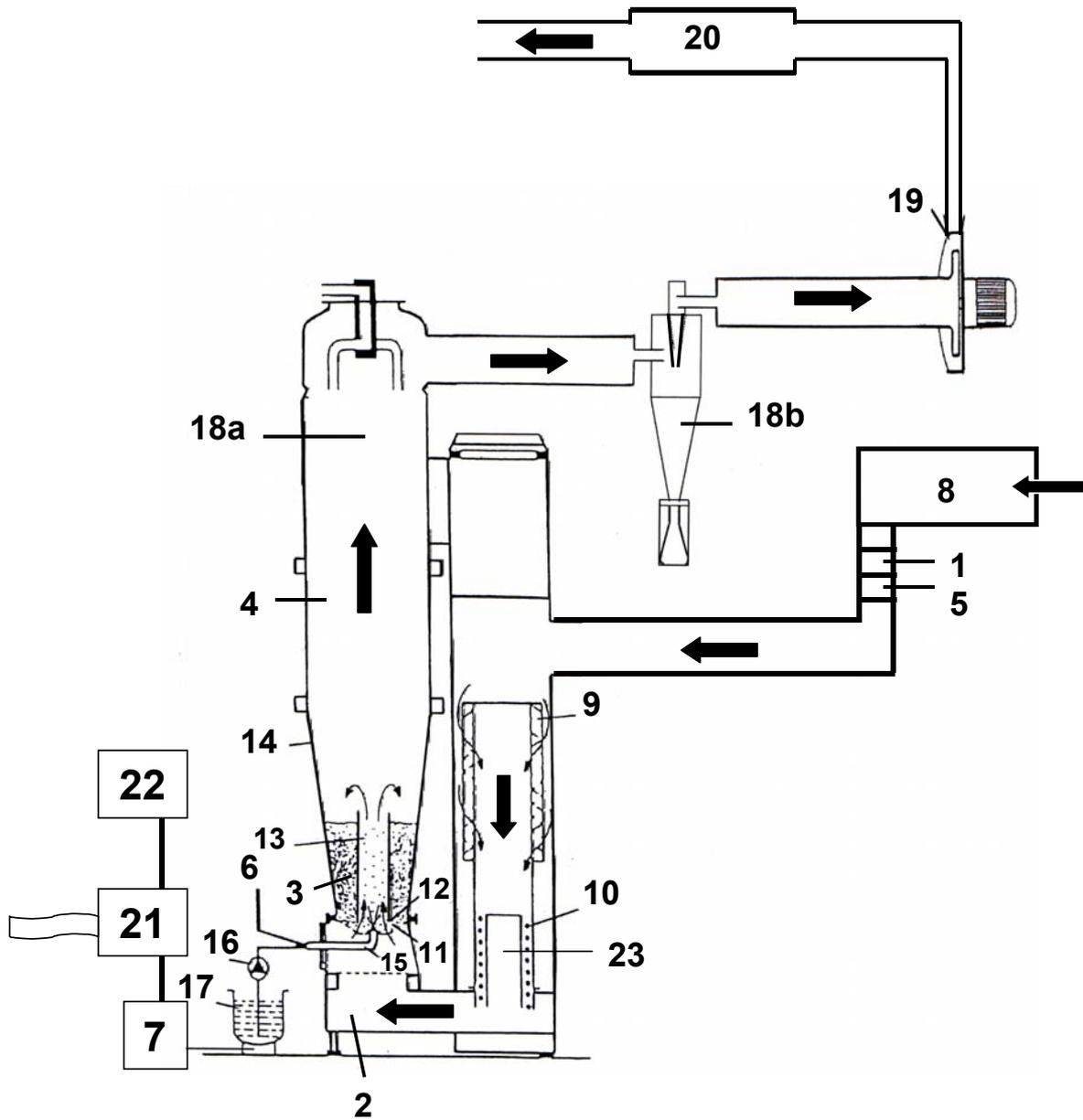


Figure 2.21: A Wurster-based fluidized-based apparatus (Aeromatic MP-1, Powder Coater) with a cyclone for the coating of pellets; Arrows show the direction of the air flow.

No. of regulator	Air flow (m ³ h ⁻¹)	$\Delta P1 \pm SD$	$\Delta P2 \pm SD$	$\Delta P3 \pm SD$	Pi	Pii	Piii
		(Pascal, Pa)					
5.0	77±2	0±6	560±13	480±13	100508	99948	99948
5.8	90±2	79±6	773±13	587±13	100508	99735	99656
6.4	98±2	99±6	1013±13	693±13	100508	99495	99396
7.2	112±2	108±6	1346±13	880±13	100508	99162	99054
8.0	127±2	147±6	1720±13	1093±13	100508	98788	98641
9.8	143±2	176±6	2173±13	1360±13	100508	98335	98159
10.0	147±2	176±6	2306±13	1386±13	100508	98202	98026

Table 2.8: Pressure differences or absolute pressure (Pa) of air in different positions of Aeromatic MP-1 with inserted filters, without pellets (n = 3); Pi = Pressure of room air, Pii = Pressure of air inside MP-1, Piii = Pressure of air in exhaust air tube after filters or cyclone, $\Delta P1 = Pii - Piii$ or pressure difference between air inside MP-1 and air inside exhaust air tube behind filters or cyclone, $\Delta P2 = Pi - Pii$ or pressure difference between air inside MP-1 and room air, $\Delta P3$ or pressure difference of air between below and above perforated plate, the highest regulator position is number 10.

No. of regulator	Air flow (m ³ h ⁻¹)	$\Delta P1 \pm SD$	$\Delta P2 \pm SD$	$\Delta P3 \pm SD$	Pi	Pii	Piii
		(Pascal, Pa)					
5.9	89±2	79±6	920±13	640±13	100508	99588	99509
6.9	99±2	79±6	1173±13	773±13	100508	99335	99256
7.3	110±2	88±6	1373±13	880±13	100508	99135	99047
7.9	120±2	99±6	1653±13	1053±13	100508	98855	98756

Table 2.9: Pressure differences or absolute pressure (Pa) of air in different positions of Aeromatic MP-1 with inserted filters, loaded with 100 g of coated pellets (n = 3);

Pi = Pressure of room air, Pii = Pressure of air inside MP-1, Piii = Pressure of air in exhaust air tube after filters or cyclone, $\Delta P1 = Pii - Piii$ or pressure difference between air inside MP-1 and air inside exhaust air tube behind filters or cyclone, $\Delta P2 = Pi - Pii$ or pressure difference between air inside MP-1 and room air, $\Delta P3$ or pressure difference of air between below and above perforated plate, the highest regulator position is number 10.

No. of Product	Air flow (m ³ h ⁻¹)	$\Delta P1 \pm SD$	$\Delta P2 \pm SD$	$\Delta P3 \pm SD$	Pi	Pii	Piii
		(Pascal, Pa)					
Filters							
1	90±1	79±6	773±13	587±13	100508	99735	99656
2	89±1	79±6	920±13	653±13	100508	99588	99509
3	90±1	49±6	1040±13	786±13	100508	99468	99419
Cyclone							
1	92±1	2403±90	857±56	623±41	100508	99651	97248
2	92±1	2395±50	884±33	649±56	100508	99624	97229
3	92±1	2382±70	960±27	782±8	100508	99548	97166

Table 2.10: *Pressure differences or absolute pressure (Pa) of air in different positions of Aeromatic MP-1 with inserted filters or with cyclone (n = 3); Pi = Pressure of room air, Pii = Pressure of air inside MP-1, Piii = Pressure of air in exhaust air tube after filters or cyclone, $\Delta P1 = Pii - Piii$ or pressure difference between air inside MP-1 and air inside exhaust air tube behind filters or cyclone, $\Delta P2 = Pi - Pii$ or pressure difference between air inside MP-1 and room air, $\Delta P3$ or pressure difference of air between below and above perforated plate, the highest regulator position is number 10, Product No. 1: no pellets, Product No. 2: coated pellets 100 g, Product No. 3: coated pellets 250 g*

2.3.3 Calibration

2.3.3.1 Calibration of thermocouples

Thermocouples made from Ni-Cr-Ni {63} were used as sensors for monitoring the temperature during the coating process. These sensors were connected to the data recording device as mentioned before. The original values from these sensors were in mV. These values were then converted into degree Celcius by the integrated program in the data recording device and the internal reference used. Before the calibration was performed the value shown on the display of the data recording device was adjusted as a one point adjustment. After this adjustment the calibration in order to prove the accuracy of values from each sensor over different temperature ranges was carried out. The temperature in the range of 0 to 100 °C was created by an ice bath and/or a water bath with thermostatic control {69}. The temperature of this bath can be controlled with a deviation of ± 0.5 °C. The reference temperatures from 0 to 100 °C were shown on the accurate thermometers {64,65}. The results showed that the deviation between the values from the display and from the thermometers was not more than ± 1 °C at all the ranges. These deviations were accepted, as the temperature of the coating process could be well controlled and the deviation could be kept within ± 2 °C of the desired temperature.

2.3.3.2 Calibration of the Hygrolog hygrometer

The Hygrolog hygrometer was used in the fluidized bed process in order to measure the relative humidity of the coating process. The principle of this apparatus was to measure temperature of the process air and the temperature at which the water from this air is condensed on the peltier-element. This is called dew point (Td). From values of air temperature and dew point the relative humidity can be calculated. For example, if the air temperature is 50 °C and Td is 20 °C, then this air has a relative humidity of 19 % or contains absolute water of 80 g/kg.

The calibration was performed by measuring temperature and humidity of the air in the room before this hygrometer was used. The values measured with the Hygrolog were compared with the values resulting from another hygrometer as a reference {34}. It was found that there were differences between air temperature of 0.5 °C and the relative

humidity of 2 % r.h. However, these differences were accepted because variations in the process conditions during the coating process did not affect the quality of the products.

2.3.4 Determination of spraying angles

The important factor also to be considered in the coating process was the spraying angle of the dispersion of the polymer. If the spraying angle is not suitable it might cause problems in the coating process. For example: if the spraying angle is too large, it would cause a loss of the polymer because of the accumulation of polymer at the inner surface of the Wurster column. If the spraying angle is too small the polymer would be concentrated at a small part of the product bed within the Wurster column and create agglomerations because of a too wet product.

The measurement outside the coating apparatus could easily be performed and therefore it was suitable to be used as a control method after a long time of coating process to observe the condition of the spraying unit.

The measurement outside the fluidized apparatus was performed as shown in Figure 2.22. The atomizing pressure was set at the same value as in the coating process, for example $2.6 \text{ m}^3\text{h}^{-1}$. The distance between the end of the spraying nozzle and the end of the air cap was 1.0 mm [8]. The spraying unit (A) and the dispersion delivery device (B) were the same as in the coating process. About 1.0 g of the water soluble red coloured powder (L-Rot Z 3020) was added into the 15 % w/w dispersion containing 33.3 g of Aquacoat CPD-30 and 2.5 g of TEC in order to improve the observation of a spraying region on the receiving paper (C). The delivery of the dispersion was performed with a peristaltic pump (D) at a spraying rate of 2 g/min. The spraying time was 1.30 min. After finishing the spraying the region after spraying was marked on the paper. The border line of the region was defined as the point where almost no colour could be seen. The radius of this region was then measured by using a ruler. The distance between the spraying nozzle and the paper was kept at 18.0 cm because this was the length of the Wurster column. Therefore the angle of spraying can be calculated as shown in Figure 2.22, at which r_1 is the radius (cm) of the spraying region and r_2 is the distance (cm) between the end of the spraying nozzle and the surface of the paper. The result of this spraying angle was compared to the dimension of the Wurster column which had an inner diameter of 5.7 cm or a radius of 2.85 cm.

The result showed that the radius of the spraying regions measured outside the coating apparatus at the distance of 18 cm was between 7 and 10 cm. This means that the spraying angles were between 21 and 29 °. When the radius of the spraying region (7.0 – 10.0 cm) was compared to the radius of the Wurster column (2.85 cm) it could be seen that the radius of the spraying region was much larger than that of the Wurster column. However, it must be considered that in the real coating process the process air came from the vertical and this may interfere the spraying angle of the solution or dispersion. The spraying angle inside the coating apparatus may be smaller than that without a process air outside the coating apparatus. Moreover, the loaded products may alter the flow pattern of the air flow. Therefore the observation was performed with the coating processes by using the coating dispersion and loading products.

After using the suitable setting e.g. atomizing pressure and distance between spraying nozzle and air cap of the spraying unit in the coating process it was found that the coating processes was well operated. There was no significant accumulation of coating materials at the inner surface of the Wurster column which indicated that the setting of the spraying unit was suitable for the coating. This test was also performed after a certain period of working time in order to control the condition of the spraying unit whether there was a blockage inside the spraying unit or not. If the spraying angle at the same setting was kept constant then this spraying unit could be used furtheron for the coating process. When the spraying angle was changed from the expected one then the reason of this occurrence could be found. For example it was found that the blockage or the damage of the spraying unit was the main reason for the change in spraying angle.

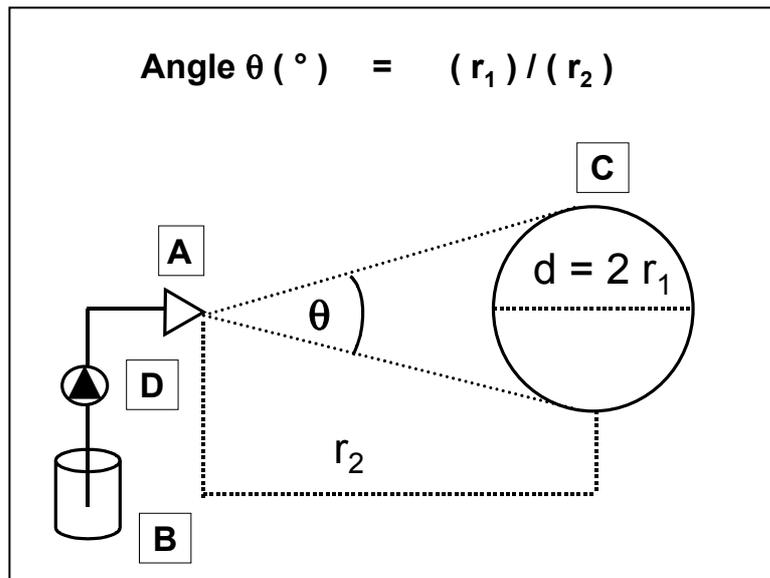


Figure 2.22: Setting of the spraying unit and the receiver of the atomizing liquid for the determination of the spraying angle outside the coating apparatus.

2.3.5 Signals from the data recording device

The examples of signals from the coating processes in the Aeromatic MP-1 {20} with inserted filters or with a cyclone {13} as a dust collector are shown in Figure 2.23 and 2.24, respectively. These signals were collected by a data recording device {14}.

2.3.5.1 Coating process by using Aeromatic MP-1 with inserted filters

Figure 2.23 shows the interruption of the coating process because filters must be changed and cleaned, X18 (Table 2.23) for the production of Product hH. The **first cycle** was carried out by pre-warming the coating apparatus without any product for 15 min (between 1 to 15 min) and then the loading material was put into the product container. The coating apparatus had to be stopped for this procedure but the atomizing air (# 4) was still in process to avoid the blockage of the spraying nozzle because of the loading material. The signal from the process air flow (# 5) was immediately decreased when the coating apparatus was stopped as shown in Figure 2.23 (a). After finishing the loading phase the inlet temperature was set to 35 °C to receive the product

temperature of about 32 °C. The pre-warming phase with the loading product was carried on for 15 min (between 15 to 30 min). At the time of 24 min from the beginning (b) the peristaltic pump {51} was started with air because this was still the pre-warming phase. The spraying of the dispersion was made 30 min after the start of the apparatus. (c). The process air flow was adjusted so that the flow was between 95 - 100 m³ h⁻¹. If the flow decreased to 95 m³ h⁻¹ then the higher position at the control switch was used so that 100 m³ h⁻¹ was achieved. Therefore the signal from the process air flow (# 5) had a zig-zag character. It was obvious that after the spraying phase the temperatures of inlet air before heating (# 1 ~ 24°C) and after heating (# 2 ~ 35 °C), the product bed temperature (# 3 ~ 32 °C), the outlet air temperature (# 7 ~ 32 °C) and its dew point (# 8 ~ 14 °C) kept constant over the coating period. The digital signal, coming from the data collecting device, was between 0.0 and 99.9 g because of the limit of the D/A converter. Therefore the signal from the used dispersion was decreased over the time. If the signal arrived 0.0 g then it began with 99.9 again. The spraying rate (g/min) can be calculated from the values from this decreasing line. For example; this process had a constant spraying rate of 0.8 g/min. At 85 min the D/A converter was stop and therefore the signal had minus values. At 88 min the tubes inside a beaker containing coating dispersion were placed into a beaker containing water to clean the tube-system. At about 93 min all tubes were taken out of a beaker. At 98 min the spraying of water started and the spraying was stopped at 106 min. The drying and cooling phase followed until 116 min. The region between 116 min to 160 min was the stop phase of Aeromatic MP-1.

The region between 161 to 176 min was the pre-warming phase of the coating apparatus without a product for the **second cycle**. After this pre-warming phase of 15 min the loading material, which came from the cycle I and was further dried in the small scale fluidized bed apparatus (Uniglatt) during the filter change phase, can be put into the product container again and the same cycle as above mentioned was carried on. The prewarming phase with a product was performed for 15 min (176 min to 190 min). Air was sprayed from 186 min to 190 min and then followed the spraying with the dispersion (191 - 265 min). After the spraying with the dispersion the distilled water was sprayed from 266 min to 269 min. Hereafter the drying phase was carried out for about 15 min.

The **third cycles** contained different phases as well i.e. loading of materials, spraying of air (356 - 360 min), spraying of the dispersion (361 - 376 min), spraying with water (377 - 381 min), drying (381 - 396 min) and cooling (397 - 410 min).

2.3.5.2 Coating process by using Aeromatic MP-1 with a cyclone

Figure 2.24 shows the continuous process without any interruptions, X21 (Table 2.24) for the production of Product oO. This process was used to coat pellets with enteric coating materials containing CAP, TEC and Aqoat-AS-MF. This coating formulation needs special control of the temperature of the coating dispersion (# 9). The temperature should be kept lower than 15 °C by using water-ice bath. If the temperature was increased to about 12 °C because ice was melting then a small amount of ice was added to the water-ice bath to reduce the temperature of the dispersion to about 9 °C. The pre-warming phase without a product of this coating apparatus was also 15 min (1 - 15 min). After this phase the coating apparatus was stopped to put the loading material into the product container. After finishing the loading then the process was continued at the set inlet temperature of 35 °C to receive the product temperature of 32 °C. The process air flow was set at the highest position which means 10 at the control switch. After pre-warming phase with the loading product for 15 min the spraying with air was performed at 19 - 30 min. Then the spraying with a dispersion started (31 - 187 min). At about 188 min the tubes were taken from the beaker containing coating dispersion and were put into the beaker containing water to clean the tubes. The spraying with water was performed at 198 - 203 min after that the drying phase was carried on. The last step was the cooling of the coating apparatus to about room temperature before the process was stopped at about 222 min.

The spraying rate could be calculated from the decreasing line (# 6) which gave the value of 0.8 g/min. After the spraying phase the temperatures of inlet air before heating (# 1 ~ 21°C) and after heating (# 2 ~ 35 °C), the product bed temperature (# 3 ~ 32 °C), the outlet air temperature (# 7 ~ 32 °C) and its dew point (# 8 ~ 3 - 4 °C) and the process air (# 5) flow kept constant at about 93 - 95 m³ h⁻¹ over the coating period.

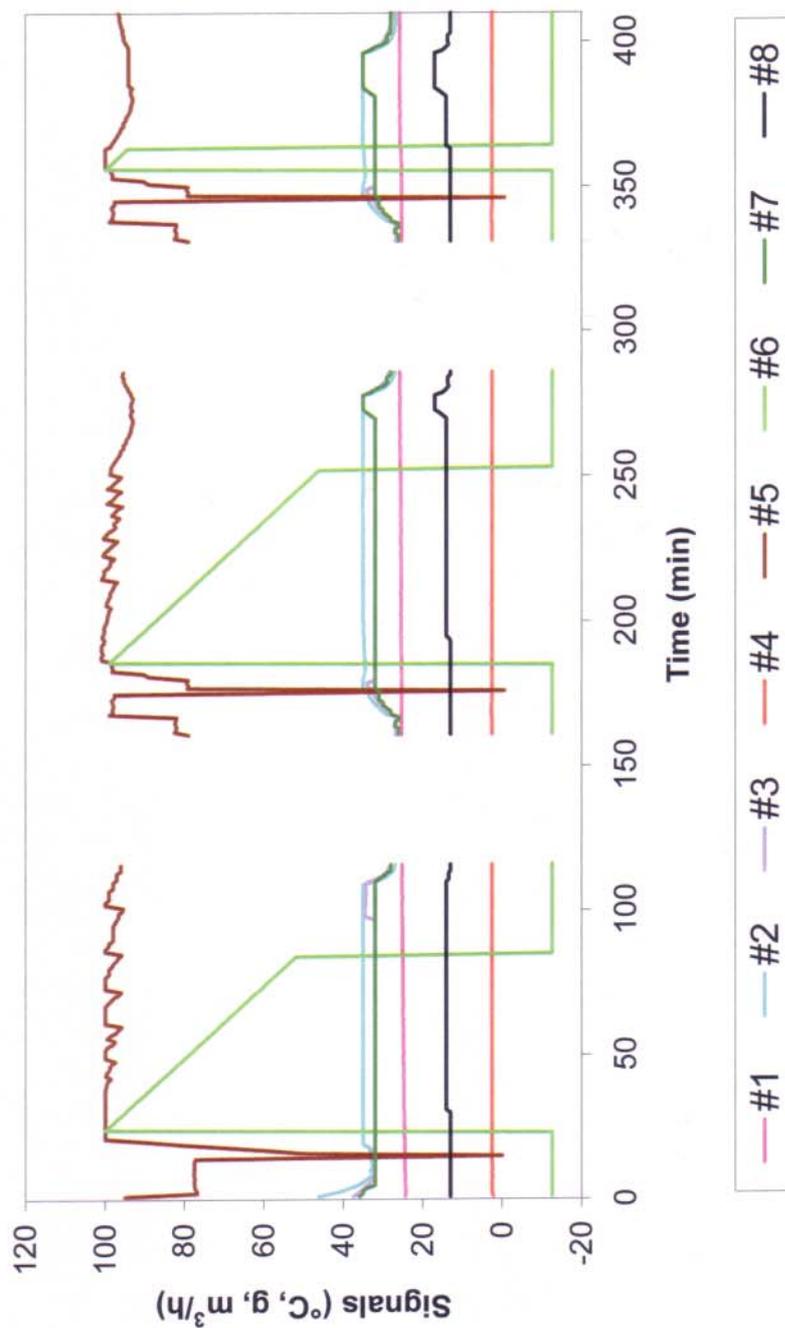


Figure 2.23: Aeromatic MP-1 with inserted filters, process X18 (Table 2.23), for the production of Product hH; #1: temperature of inlet air before heating, ~ 24 °C, #2: temperature of inlet air after heating, ~ 35 °C, #3: temperature of product bed, ~ 32 °C, #4: mass flow of atomizing air, ~ 2.6 m³h⁻¹, #5: volume stream of process air, $\sim 95 - 100$ m³h⁻¹, #6: weight decrease of used dispersion, 99.9 - 0.0 g, #7: temperature of outlet air, ~ 32 °C, #8: dew point of outlet air, $\sim 13 - 14$ °C.

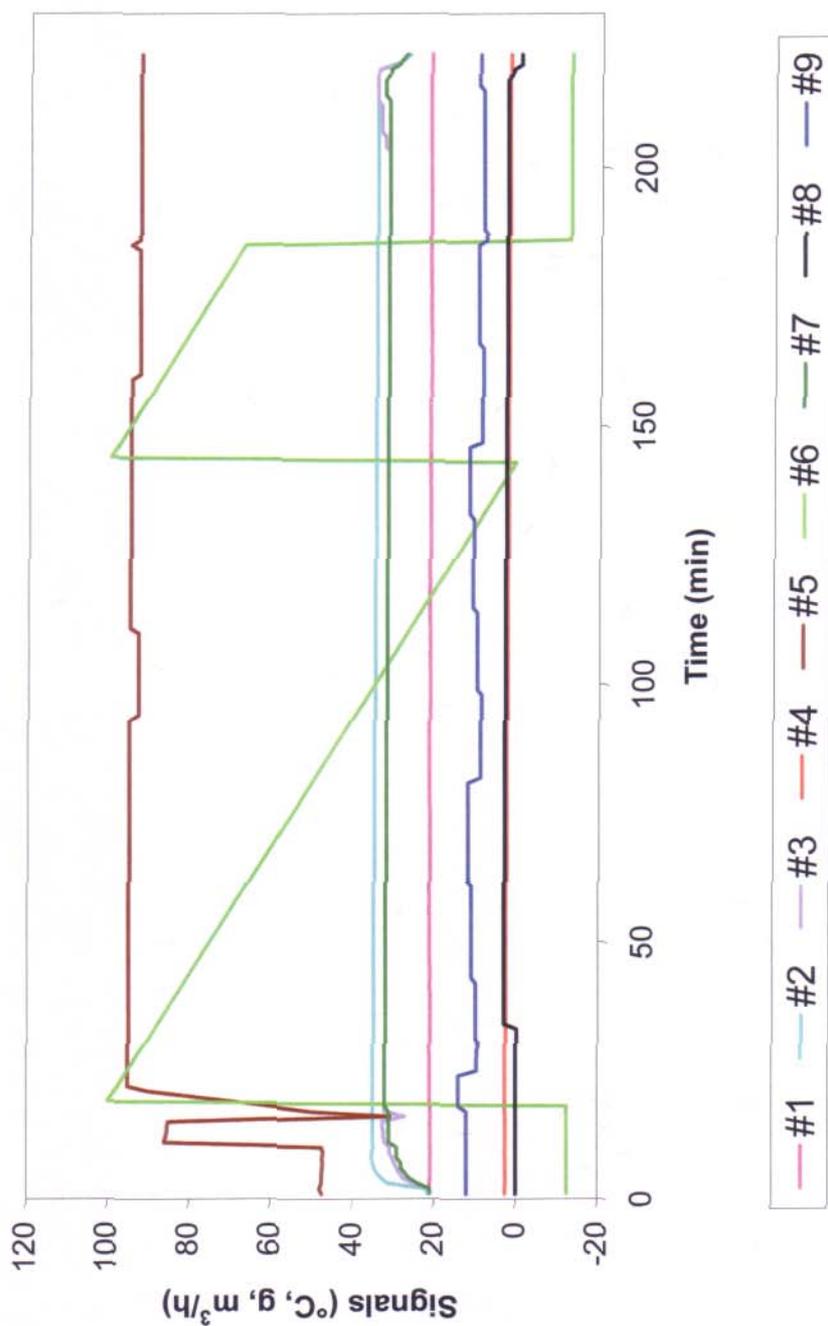


Figure 2.24: Aeromatic MP-1 with a cyclone, process X21 (Table 2.24), for the production of Product oO;
 #1: temperature of inlet air before heating, ~ 21 °C, #2: temperature of inlet air after heating, ~ 35 °C, #3: temperature of product bed, ~ 32 °C, #4: mass flow of atomizing air, ~ 2.6 m^3h^{-1} , #5: volume stream of process air, $\sim 93 - 95$ m^3h^{-1} , #6: weight decrease of used dispersion, $99.9 - 0.0$ g, #7: temperature of outlet air, ~ 32 °C, #8: dew point of outlet air, $\sim 3 - 4$ °C, #9: temperature of used dispersion, $\sim 9 - 12$ °C.

2.4 Preparative Methods

2.4.1 Preliminary Experiments

The preliminary experiments were performed in order to become familiar with the fluidized bed apparatus and to select the suitable process conditions and formulation for preparing the dosage form. The model dosage form used in this present study should contain a thin layer of nicotinamide and thereafter a layer of a subcoat with different thicknesses. Different film-forming polymers, i.e. HPMC, PVA and EC which can be used as a subcoat because of their properties of moisture barrier were tested. They have different physical properties such as glass transition temperature (T_g), minimum film-forming temperature (MFFT), compatibility with plasticizers and viscosity. Therefore the preliminary test was to be carried out for each polymer.

2.4.1.1 Coating of tablets

In order to become familiar with the fluidized bed apparatus and the accessories the coating trials were carried out by using placebos. The suitable placebo for the first step were tablets. These tablets were produced by using the direct compression filler - Ludipress {Batch No. 340402, BASF, Ludwigshafen} and a direct compression technique. Ludipress is composed of ~ 93 % α -lactose-monohydrate, ~ 3.5 % Kollidon 30 (soluble PVP) and ~ 3.5 % Kollidon CL (insoluble PVP) <156>. This material was already available in the laboratory and some parameters for the tableting was already mentioned <109,156>. Magnesium stearate {Lot No. 91320, Riedel-de Haen, Seelze} was used as a lubricant at 1.0 % w/w. These two components were mixed in a mixing machine {45} at a mixing time of 10 min.

The manufacturer of the Aeromatic MP-1 recommended that about 1 kg of loading substance should be used for one coating process. For this reason about 10 kg of tablets were produced in a rotary tableting machine, Korsch PH 106 {60}. Only three pairs of punches with a curve radius of 3.5 mm and a diameter of 5 mm were used. This condition gave more uniform tablets with smaller variation in the finished product. The upper punch produced a carve on the tablets. The rotation speed of the tableting machine was 22 - 25 rpm. The height of filling was 6 mm and the height of tablets was

4.6 mm. The hardness of the tablets was regulated by adjusting the upper punch so that the hardness of about 35 N was achieved.

The resulted tablets had mean weight {1} of 52 ± 2 mg, mean diameter {62} of $5 \text{ mm} \pm 0.5$ mm, mean thickness {62} of 2.8 ± 0.5 mm and mean hardness {61} of 35 ± 5 N.

These tablets served to develop the working principle of the coating apparatus. The solution of 10 % w/w of Pharmacoat 603W in water was used as a coating polymer because it was easy to be prepared and some coating parameters were known from the work of Nguyen <109>.

The result showed that these tablets can be coated with the solution of Pharmacoat 603W and the process number X1 (Table 2.11) in the fluidized bed apparatus. The resulting tablets showed an acceptable quality of the coating layer. Therefore the change from tablets to pellets was done because the properties of these two products were different e.g. friability, surface area, hardness, form, etc.

Process number \ Parameter	X1	X2	X3	X4	X5	X6
Loading weight (g)	1000	1000	1000	1000	1000	300
Core material	T	S	S	S	S	S
Atomizing pressure ($\text{m}^3 \text{h}^{-1}$)	2.4	2.4	2.4	2.4	2.4	2.4
Orifice diameter (mm) {48}	0.8	0.8	0.8	0.8	0.8	0.8
Distance from bottom to column (mm)	0.8	0.8	0.8	0.8	0.8	0.8
Perforated bottom (% free)	20	20	20	20	20	13
Pre-warming with product (min)	15	15	15	15	15	15
With dehumidified process air	y	y	y	y	y	y
With cyclone instead of filters	n	n	n	n	n	n
Room temperature/humidity ($^{\circ}\text{C}$, % r.h.)	20, 50	20, 60	22, 50	22, 50	22, 50	22, 50
Inlet temperature ($^{\circ}\text{C}$)	60	60	60	60	60	60
Product temperature ($^{\circ}\text{C}$)	54	54	54	54	54	54
Outlet temperature ($^{\circ}\text{C}$)	52	52	52	52	52	52
Outlet humidity (% r.h.)	18	18	18	18	18	17
Spraying rate (g min^{-1})	3.0	1.7	1.7	1.7	1.7	0.5
Initial spray	air	water	water	water	water	water
Process air velocity ($\text{m}^3 \text{h}^{-1}$)	50-55	50-55	50-55	50-55	50-55	50-55
Drying in Uni-Glatt ($^{\circ}\text{C}$, min)	-	-	-	-	-	-
Postdrying inside the machine ($^{\circ}\text{C}$, min)	54,15	54,15	54,15	54,15	54,15	54,15
Postdrying outside the machine ($^{\circ}\text{C}$, h)	22, 24	22, 24	22, 24	22, 24	22, 24	22, 24

Table 2.11: Coating conditions of different processes X1 to X6;

T = Tablets with a diameter of 5 mm

S = sugar spheres size range 1000-1180 μm

y = yes; n = no

Process number / Parameter	X7	X8	X9	X10	X11	X12
Loading weight (g)	1000	500	200	200	200	200
Core material	SS	PP	M1	M2	M3	M4
Atomizing pressure (m ³ h ⁻¹)	2.4	2.4	2.4	2.6	2.6	2.6
Orifice diameter (mm) {48}	0.8	0.8	0.8	1.2	1.2	1.2
Distance from bottom to column (mm)	0.8	0.8	0.8	0.8	0.8	0.8
Perforated bottom (% free)	20	20	13	13	13	13
Pre-warming with product (min)	15	15	15	15	15	15
With dehumidified process air	y	y	y	y	y	y
With cyclone instead of filters	n	n	n	n	n	n
Room temperature/humidity (°C, % r.h.)	22, 50	22, 50	22, 50	23, 50	24, 50	22, 50
Inlet temperature (°C)	60	55	60	60	60	60
Product temperature (°C)	54	50	54	50	55	58
Outlet temperature (°C)	52	48	52	49	50	57
Outlet humidity (% r.h.)	17	18	17	18	18	17
Spraying rate (g min ⁻¹)	1.7	0.8	0.8	1.7	1.7	0.8
Initial spray	water	water	water	water	water	water
Process air velocity (m³ h⁻¹)	50-55	55-60	55-60	55-60	55-60	65-70
Drying in Uni-Glatt (°C, min)	-	-	-	-	-	-
Postdrying inside the machine (°C, min)	54, 15	50, 15	54, 15	50, 30	50, 30	50, 15
Postdrying outside the machine (°C, h)	22, 24	22, 24	22, 24	50, 24	50, 24	50, 24

Table 2.12: Coating conditions of different processes X7 to X12;

SS = sugar spheres size range 800-1000 µm

PP = placebo or HPMC pellets size ~ 800 µm

M1 = Nico pellets (Product AA)

M2 = Nico pellets (Product Aa)

M3 = Nico pellets (Product aA)

M4 = Nico pellets (Product aa)

y = yes; n = no.

2.4.1.2 Coating of sugar spheres

One of the important factors of a coating process is a fluidized flow of the product bed. Normally if tablets are the loading material then the flow pattern in the product container outside the Wurster column would be the continuous flow without any bubble in the product bed. This phenomenon was also recommended by the manufacturer of the Aeromatic MP-1 <120>. In this present work it was also found out that the continuous flow without any bubbles or the so called **incipiently fluidized bed** <122> was suitable for the coating process because twins or agglomerations of tablets did not occur. However, if sugar spheres are the loading product then the higher process air flow should be used. A so called **bubbling bed** <122> was found to be suitable for the coating because no big agglomerations occurred. The difference between incipiently fluidized bed and bubbling bed was shown in Figure 2.25. The reason for the difference of the suitable product bed flow would be the packing of sugar spheres in the product bed during the coating process. Sugar spheres are almost spherical and therefore they can create the rhombohedral packing <40>. The small process air flow would allow the coated pellets to fall too fast to the upper part of the product bed and this air flow would not be enough to dry the wet pellets before they arrived the upper part of the product bed. If the wet coated pellets were fallen to the product bed and they have not been dried then the rhombohedral packing would accelerate the sticking between the wet coated pellets. This was confirmed by the formation of big agglomerations of pellets. On the other hand if tablets were used as a loading material their packing will not be rhombohedral but may be cubic because the tablets did not have a spherical dimension <40>. The cubic packing may hinder the sticking between tablets. Therefore if tablets were used as a loading material a smaller air flow can be used in comparison with sugar spheres.

The different flow pattern of the bed can be achieved with the help of a perforated bottom with different free holes outside the region of the Wurster column <122>. It was also found that the different amounts of loading core materials need different free holes in the perforated bottom outside the region of the Wurster column. For example for 1000, 500 or 100 g of pellets the suitable perforated bottom is 20 %, 13 % and 8 % free holes, respectively.

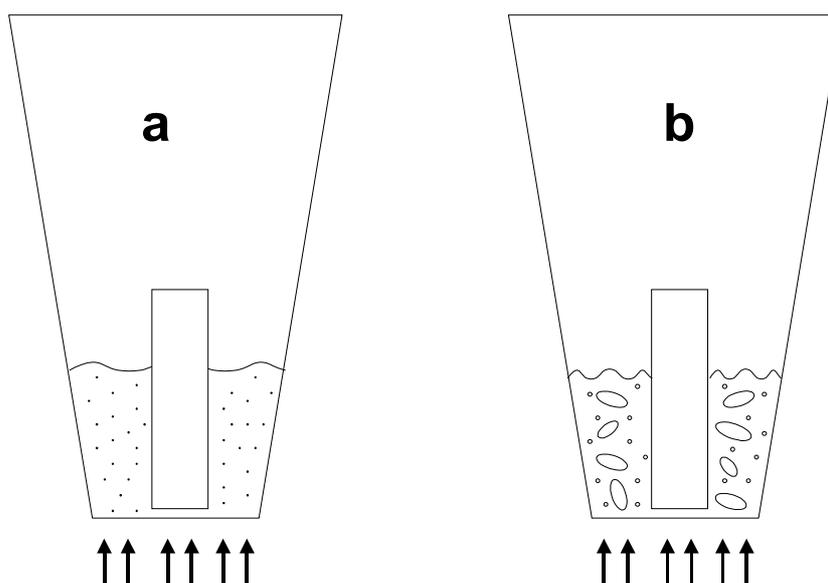


Figure 2.25: Two types of fluidized beds; a) incipiently bed, b) bubbling bed; small circles or ellipsoids demonstrate the air bubbles <122>.

The spraying rate should also be well selected in order to have the continuous flow with a balance between a wetting phase and a drying phase. If the spraying rate is too high it may cause the agglomeration of a product bed because of over wetting. If the spraying rate is too low it may take a long time to finish the coating process and sometimes a high amount of dust would occur because of spray drying.

The suitable combination was selected from the result that about 1000 g pellets show well-fluidized flow at a given spraying rate and product bed temperature, no blockage of the nozzle, and even a film structure with almost no bubbles as demonstrated from the cross section by SEM.

2.4.1.2.1 Trials with HPMC

HPMC was copulently used as a subcoat in different works <109,187>. Therefore HPMC was used in this work in order to compare with the other film-forming polymers such as PVA or EC. The preliminary study was carried out by using a method modified from the recommended one <77> to coat the 1000 g sugar spheres.

For this present work the first trials were carried out by using a solution of Pharmacoat 603W at concentrations varying from 5 to 10 % w/w because the spraying rate depends on the concentration of the polymer solution. Therefore varying of the spraying rate from 1 to 9 g/min was carried out while using the different concentrations of HPMC. The suitable combination to allow the uniform flow of 1000 g seemed to be a concentration of 5 % w/w Pharmacoat 603W and a spraying rate of 1.7 g/min, i.e. process number X2, Table 2.11. However, some twins and small agglomerations of 3 to 5 pellets occurred during the coating process. The resulting HPMC layer at the thickness of about 10 μm coated on sugar spheres (Product P) with some bubbles in the structure of the HPMC-layer can be seen in Figure 2.26.

This preliminary study showed that the HPMC film layer was not free from bubbles. Therefore the other formulations were investigated. According to the literature <77> there were two types of HPMC i.e. Pharmacoat 603W and Pharmacoat 645W that can be used as coating materials for sugar spheres. Therefore both types were tested but no significant difference was found at the same formulation and conditions of coating.

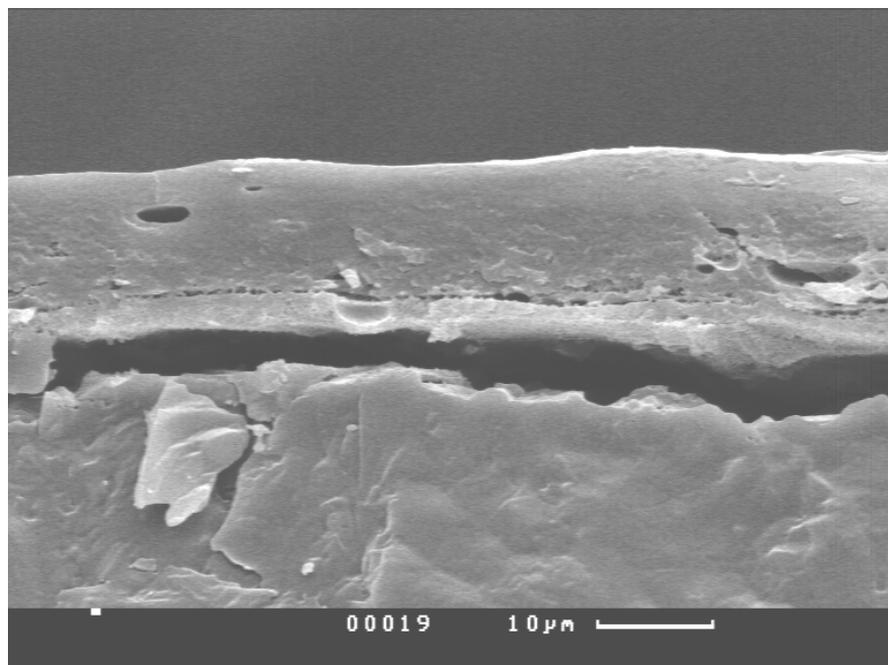


Figure 2.26: HPMC-coated pellet (Product P) shows bubbles in the HPMC film layer.

2.4.1.2.2 Trials with Sepifilm LP 010

The first trial in 2.4.1.2.1 with HPMC as a film-forming polymer alone did not give a satisfying result and therefore Sepifilm LP 010 was used instead. Sepifilm LP 010 is a combination of HPMC and other ingredients as already detailed in 2.1.3. Therefore a better outcome was expected. This polymer may hinder the formation of twins and agglomerations. The trial was first carried out by varying spraying rates from 1 g/min to 5 g/min and concentrations of aqueous dispersions from 5 to 15 % w/w. The formulations and coating conditions used in the preliminary test were created on the basis of the recommended ones <171>.

The formulation containing 5 % w/w Sepifilm LP 010 and the process number X3, Table 2.11 resulted in Product Z1 with a film-thickness of about 10 μm. Films resulted from this condition showed no significant difference in physical character compared to the HPMC film (2.4.1.2.1) as demonstrated in the SEM (data not shown). Only the flow character of pellets during coating was better because almost no agglomeration

occured. During the coating process the dispersion tended to sediment and caused unhomogeneous dispersion. After a certain coating time blockage of the nozzle occurred. This was not a satisfying result. Therefore Sepifilm LP 010 was not used to form a subcoat.

2.4.1.2.3 Trials with other additives

As the trial in part 2.4.1.2.1 to 2.4.1.2.2 showed no satisfying result a combination of HPMC and other additives was tested. The examined additives were water insoluble (talc, magnesium stearate) or water soluble (polyethylene glycol 400 or 4000).

The particle sizes of the water insoluble additives were determined before they were added in the coating formulation in order to hinder the blockage of the fluid nozzle as mentioned before. The example of the measurement of the particle sizes was shown by using talc.

The largest particle size of talc with or without grinding {38} were $60 \pm 10 \mu\text{m}$ ($n = 20$ and $p < 0.05$). There was no difference in the mean largest particle size of talc before and after grinding. Therefore the grinding was not necessary before talc was added to the coating formulation.

Particle size and form of magnesium stearate (Mgst) was determined under a light microscope as well and the result showed that their largest particles were not bigger than $70 \pm 10 \mu\text{m}$ ($n = 20$ and $p < 0.05$).

These insoluble additives were added separately at 10 % w/w to a solid content of Pharmacoat 603W. The total concentration of solid content in water was 10 % w/w. The result showed that pellets coated with the dispersion containing Pharmacoat 603W and talc or magnesium stearate using the process number X4, Table 2.11 did not have better film structure compared to the formula using HPMC alone.

Films resulting from Pharmacoat 603W and talc or Mgst always contained small bubbles. Moreover these dispersions also caused a sedimentation of insoluble particles during a long processing time. Therefore the combinations between Pharmacoat 603W and insoluble additives (talc or Mgst) will not be used to form a subcoat.

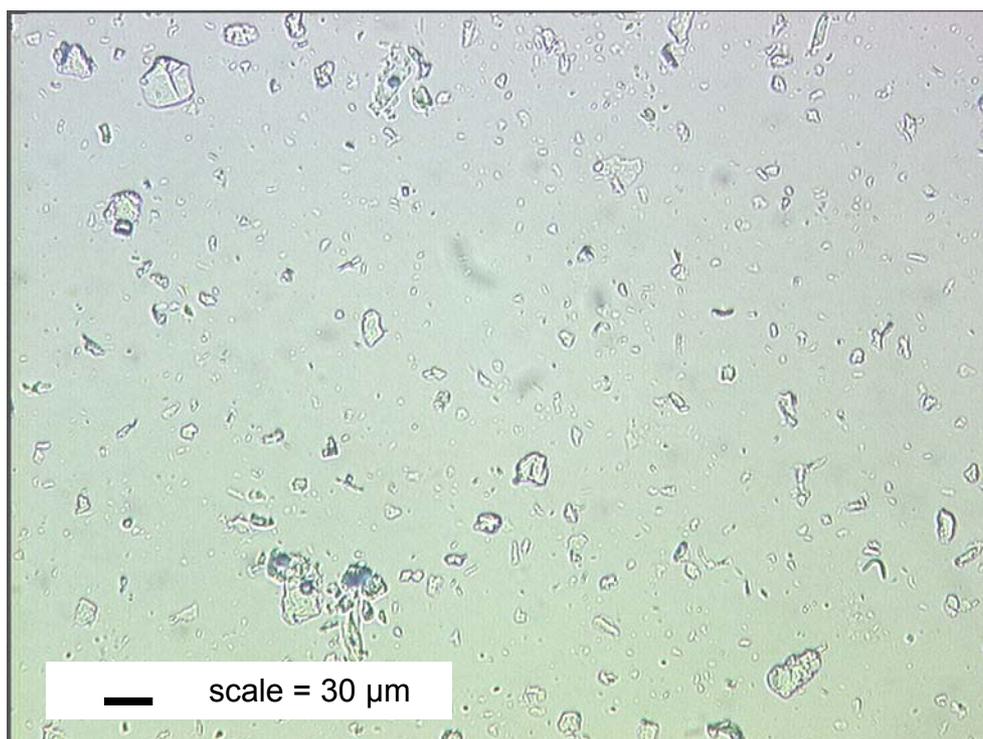


Figure 2.27: Microscopic picture of talc dispersed in glycerol 85 %.

The water soluble additive such as PEG was added at 7 % w/w to a solid content of Pharmacoat 603W. Two types of PEG i.e. PEG 4000 and PEG 400 were used. The total concentration in water was kept at 10 % w/w. The result of pellets coated with the 10 % w/w solution of Pharmacoat 603W and one of the PEGs using a process number X5, Table 2.11 showed that during the coating process the spraying nozzle was blocked. Therefore the solution of 10 % w/w total concentration of Pharmacoat 603W and PEG 4000 was diluted with water to have a concentration of 5 % w/w. It was found that this solution can be coated onto pellets at a spraying rate of 1.7 g/min. However, the film morphology resulting from this combination was not different from Pharmacoat 603W alone (data not shown).

Therefore the combinations between Pharmacoat 603W and soluble additives (PEG 400 or 4000) will not be used to form a subcoat.

Consequently, the solution to be used to form a subcoat was the formulation R1 (Table 2.15) by using the process number X9 (Table 2.12). This formulation, R1, was also applied to form the mechanical protecting layer by using the process number X7 (Table 2.12).

2.4.1.2.4 Trials with polyvinyl alcohol (PVA)

PVA was reported to be suitable for use as a moisture barrier film coated on the product <142>. Therefore different types of PVAs such as Mowiol 3-83, 3-98, 4-88, 4-98, 8-88, 10-98, 18-88, 20-98 and 26-88 as described in the part 2.1.5 were used. The 5 % w/w solution of each type was prepared in a hot water of 80 °C as a solvent. Batches of 300 g of sugar spheres were coated with each one of these solutions. Spraying rates were varied from 0.5 to 5 g/min. It was found that only the lowest spraying rate of 0.5 g/min can be used because in case of higher spraying rates big agglomerates developed and caused a blockage inside the Wurster column. Consequently 6 different types of PVA coated pellets (Product Z2 to Z7) using the process number X6, Table 2.11 were prepared so that the thickness of the PVA-film was about 10 µm. These pellets were used to determine the moisture barrier property of coated pellets compared to pellets coated with HPMC and Sepifilm LP 010, details shows in part 2.4.2.

However, the coating process with a PVA solution takes a long time of coating due to a very low spraying rate of about 0.5 g/min. For this reason a PVA solution alone was not used as a subcoat because it may take a too long time until the required thickness is achieved.

2.4.1.2.5 Trials with ethyl cellulose (EC)

Ethyl cellulose was in many cases used as a film-forming agent for the delay released dosage form <179,118,205,21,67>. The delay of release mostly depends on the thickness and the structure of EC-film. However, because of the insoluble and non-hygroscopic property of EC in weakly acidic and basic medium it can be used as a moisture barrier. The suitable thickness should be selected so that no delay of release occurred.

In this preliminary test the dispersion of EC was prepared from Aquacoat ECD on the basis of a recommended formula and the coating conditions modified from the recommended ones <8>. The concentration of dibutyl sebacate based on the solid content of Aquacoat ECD was varied from 20 to 25 % w/w. The prepared dispersion at the total concentration of 20 % w/w was for the coating of sugar spheres of about 200 g. Different spraying rates were tested and the suitable one that did not cause agglomerations was chosen for the further preparations.

The results show that the suitable coating dispersion was the formulation number R5 in Table 2.15 which was used to form a subcoat by applying the process number X10 in Table 2.12.

2.4.1.2.6 Trials with a combination of EC and PVA at two ratios

Because PVA alone will not be used to form a subcoat as mentioned in 2.4.1.2.4, the possibility to utilize PVA in a combination with another polymer to increase the spraying rate and to reduce the sticking of coated pellets was tested. Some research works have used EC in combination with hydrophilic polymer such as HPMC <63,59,149>. Therefore the comparison by applying a combination of EC and PVA may be of interest. The dispersion of a combination of EC and PVA for the preliminary test was prepared according to the modified formula as well as the coating conditions based on the details mentioned in 2.4.1.2.4 – 2.4.1.2.5. Two different ratios of EC and PVA were prepared to observe the different physical property after coating. Mowiol 4-98 was used as source for PVA because it has a low mean molecular mass of about 27000 g/mol and the 4 % w/w solution at 20 °C has a low viscosity of about 4.5 mPa.s. If two polymers have different chemical structures they should be mixed by adding not more than 30 parts of the polymer type-I to the polymer type-II to avoid phase separation. DBS was used at the same concentration to Aquacoat ECD i.e. 20 % w/w to Aquacoat ECD solid content. PVAs normally do not need any plasticizer and therefore no further amount of DBS was added.

The results show that the suitable coating dispersion containing 100 parts of Aquacoat ECD and 30 parts of Mowiol 4-98 was the formulation R6 (Table 2.15). The suitable coating process was X11 (Table 2.12). The suitable coating formulation containing 30 parts of Aquacoat ECD and 100 parts of PVA was R7 (Table 2.15) and the suitable coating conditions was the process number X12 (Table 2.12).

2.4.2 Determination of a moisture barrier property of films coated on pellets

Pellets coated with different types of PVA, HPMC and Sepifilm LP 010 were stored as mentioned in 2.2.14. They were used to determine the water content as mentioned in 2.2.14 in order to observe the properties of the moisture barrier of films coated on the

pellets. The results in Table 2.13 show that the water content of PVA-coated pellets was not more than 3 % w/w even under a high stress condition of 50 °C and 79 % r.h. This may indicate that every types of PVAs can protect the core from the vapor water diffusion and thus may reduce the chemical degradation.

The HPMC-coated pellets (Product P) and the Sepifilm LP 010-coated pellets (Product Z1) were also stored under the same conditions for a comparison. The determination of water content after the storage was carried out. The results in Table 2.13 also showed that the water content of these products was not more than 3 % w/w even under a high stress condition of 50 °C and 79 % r.h. This means that films from HPMC, Sepifilm LP010 and different types of PVAs can protect cores from the vapor water diffusion.

Roxin, Karlsson and Singh <155> have used Karl Fischer titration to determine the water content in the CAP powder. They used methanol and pyridine (1:1) as a solvent and KF solution A and KF solution B (1:1) as a reagent. The resulted data from KF-titration was compared with the data from thermogravimetric analysis, DSC-method, loss on drying test and the certificate. They found that the data of water content were comparable i.e. the CAP powder contained about 1.5 – 2.5 % w/w water.

Sepifilm LP consists of HPMC (60 - 70 %), microcrystalline cellulose (5 – 15 %) and stearic acid (20 – 30 %) <171,172>. The number 010 of Sepifilm LP means that it is uncoloured. The protection against moisture under the stress conditions of 40 °C and 90 % r.h. was reported. The fumitory tablets coated with uncoloured Sepifilm LP 010 were stored for 1 month under the above stress condition. It was found that tablets coated with Sepifilm LP 010 remained unchanged whereas tablets without coats or coated with a combination of HPMC and TiO₂ contained spots or had a black colour. The moisture intake of the fumitory tablets coated with Sepifilm LP 010 (5 – 10 % weight gain) was half of that intake from tablets coated with HPMC and TiO₂. This report showed that Sepifilm LP 010 seems to be suitable for being used as a protection film against moisture.

Product	Water in the product (% w/w) after a period of storage under different conditions (% r.h., °C, days)												
	r.t.	~ 50 % r.h.						~ 80 % r.h.					
		25 °C			50 °C			25 °C			50 °C		
	15	7	14	21	7	14	21	7	14	21	7	14	21
	(days)												
S	1.8	n	n	n	n	n	n	n	n	n	n	n	n
P	1.7	1.7	1.7	1.7	1.6	1.5	1.5	2.2	2.4	2.8	2.3	2.8	3.0
Z1	1.7	1.7	1.7	1.7	1.5	1.5	1.5	2.2	2.4	2.5	2.3	2.5	2.8
Z2	1.4	1.4	1.4	1.4	1.4	1.3	1.3	1.5	1.6	1.7	2.3	2.4	2.5
Z3	1.3	1.3	1.3	1.3	1.4	1.2	1.0	1.6	1.9	2.0	2.2	2.3	2.4
Z4	1.5	1.5	1.5	1.5	1.4	1.3	1.1	1.6	1.8	2.0	2.3	2.4	2.7
Z5	1.5	1.5	1.5	1.5	1.5	1.4	1.3	1.6	1.7	1.9	2.0	2.2	2.3
Z6	1.4	1.4	1.4	1.4	1.2	1.1	1.0	2.0	2.1	2.2	2.4	2.5	3.0
Z7	1.4	1.4	1.4	1.4	1.4	1.3	1.3	1.8	1.9	2.0	2.0	2.1	2.2

Table 2.13: *Percentage of water in the product after a period of storage under different conditions; P: HPMC-coated pellets; Z1: Sepifilm-coated pellets; Z2: Mowiol 3-88 coated pellets; Z3: Mowiol 3-98 coated pellets; Z4: Mowiol 4-88 coated pellets; Z5: Mowiol 4-98 coated pellets; Z6: Mowiol 8-88 coated pellets; Z7: Mowiol 10-98 coated pellets; r.t.: room temperature (22 °C, 50 % r.h.); n: not measured.*

2.4.3 Preliminary studies of layering of nicotinamide onto pellets

HPMC was used as a binder to fixed nicotinamide onto the surface of pellets. The amount of HPMC was varied between 5 - 10 % w/w to nicotinamide content. The concentration of total solid content between 5 - 20 % w/w was tested whether it can be sprayed in the layering process or not. It was found from SEM micrograph that nicotinamide was recrystallized as rods on the surface of the HPMC-coated pellets (Fig 2.28). The lowest amount of HPMC was selected to produce the Product PN. The highest concentration of 20 % w/w could not be sprayed at a rate of 1 - 2 g/min. Therefore the conditions X8 as demonstrated in Table 2.12 was chosen to prepare nicotinamide-loaded pellets.

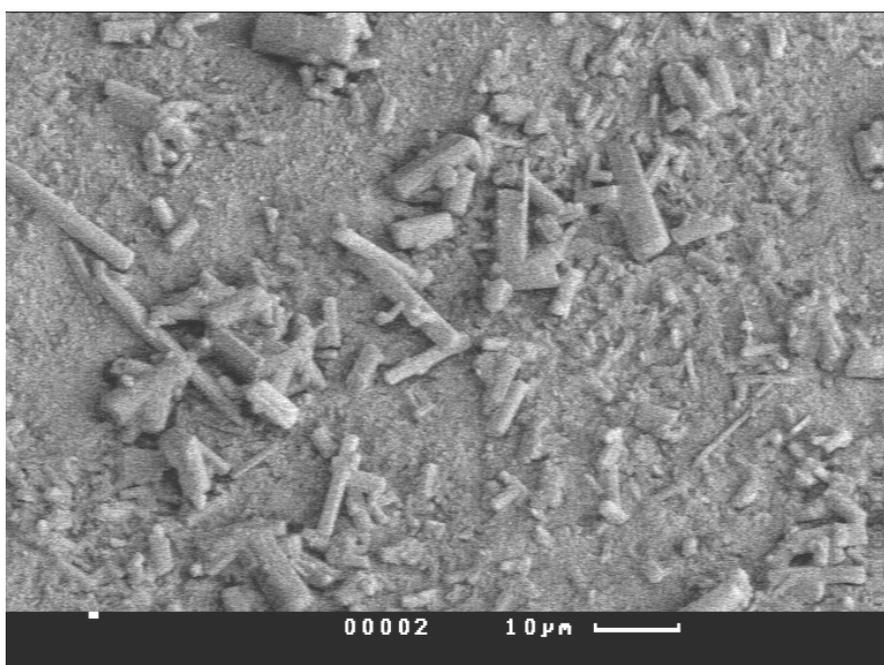


Fig 2.28: SEM-micrograph of nicotinamide recrystallized on the surface of HPMC-coated pellet.

2.4.4 Preparation of placebo

Placebo or HPMC-coated pellets (HPMC pellets) were made in order to have a thin layer of polymer that protects the inner core (sugar) from a mechanical stress and to avoid dissolution of the core surface by spraying an aqueous dispersion during the enteric coating phase. These placebos were prepared in two different sizes i.e. Product P and Product PP. They were intended for the mixture with the other products to receive the required amount of loading weight for a coating process.

2.4.4.1 Preparation of HPMC solution

As shown in the formulation R1 in Table 2.15, a 5 % w/w solution of HPMC in water was prepared from 100.0 g of Pharmacoat 603W. Purified water of about 2/3 of total weight was heated to 70 °C, before Pharmacoat 603W powder was slowly dispersed into the warm water constantly stirring with a magnetic stirrer {44}. Pharmacoat 603W was completely dissolved after the dispersion was cooled down to room temperature. The rest of the water was added to the solution to achieve a solid content of 5 % w/w.

2.4.4.2 Coating process

HPMC coated pellets (Product P or PP) were prepared by using a combination of the formulation R1 (Table 2.15) and the process number X2 (Table 2.11). The sugar spheres fraction size 1000 - 1180 µm, Product S, were cores for preparing Product P and the sugar spheres fraction size of 800 - 1000 µm were cores for preparing Product PP.

The fluidized bed apparatus containing filters collected the fine dust that occurred during the process. The loading weight was 1000 g in order to get a big batch for various further trials. Sugar spheres were used because they have almost spherical geometry and smooth surfaces. They do not show high friability so that they were suitable as cores for a coating process with a fluidized bed apparatus. The inlet processing air was first dehumidified to achieve the constant water content because the room climate was 20 °C and 60 % r.h.. The pre-warming phase was 15 min to achieve the desired temperature of the product before coating with the polymer solution. The initial spraying with water was necessary to remove static charges from the product bed during the pre-heating phase. The inlet air was heated up to a temperature of 60 °C to obtain the

product temperature of 54 °C. All the temperatures (inlet air, product bed, outlet) were varied in the range of ± 2 °C. The solution of HPMC could be well atomized by an air stream of $2.4 \text{ m}^3 \text{ h}^{-1}$. By spraying the HPMC solution at a spraying rate of 1.7 g min^{-1} into the coating chamber, the relative humidity increased from 4.3 % r.h. to 18 % r.h. which was observed from the outlet air. The process air velocity was set at about 50 - $55 \text{ m}^3 \text{ h}^{-1}$ to avoid a high formation of dust, yet allowing a good fluidization of 1000 g of pellets. The postdrying of coated products was carried out inside the fluidized bed machine at the product bed temperature of 54 °C for 15 min. Hereafter, the finished coated pellets have been further dried at room temperature over night before storage. The resulting real coating level was lower than the theoretical coating level as demonstrated in Tables 2.25 - 2.26 because of the loss as a fine dust during the process. The finished coated pellets (Product P or PP) have a white colour because of a colourless clear film, which was formed around the pellets surface. The quality control using sieve analysis showed that the product was well prepared because the fraction sizes were concentrated in the small ranges as stated in Table 2.14. These pellets were later on used as placebo while mixing with other pellets to get the required total weight for a coating batch.

The theoretical and real coating level (% w/w) can be calculated as follows;

$$\text{A theoretical coating level} = \frac{A \times B}{D}$$

$$\text{A real coating level} = \frac{100 (C - D)}{D}$$

A = concentration of a dispersion used (% w/w)

B = real weight of a dispersion used (g)

C = weight of finished coated pellets (g)

D = weight of loaded pellets (g)

Size fraction (μm)	Type of Product / (%w/w)			
	SS	PP	S	P
< 800	0.5	0.3	0.0	0.0
800 - 1000	95.3	57.3	1.2	0.0
1000 - 1120	4.2	42.3	70.5	4.6
1120 - 1250	0.0	0.1	28.3	93.3
1250 - 1400	0.0	0.0	0.0	2.1
> 1400	0.0	0.0	0.0	0.0

Table 2.14: Sieve analysis of HPMC-coated pellets compared to cores.

For example, Product P, was prepared starting with a loading weight of 1000 g cores, X2 (Table 2.11). The solution of HPMC totally used was 400.0 g which means the theoretical weight gain should be 2.0 % w/w. However, after weighing the finished coated product the real weight gain was only 1.8 % w/w (Table 2.25). For other finished products the theoretical and real weight gains can be calculated in the same way.

The amount of coating materials on the pellets was also calculated by the ratio between the amount of coating materials coated on the surface of one pellet to its surface area. This parameter was calculated as mg cm^{-2} . The amount of coating materials was calculated by weighing 100 pellets before and after coating. The surface area of pellets have been calculated from the mean diameter of one pellet basing on an image analysis method.

Formulation Ingredients	R1	R2	R3	R4	R5	R6	R7
HPMC solid (g)	100	100	3	100	-	-	-
Methyl orange (g)	-	2	-	-	-	-	-
Nicotinamide (g)	-	-	60	-	-	-	-
L-Orange Z 2010 (g)	-	-	-	2	-	-	-
Indigotin (g)	-	-	-	-	-	-	2
L-Rot Z 3020 (g)	-	-	-	-	2	-	-
L-Grün Z 6130 (g)	-	-	-	-	-	2	-
Polyvinyl alcohol (g)	-	-	-	-	-	30	100
(Aquacoat ECD liquid (g))	-	-	-	-	(333)	(333)	(100)
~ Aquacoat ECD solid (g)	-	-	-	-	100	100	30
DBS (g)	-	-	-	-	20	20	6
Concentration (% w/w)	5	5	20	5	20	20	7

Table 2.15: *Different coating formulations (R1- R7);*

R1: A 5 %w/w solution of HPMC

R2: A 5 % w/w solution of HPMC and dissolved methyl orange

R3: A 20 % w/w solution of nicotinamide and HPMC

R4: A 5 % w/w solution of HPMC with an orange colour to prepare a subcoat from HPMC

R5: A 20 % w/w dispersion of EC with a red colour to prepare a subcoat from EC

R6: A 20 % w/w dispersion of EC and PVA with a green colour to prepare a subcoat from EC and PVA (100 + 30 parts)

R7: A 7 % w/w dispersion of PVA and EC with a blue colour to prepare a subcoat from PVA and EC (100 + 30 parts)

2.4.5 Preparation of a product containing HPMC and methyl orange

This product was prepared in order to optimize the formulation and process conditions of enteric coating containing Aquacoat CPD, TEC and/or other additives. However, the varying of the enteric formulations and process conditions were based on the recommendation from the FMC <25,7> and the reasearch work of Williams and Liu <200>. The coated pellets with a primary thin layer of HPMC containing methyl orange (MO pellets) were used for the fast test of the resistance to 0.1 N HCl of the film coated above the pellets. Methyl orange as an indicator allowed the fast observation of the colour change with naked eyes without any complicated spectroscopic methods. The details of this characterization method were mentioned in 2.2.7. Figure 2.29 shows the building up of the finished products.

2.4.5.1 Preparation of a solution containing HPMC and methyl orange

As shown in Table 2.15, R2, a 5 % w/w solution of HPMC containing methyl orange was prepared from 100.0 g {16} of Pharmacoat 603W and 2.0 g {1} of methyl orange. First purified water of about 2/3 of total weight was heated to 70 °C. Pharmacoat 603W powder was slowly dispersed into the warm water constantly stirring with a magnetic stirrer {44}. Hereafter two parts of methyl orange were slowly distributed into the HPMC solution after cooling down to room temperature. The mixture was stirred until it became a gold coloured solution.

2.4.5.2 Coating process

MO pellets (Product A, Table 2.25) were prepared in accordance with the combination of the formulation number R2, Table 2.15 and the process number X13, Table 2.23. The coating process was performed using a fluidized bed apparatus inserted with filters in the same way as already mentioned. Finished coated pellets had a gold colour, which originated from methyl orange which was used as an indicator. Therefore a mixture of placebo pellets (Product P) and MO pellets (Product A) will not cause demixing or non homogeneous flow in the fluidized bed apparatus during the coating process because they have almost the same size fraction about 1120 µm.

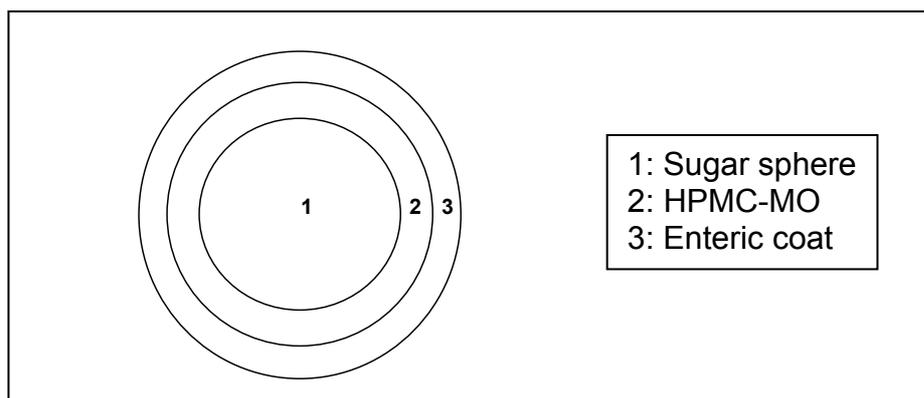


Figure 2.29: Finished enteric coated pellets with a layer containing dissolved methyl orange.

2.4.6 Preparation of products containing nicotinamide with or without a subcoat

Coated pellets containing nicotinamide for the main work were prepared with or without subcoats. Four different subcoats were used i.e. HPMC, EC, and a combination of EC and PVA at two ratios. Sugar spheres were coated first with HPMC to have a thin layer of about 10 μm . Hereafter the thin and homogeneous layer with primary nicotinamide was coated on the HPMC pellets. Each subcoat was then layered in different thicknesses. If pellets without any subcoats were required then enteric coat was directly applied on the nicotinamide loaded pellets. Figure 2.30 shows the building up of the expected finished products.

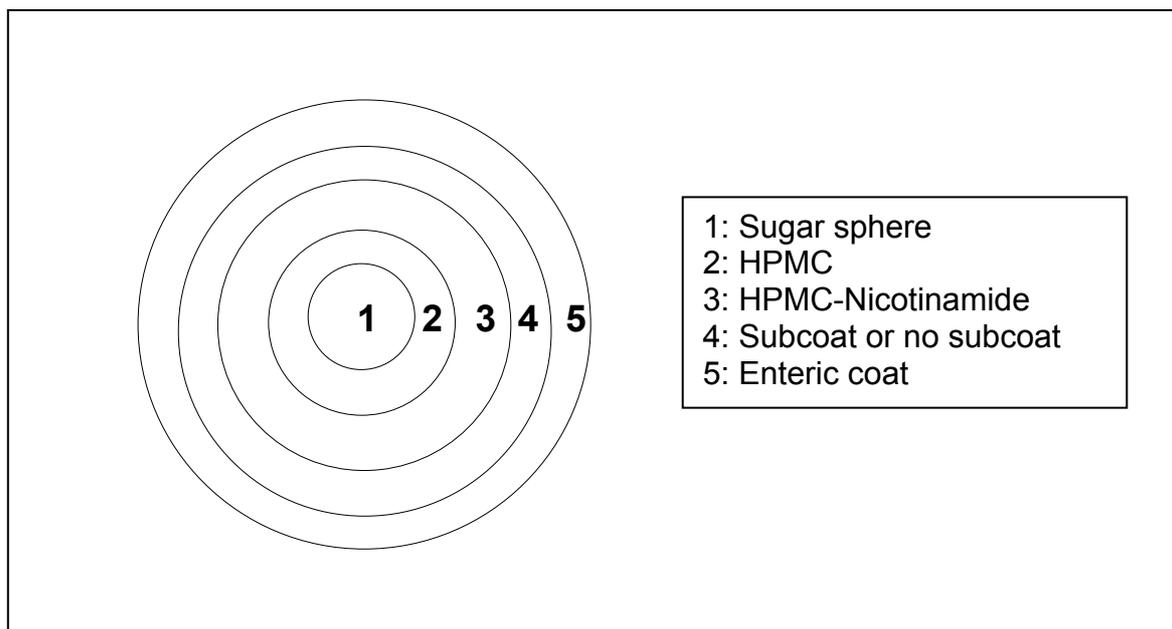


Figure 2.30: Finished enteric coated pellets containing nicotinamide and different subcoats.

2.4.6.1 The first layer: HPMC

The first layer made from HPMC was used as a mechanical protecting layer of cores. HPMC coated pellets (Product PP) were prepared from sugar spheres fraction size 800 - 1000 μm . The preparing technique of the solution, formulation R1, was as prescribed in 2.4.4.1. The product was manufactured on an Aeromatic MP-1 with inserted filters and process number X7, Table 2.12.

2.4.6.2 The second layer: Nicotinamide-HPMC

The thin layer containing nicotinamide was prepared by layering the solution containing nicotinamide and HPMC as a binder by using HPMC coated pellets (Product PP) as a loading material. These nicotinamide loaded pellets (Product AA, Aa, aA and aa) were used as a loading material to be coated with different subcoats later on. If no subcoat

was needed then these nicotinamide loaded pellets (Nico pellets) were used directly as a loading material for the coating with the dispersion containing CAP and a plasticizer.

2.4.6.2.1 Preparation of a solution containing nicotinamide

As shown in Table 2.15, R3, the 20 % w/w solution of nicotinamide and Pharmacoat 603W as a binder was prepared. Nicotinamide is a well soluble water substance and therefore it was added into water of 2/3 total amount while stirring. The small amount of 3.0 g of Pharmacoat 603W accurately weighed was slowly dispersed into the solution of nicotinamide after nicotinamide was totally dissolved while constantly stirring with a magnetic stirrer {44}.

2.4.6.2.2 Coating process

Coated pellets containing nicotinamide (Nico pellets) were prepared according to the process number X8, Table 2.12. HPMC coated pellets (Product PP, Pp, pP and pp) 500 g were used as cores to prepare four charges of Nico pellets (Product AA, Aa, aA and aa), respectively.

2.4.6.3 The third layer: Different intermediate coats (subcoats)

A subcoat from four different formulations were prepared by using Nico pellets (Product AA, Aa, aA, aa) as a loading material.

2.4.6.3.1 Subcoat from HPMC

The preparing technique of solution was almost the same as mentioned in 2.4.4.1 on basis of the formulation R4, Table 2.15. The difference was that the orange colour powder (L-orange Z 2010, part 2.1.10.3) was added into heated water. Pharmacoat 603W was added after the colour powder was totally dissolved. The process number X9, Table 2.12 and the Aeromatic MP-1 {20} with inserted filters were used for the manufacture of this product. The resulted product has an orange colour which came from the marker incorporated in the subcoat layer.

2.4.6.3.2 Subcoat from EC

2.4.6.3.2.1 Preparation of a dispersion containing Aquacoat ECD and DBS

All substances i.e., Aquacoat ECD, DBS and red colour powder were exactly weighed using a digital balance {17}. 20.0 g of DBS was added into 333.0 g of Aquacoat ECD-30 while constantly stirring with a magnetic stirrer {43}. After DBS was homogeneous dispersed i.e. about 15 min, 2 g of red colour powder (L-Rot Z 3020, part 2.1.10.2) was added. Finally the rest amount of water was added into the dispersion to receive the concentration of 20 % w/w. Further mixing for at least one hour followed. The dispersion was filtered through the 100 µm sieve before use as a coating dispersion and the constant stirring {43} of the dispersion during the coating process was performed.

2.4.6.3.2.2 Coating process

The formulation R5, Table 2.15 and the process number X10, Table 2.12 and the Aeromatic MP-1 with inserted filters served for the production. The resulted product has a pink colour.

2.4.6.3.3 Subcoat from E&P

2.4.6.3.3.1 Preparation of a dispersion containing Aquacoat ECD and PVA

All substances i.e., Aquacoat ECD, DBS, Mowiol 4-98 and green colour powder were exactly weighed on a digital balance {16,1}. The first liquid was prepared by adding 2.0 g of green colour powder (L-Grün Z 6130, 2.1.10.4) into 1/3 of total required amount of water which hereafter was heated to 80 °C. 30.0 g of Mowiol 4-98 was slowly added into this heated water while constantly stirring {44}. The second liquid was prepared by adding 20.0 g of DBS into 333.0 g of Aquacoat ECD-30 while constantly stirring with a magnetic stirrer {43}. After DBS was homogeneously dispersed i.e. about 15 min, the first liquid containing green colour was added into the white coloured dispersion while constantly stirring. The rest amount of water was added into the dispersion to receive the concentration of 20.0 % w/w. Further mixing for at least one hour followed {43}. The

dispersion was filtered through the 100 µm sieve before coating and the constant stirring {43} of the dispersion during the coating process was performed.

2.4.6.3.3.2 Coating process

This product was manufactured on the basis of the formulation R6, Table 2.15 and the process number X11, Table 2.12 using Aeromatic MP-1 with inserted filters. The resulted product had a green colour.

2.4.6.3.4 Subcoat from P&E

2.4.6.3.4.1 Preparation of a dispersion containing PVA and Aquacoat ECD

All substances i.e., Mowiol 4-98, Aquacoat ECD, DBS and blue colour powder (Indigotin, 2.1.10.1) were exactly weighed on a digital balance {16,1}. The first liquid was prepared by adding 2 g of blue colour powder into 1/3 of total required amount of water which was then heated up to 80 °C. 100.0 g of Mowiol 4-98 were slowly added into this heated water while constantly stirring {44}. The second liquid was prepared by adding 6.0 g of DBS into 100.0 g of Aquacoat ECD-30 while constantly stirring with a magnetic stirrer {43}. After DBS was homogeneously dispersed i.e. about 15 min, the first liquid containing blue colour was added into the white coloured dispersion while constantly stirring. The rest amount of water was added into the dispersion to receive the concentration of 7.0 % w/w. Further mixing for at least one hour followed. The dispersion was filtered through the 100 µm sieve before use as a coating dispersion and the constant stirring of the dispersion during the coating process was performed.

2.4.6.3.4.2 Coating process

The product was manufactured according to the formulation R7, Table 2.15 and the process number X12, Table 2.12 using Aeromatic MP-1 with inserted filters. The finished coated product has a blue colour.

2.4.7 Preliminary studies of enteric coating with CAP and different plasticizers.

The dispersion of cellulose acetate phthalate was prepared from Aquateric or Aquacoat CPD. As mentioned by the supplier, Aquateric needs more plasticizer than Aquacoat CPD and therefore the formulation of the coating dispersion was prepared basing on the recommendation. Diethyl phthalate (DEP) and dibutyl sebacate (DBS) and triethyl citrate (TEC) were used as a plasticizer in the enteric coating formulation. The formulations and coating conditions were modified on bases of the publications <200,31,25,7,9>. The concentration of the dispersion was varied from 10 to 20 % w/w and the highest concentration that allowed good conditions of coating was chosen. After tests of different spraying rates the highest one which did not cause agglomerations was chosen.

2.4.7.1 Enteric coating of pellets using Aquateric

Aquateric was the powder product which can be used as an enteric film-forming agent as already detailed in 2.1.6.1. This product was in the market since long and therefore it was used to compare the result with formulations using Aquacoat CPD-30 which was the new ready-to-use 30 %w/w dispersion. The preparing technique of the dispersion and the process conditions were modified from the recommended ones <9>.

a) Preparation of an enteric coating dispersion by using Aquateric

All substances were accurately weighted on a digital balance {16,1}. Tween 80 was added as emulsifier to about 2/3 of total amount of purified water and mixed for 5 min. Plasticizer was slowly added into the above mentioned solution and further mixed for 15 min. Aquateric powder was slowly added by using a magnetic stirrer {43} and mixed over night without heating or cooling. Purified water was added afterwards to obtain a required concentration. Further mixing for about 30 min followed. The dispersion was filtered through the 100 µm sieve before use as a coating dispersion and the constant stirring of the dispersion during the coating process was performed.

2.4.7.2 Enteric coating of pellets using Aquacoat CPD-30

Aquacoat CPD-30 was used as an enteric film-forming polymer because it is a new product containing CAP. The ready-to-use 30 % w/w dispersion is already mentioned before in 2.1.6.2. Therefore it is interesting to compare the result with Aquateric which needed more steps and substances (e.g Tween 80) to prepared the dispersion. The preparing technique of the dispersion and the process conditions were modified from the recommended ones <7>.

a) Preparation of an enteric coating dispersion from Aquacoat CPD and other additives

If any other additional substances should be added e.g. talc, magnesium stearate, PVA etc. the following modified method should be used. The first dispersion containing Aquacoat CPD was prepared by moderately stirring {43} the dispersion of Aquacoat CPD while a plasticizer e.g. DEP, DBS or TEC was slowly added and further stirring of about 15 min was required. The second dispersion was prepared from water with or without Poloxamer 407 as a medium for dispersing magnesium stearate (Mgst) or talc with a mixer {46}. These two dispersions were mixed together by pouring the second dispersion to the CAP-dispersion while constantly mixing. Water was added to bring the required concentration with additional mixing over night. The plasticized dispersions of Aquacoat CPD were sieved through a 100 µm sieve prior to coating and they were continuously mixed {43} during the coating process.

2.4.7.3 Enteric coating process of pellets containing nicotinamide

The white pellets containing nicotinamide (Product PN, part 2.4.3) were used in different trials to find out the optimum condition for the enteric coated process applying formulations containing Aquacoat CPD and plasticizer. The pink coloured placebo pellets were mixed with nicotinamide-loaded pellets (Product PN) to reach a loading weight for the coating process in different trials. The mixture of these pellets was coated with different CAP aqueous dispersions (PR1 – PR18) as demonstrated in Tables 2.16-2.19.

Composition / Coating conditions	PR1	PR2	PR3	PR4	PR5
Aquateric (g)	-	-	-	50	60
Aquacoat CPD (g)	527	150	283	-	-
Polymer solid (g)	158	45	85	50	60
DEP (% w/w to polymer)	20	20	20	10	40
DBS (% w/w to polymer)	-	-	-	-	-
TEC (% w/w to polymer)	-	-	20	-	-
Triacetin (% w/w to polymer)	-	-	-	20	-
Tween80 (% w/w to polymer)	-	-	-	1	1
Concentration (% w/w)	20	15	15	15	20
Load (g)	1000	900	850	850	400
Material	PN	PN	PN	PN	PN
Atomizing pressure (m ³ /h)	2.9	2.9	2.9	2.8	2.7
Orifice diameter (mm)	1.2	1.2	1.2	1.2	1.2
Distance from bottom to column (mm)	0.8	0.8	0.8	0.8	0.8
Perforated bottom (% free holes)	20	20	20	20	20
Pre-warming (min)	15	15	15	15	15
with dehumidifying device (y/n)	y	y	y	y	y
with cyclone (y/n)	n	n	n	n	n
Room temp/humidity (°C, % r.h.)	25, 35	25, 34	24, 30	24, 29	25, 25
Inlet temp (°C)	35	35	35	50	50
Product Temp (°C)	34	34	34	45	45
Outlet temp (°C)	34	34	34	45	45
Outlet humidity (% r.h.)	25	25	25	20	20
Spraying rate (g/min)	1.7	1.7	1.7	1.7	1.7
Initial spray	water	water	water	water	water
Process with stop (y/n)	y	y	y	y	y
Air flow (m ³ /h)	60-65	60-65	60-65	60-65	55-60
Postdrying in machine (°C, min)	35, 30	50, 30	35, 40	50, 60	60, 30
Postdrying temp/time outside machine (°C, h)	30, 24	50, 24	50, 24	22, 24	50, 24
Coating amount (% w/w)	10	10	10	10	10

Table 2.16: Composition and coating conditions of coating processes with aqueous dispersions of CAP and DEP (PR1 - PR5).

2.4.7.3.1 Discussion of preliminary studies of coating processes of pellets with CAP and DEP

PR1

It was found that the partition part between the Wurster column and the perforated bottom of 0.8 mm seemed to be suitable. The product bed temperature was kept at about 34 °C, spraying rates were varied from 1.3 - 1.8 g/min. The air volume was about 60 m³/h. It was found that the flow of the loading product in the coating apparatus was not continuous because there were big holes inbetween the product bed during the spraying of the coating material. The finished coated product was further dried in a hot

air oven at 30 °C overnight. However, the coated products after drying overnight were not resistant to the artificial gastric fluid.

PR2

The smaller concentration of the dispersion was tested to see whether the flow pattern was improved or not. There was no significant difference between the polymer concentration in flow pattern. The higher curing temperature did not improve the structure of the coated pellets as well. The surface still contained crack and non-coalesced particles. The coated pellets did not resist to 0.1 N HCl.

PR3

The addition of another the plasticizer (TEC) was experimented. However, the coated pellets after curing stucked together. This may be due to the high amount of plasticizer mixture which will have a high efficiency to reduce the MFFT and Tg.

PR4

The combination of plasticizers (DEP and Triacetin) were also tested. The coated pellets after curing also stucked together.

PR5

The higher amount of DEP at 40 % w/w to Aquateric solid content was tested. The coated pellets, however, were not resistant to 0.1 N HCl which may be due to the incomplete coalescence.

PR6

The lower product bed temperature of about 27 °C and the higher spraying rate of 2.8 g/min to increase the relative humidity during coating process was tested. The coated pellets were not resistant to 0.1 N HCl.

PR7

The higher product bed temperature of about 41 °C was used to increase the coalescence. The structure of film still contained cracks.

Composition / Coating conditions	PR6	PR7	PR8	PR9	PR10
Aquateric (g)	150	300	87	30	50
Aquacoat CPD (g)		-	-	-	-
Polymer solid (g)	150	300	87	30	50
DEP (% w/w to polymer)	35	35	35	35	35
DBS (% w/w to polymer)	-	-	-	-	-
TEC (% w/w to polymer)	-	-	-	-	-
PVA (% w/w to polymer)					
Talc (% w/w to polymer)	-	-	10	-	-
Tween80 (% w/w to polymer)	1	1	1	1	1
Concentration (% w/w)	20	20	20	15	20
Load (g)	360	350	300	100	100
Material	PN	PN	PN	PN	PN
Atomizing pressure (m ³ /h)	2.6	2.6	2.6	2.2	2.2
Orifice diameter (mm)	1.2	1.2	1.2	1.2	1
Distance from bottom to column (mm)	0.8	0.8	0.8	1	1
Perforated bottom (% free holes)	13	13	13	Uniglatt	Uniglatt
Pre-warming (min)	15	15	15	15	15
with dehumidifying device (y/n)	y	y	y	n	n
with cyclone (y/n)	n	n	n	y	y
Room temp/humidity (°C, % r.h.)	24, 30	24, 28	24, 24	-	-
Inlet temp (°C)	35	50	35	65	73
Product Temp (°C)	27	41	30	63	66
Outlet temp (°C)	27	40	30	60	64
Outlet humidity (% r.h.)	35	20	31	-	-
Spraying rate (g/min)	2.8	2.8	2.8	1.7	1.7
Initial spray	water	water	water	water	water
Process with stop (y/n)	y	y	y	n	n
Air flow (m ³ /h)	30-35	30-35	30-35	30%	30%
Postdrying in machine (°C, min)	60, 30	30, 20	35, 20	70, 60	80, 60
Postdrying temp/time outside machine (°C, h)	35, 24	35, 24	35, 24	50, 24	50, 24
Coating amount (% w/w)	10	10	10	10	10

Table 2.17: Composition and coating conditions of coating processes with aqueous dispersions of CAP and DEP (PR6 - PR10).

PR8

Talc was added to the coating formulation to improve the resistance to 0.1 N HCl but the coated pellets were not resistant to gastric fluid. This may be due to the incomplete coalescence.

PR9 - PR10

The higher product bed temperatures of about 63 - 66 °C were investigated by using the small scale fluidized bed apparatus {19}. The coated pellets were not resistant to 0.1 N HCl.

Composition / Coating conditions	PR11	PR12	PR13	PR14
Aquateric (g)	200	30	30	30
Aquacoat CPD (g)	-	-	-	-
Polymer solid (g)	200	30	30	30
DEP (% w/w to polymer)	40	40	40	40
DBS (% w/w to polymer)	-	-	-	-
TEC (% w/w to polymer)	-	-	-	-
PVA (% w/w to polymer)	-	20	5	5
Tween80 (% w/w to polymer)	1	1	1	1
Concentration (% w/w)	20	15	15	15
Load (g)	100	100	100	280
Material	PN	PN	PN	PN
Atomizing pressure (m ³ /h)	2.2	2.2	2.2	2.6
Orifice diameter (mm)	1	1	1	1.2
Distance from bottom to column (mm)	1	1	1	0.8
Perforated bottom (% free holes)	Uniglatt	Uniglatt	Uniglatt	13
Pre-warming (min)	15	15	15	15
with dehumidifying machine (y/n)	n	n	n	y
process with Uniglatt	y	y	y	n
Room temp/humidity (°C, % r.h.)	-	-	-	24, 25
Inlet temp (°C)	55	55	54	50
Product Temp (°C)	51-53	54	53	45
Outlet temp (°C)	50-52	51	52	45
Outlet humidity (% r.h.)	-	-	-	19
Spraying rate (g/min)	1.7	1.7	0.8	1.7
Initial spray	water	water	water	water
Process with stop (y/n)	n	n	n	y
Position at Uniglatt (%) or air flow (m ³ /h)	55%	50%	35%	35
Postdrying in machine (°C, min)	60, 30	50, 60	50, 60	50, 60
Postdrying temp/time outside machine (°C, h)	50, 24	50, 24	50, 24	50, 24
Coating amount (% w/w)	10	10	10	10

Table 2.18: Composition and coating conditions of coating processes with aqueous dispersions of CAP and DEP (PR11 - PR14).

PR11

The lower product bed temperatures of about 51 - 53 °C were tested in Uniglatt {19} but the coated pellets were not resistant to 0.1 N HCl.

PR12

The addition of PVA as a additional plasticizer was tested, but there was high agglomeration because of sticking of pellets during coating process.

PR13 – PR14

The concentration of PVA was reduced to 5 % w/w. The product bed temperatures were between 45 - 53 °C, but the coated pellets were not resistant to 0.1 N HCl.

2.4.7.3.2 Discussion of preliminary studies of coating processes of pellets with CAP and DBS

PR15

The product bed temperature was kept lower than 35 °C. The spraying rate was high at about 2.8 g/min. It was found that there were holes in between the product bed inside the product container during the coating process. The flow pattern was not continuous. This means the possibility to improve the flow pattern should be found. Moreover, the structure of the coated pellets was not homogeneous. Many uneven regions were distributed around the surface of the pellets. The coated pellets were not resistant to 0.1 N HCl.

PR16

Talc was added into the formulation to improve the resistance to 0.1 N HCl and therefore the amount of DBS was increased. However, the coated pellets were not resistant to 0.1 N HCl.

PR17

A higher product bed temperature and less atomizing pressure was tested. The curing after coating process was performed at 50 °C for 24 h. The coated pellets were not resistant to 0.1 N HCl as well. The structure of film still unhomogeneous with uneven regions.

PR18

The higher product bed temperature of 45 °C was tested. PVA was added to have a combination of two plasticizers (water-soluble and water-insoluble plasticizer). The curing was performed at high temperature of 50 °C inside the coating apparatus to avoid agglomeration at high temperature. The spraying rate was reduced because the formulation containing PVA tended to cause sticking during the coating process.

Composition / Coating conditions	PR15	PR16	PR17	PR18
Aquateric (g)	100	100	100	100
Aquacoat CPD (g)	-	-	-	-
Polymer solid (g)	100	100	100	100
DEP (% w/w to polymer)	-	-	-	-
DBS (% w/w to polymer)	35	40	35	30
TEC (% w/w to polymer)	-	-	-	-
PVA (% w/w to polymer)	-	-	-	10
Talc (% w/w to polymer)	-	10	-	-
Tween80 (% w/w to polymer)	1	1	1	1
Concentration (% w/w)	25	25	20	20
Load (g)	300	300	300	300
Material	PN	PN	PN	PN
Atomizing pressure (m ³ /h)	2.6	2.6	2.2	2.6
Orifice diameter (mm)	1.2	1.2	1.2	1.2
Distance from bottom to column (mm)	0.8	0.8	0.8	0.8
Perforated bottom (% free holes)	13	13	13	13
Pre-warming (min)	15	15	15	15
with dehumidifying device (y/n)	y	y	y	y
with cyclone (y/n)	n	n	n	n
Room temp/humidity (°C, % r.h.)	24, 25	24, 25	23, 25	24, 25
Inlet temp (°C)	35	35	40	50
Product Temp (°C)	30	30	35	45
Outlet temp (°C)	30	30	35	45
Outlet humidity (% r.h.)	29	29	26	18
Spraying rate (g/min)	2.8	2.8	2.8	1.7
Initial spray	water	water	water	water
Process with stop (y/n)	y	y	y	y
Air flow (m ³ /h)	50	50	50	50
Postdrying in machine (°C, min)	60, 60	60, 60	40, 30	50, 60
Postdrying temp/time outside machine (°C, h)	25, 24	25, 24	50, 24	25, 24
Coating amount (% w/w)	40	40	40	40

Table 2.19: Composition and coating conditions of coating processes with aqueous dispersions of CAP and DBS (PR15 - PR18).

2.4.7.4 Enteric coating process of pellets containing methyl orange

The gold-yellow pellets were used in different trials to find out the optimum condition for the enteric coated process applying formulations containing Aquacoat CPD and TEC. The white coloured placebo pellets (Product P) were mixed with orange coloured MO-loaded pellets (Product A) to reach a loading weight for the coating process in different trials. The mixture of these pellets was coated with different CAP aqueous dispersions (PR19 - PR30) as demonstrated in Table 2.20 - 2.21.

2.4.7.4.1 Discussion of preliminary studies of coating processes of pellets with CAP and TEC.

Williams and Liu <200> have studied the effect of process conditions to the finished CAP-coated pellets. The parameters that they studied were as follows; the outlet temperatures of 36 or 48 °C, the spray rates of 2 or 3.2 g/min and the fluidizing air velocities of 50 or 90 m³ h⁻¹. They used 250 g of theophylline pellets as cores and the coating process was performed in a fluidized-bed coater assembled with a Wurster insert. The 1.2 mm spray nozzle was inserted and the atomizing pressure was adjusted at 1.5 bar. The core pellets were coated with aqueous dispersions containing two levels of plasticizer DEP i.e. 30 and 35 %.

PR19

The coating process with a high loading weight of about 900 g was performed and the product bed temperature was kept at about 34 °C. The spraying rate was at 1.5 g/min. The air flow was set at about 60 m³/h so that the flow pattern of pellets was not higher than the upper edge of the product container. It was found that big holes occurred within the product bed during the coating process. There was a high amount of twins or agglomerations of coated pellets. It took a long time until the coating level was achieved. Therefore it should be tested whether the coating process can be performed with a smaller loading amount or not. At the coating amount of 16 % w/w the coated pellets were not resistant to 0.1 N HCl.

PR20

The smaller loading amount was tested and it was possible to perform the coating process with the loading amount of about 100 - 400 g. The higher product bed temperature of 45 °C was tested and the spraying rate was at 1.5 g/min. The air flow was adjusted so that the flow pattern was not higher than the upper edge of the product container. There was a high amount of fine dust which accumulated at the filters. These coated pellets were also not resistant to 0.1 N HCl.

Composition / Coating conditions	PR19	PR20	PR21	PR22	PR23	PR24
Aquateric (g)	-	40	60	-	-	-
Aquacoat CPD (g)	808	-	-	200	200	200
Polymer solid (g)	129	40	60	60	60	60
DEP (% w/w to polymer)	-	-	-	-	-	-
DBS (% w/w to polymer)	-	-	-	-	-	-
TEC (% w/w to polymer)	25	35	35	25	25	25
Triacetin (% w/w to polymer)	-	-	-	-	-	-
Talc (% w/w to polymer)	-	-	-	-	-	-
Mgst (% w/w to polymer)	-	-	-	-	10	10
Poloxamer (% w/w to Mgst)	-	-	-	-	1	1
EC (% w/w to polymer)	-	-	-	-	-	-
Tween80 (% w/w to polymer)	-	1	1	-	-	-
Concentration (% w/w)	15	20	20	15	15	15
Load (g)	870	370	360	300	300	300
Material	MO	MO	MO	MO	MO	MO
Atomizing pressure (m ³ /h)	2.8	2.9	2.6	2.6	2.6	2.6
Orifice diameter (mm)	1.2	1.2	1.2	1.2	1.2	1.2
Distance from bottom to column (mm)	0.8	0.8	0.8	0.8	0.8	0.8
Perforated bottom (% free holes)	20	13	13	13	13	13
Pre-warming (min)	15	15	15	15	15	15
with dehumidifying device (y/n)	y	y	y	y	n	n
with cyclone (y/n)	n	n	n	n	n	n
Room temp/humidity (°C, % r.h.)	25, 34	25, 26	25, 26	23, 31	21, 59	20, 60
Inlet temp (°C)	35	50	35	40	40	50
Product Temp (°C)	34	45	33	35	36	45
Outlet temp (°C)	34	45	33	35	36	45
Outlet humidity (% r.h.)	26	20	28	21	31	23
Spraying rate (g/min)	1.5	1.5	1.8	1.8	1.8	1.8
Initial spray	water	water	water	air	air	air
Process with stop (y/n)	y	y	y	y	y	y
Air flow (m ³ /h)	60	40	44	45	55	55
Postdrying in machine (°C/min)	50, 40	50, 30	60, 15	35, 15	36, 15	45, 15
Postdrying temp/time outside machine (°C, h)	50, 48	50, 3	22, 24	22, 24	22, 24	22, 24
Coating amount (% w/w)	16	20	33	7 - 22	5	8

Table 2.20: Composition and coating conditions of coating processes with aqueous dispersions of CAP and TEC (PR19 – PR24); MO: Product A (Table 2.25).

PR21

The atomizing pressure was reduced to 2.6 m³/h and the product bed temperature was reduced to about 33 °C in order to avoid spray drying which means a high loss of coating materials. Though there was a high amount of coating materials the coated pellets were not resistant to 0.1 N HCl.

PR22

The coating formulation contained TEC (25 % to Aquacoat solid content) as a plasticizer. This coating process (PR22) was performed and then compared to the coating process using Aquateric and TEC (PR21). The postdrying was performed at the product bed temperature because it was recommended not to use high temperatures <360>. The resistance test was not satisfactory as well.

PR23

The dehumidifying device was not used because the coating process at a higher relative humidities should be performed. The incorporation of magnesium stearate was tested whether it can hinder the formation of the agglomerations or not. It was found that a smaller amount of agglomerates was formed but non-coalesced polymer particles were presented under the SEM.

PR24

The higher product bed temperature of 45 °C was used in order to improve the formation of the well coalesced continuous film, but the non-coalesced polymer particles were presented under the SEM as well.

PR25

The process number PR25 (Table 2.21), was performed with a low product temperature of 32 °C and low air velocity of 50 - 55 m³ h⁻¹. The spraying rate was kept low of 0.8 g/min to avoid agglomerations and uncontinuous flow of product bed inside the container, but this condition still caused a high agglomeration of the pellets and then a formation of holes in the outer CAP film layer. The agglomeration of pellets (twins or groups of more than two pellets) caused defects of the CAP films when they separated from each other. The film defect can be clearly seen under a light microscope.

PR26

The same condition with a higher product bed temperature of 55 °C, the process number PR26, Table 2.21 was performed in order to observe the affect of the higher temperature though it was not recommended <25,200>. The problem of a blockage of the spraying nozzle occurred. For this reason the high process temperature was not further investigated.

Composition / Coating conditions	PR25	PR26	PR27	PR28	PR29	PR30
Aquateric (g)	-	-	-	-	-	-
Aquacoat CPD (g)	200	200	200	217	100	167
Polymer solid (g)	60	60	60	65	30	50
DEP (% w/w to polymer)	-	-	-	-	-	-
DBS (% w/w to polymer)	-	-	-	-	-	-
TEC (% w/w to polymer)	25	25	25	54	25	25
Triacetin (% w/w to polymer)	-	-	-	-	-	-
Talc (% w/w to polymer)	-	-	-	-	-	-
Mgst (% w/w to polymer)	-	-	-	-	-	-
Poloxamer (% w/w to Mgst)	-	-	-	-	-	-
EC (% w/w to polymer)	-	-	-	-	-	-
Tween80 (% w/w to polymer)	-	-	-	-	-	-
Concentration (% w/w)	15	15	15	15	15	15
Load (g)	250	250	250	250	250	100
Material	MO	MO	MO	MO	MO	MO
Atomizing pressure (m ³ /h)	2.6	2.6	3.5	3.5	2.6	2.6
Orifice diameter (mm)	1.2	1.2	1.2	1.2	1.2	1.2
Distance from bottom to column (mm)	0.8	0.8	0.8	0.8	0.8	0.8
Perforated bottom (% free holes)	13	13	13	13	13	8
Pre-warming (min)	15	15	15	15	15	15
with dehumidifying machine (y/n)	n	n	n	n	n	n
with cyclone (y/n)	n	n	n	n	n	n
Room temp/humidity (°C, % r.h.)	22, 45	23, 45	22, 39-43	21, 39	21, 45-53	24, 46-65
Inlet temp (°C)	35	60	35	37	35	35
Product Temp (°C)	32	55	33	35	32	32
Outlet temp (°C)	32	52	31	32	32	32
Outlet humidity (% r.h.)	25	20	27-32	25	30-41	35-45
Spraying rate (g/min)	0.8	0.8	0.8	0.8	0.8	0.8
Initial spray	air	air	air	air	air	air
Process with stop (y/n)	y	y	y	y	y	y
Drying in glatt (°C, min)	-	-	-	-	-	32, 60
Air flow (m ³ /h)	50-55	50-55	80-90	90-95	90-95	93-95
Postdrying in machine (°C/min)	32, 15	55, 15	33, 10	35, 15	32, 15	32, 15
Postdrying temp/time outside machine (°C, h)	22, 24	22, 24	22, 24	22, 24	22, 24	22, 24
Coating amount (% w/w)	10	10	8 - 20	5	5 - 11	5 - 30

Table 2.21: Composition and coating conditions of coating processes with aqueous dispersions of CAP and TEC (PR25 – PR30); MO: Product A (Table 2.25).

PR27

The higher air flow of about 90 m³/h was used in order to avoid agglomerations. The atomizing pressure (about 1.5 bar) as mentioned in the work of Williams and Liu <200> was used. The product bed temperature was kept at about 33 °C. Spraying rates higher than 0.8 g/min were not used in order to avoid a formation of agglomerations. It was found that a high amount of fine dust was formed because of spray drying. The film thickness was varied from 8 to 20 % w/w. Even with the highest thickness the coated

pellets were not resistant to 0.1 N HCl. The release of methyl orange achieved 100 % less than 30 min. The uncoalesced polymer particles can be observed under the SEM.

PR28

The coating formulation was varied by increasing the concentration of the plasticizer to 54 % w/w in order to observe whether the high concentration of TEC can improve the film formation or not. The comparison with the coating process C35 was performed. However, the uncoalesced polymer particles still occurred.

PR29

Because of a high amount of fine dust in PR27 and PR28 a reduction of an atomizing pressure was tested. It was found that less amount of fine dust was formed in the process using atomizing pressure of 2.6 m³/h at the same product bed temperature of about 32 °C. However, the coated pellets were not resistant to 0.1 N HCl.

PR30

The smaller loading amount of 100 g was tested and the smaller perforated bottom plate was used to adjust the flow pattern. As the fine dust was accumulated at the filters, the coating process had therefore to be interrupted after a certain time (about 70 min) and it was necessary to change the filters. The product was further dried inside a small scale of a fluidized bed apparatus during the cleaning process.

In summary, it was found that the coating process at the almost high atomizing pressure of 1.5 bar (about 3.5 m³/h) and a high air velocity of 90 m³/h caused a spray-drying which produced a lot of fine dust during the process. The spray rate of 2 to 3 g/min cannot be used in the process running with 100 g loading pellets because of agglomerations of coated pellets during the coating process after a short time of coating. Therefore only the spraying rate of 0.8 g/min was used further in this present study. However, the pellets stucked together during the coating process at the lower air velocity. They were separated from each other during the flowing phase, which will cause a defect of film around the surface. The formation of holes can be seen under a light microscope (data not shown).

2.4.8 Main part of studies

Products containing nicotinamide with or without subcoats were used as a loading material. In some cases pellets containing methyl orange were also incorporated as a loading material. Resulted products are shown in Table 2.25 to 2.30.

2.4.8.1 Enteric coating of pellets using Aquateric and DEP

The particular preparing technique of the dispersion and the coating conditions were as follows.

a) Preparation of an enteric coating dispersion

All substances were accurately weighted on a digital balance {16,1}. 1.0 g of Tween 80 was added as emulsifier to about 2/3 of total amount of purified water and mixed for 5 min. 35.0 g of DEP was slowly added into the above mentioned solution and further mixed for 15 min. 100.0 g of Aquateric powder was slowly added by using a magnetic stirrer {43} and mixed over night without heating or cooling. Purified water was added afterwards to obtain a concentration of 20.0 % w/w. Further mixing for about 30 min followed. The dispersion was filtered through the 100 µm sieve before use as a coating dispersion and the constant stirring of the dispersion during the coating process was performed.

b) Enteric coating process of pellets containing nicotinamide and subcoats

The Aeromatic MP-1 with inserted filters, the formulation R9, Table 2.22 and the process number X17, Table 2.23 served for this production. The loading material in this process was the mixture of five different products i.e. placebo (Product P), pellets containing nicotinamide and HPMC as a subcoat (Product DD), pellets containing nicotinamide and EC as a subcoat (Product Ee), pellets containing nicotinamide and E&P as a subcoat (Product cC), and pellets containing nicotinamide and P&E as a subcoat (Product bb).

The finished coated pellets were divided into two groups. One half of it was mixed with 0.5 % w/w of Aerosil 200 to avoid sticking during the storage before the dissolution test

was performed. Another half was stored without Aerosil 200 for use as products for the analysis of thickness, morphology, weight, etc. The enteric coated pellets still contained their different colours from the markers incorporated in the subcoat layer and therefore after finishing the coating process they could be separated from each other by manual selection. These selected enteric coated pellets were used for further characterizations.

2.4.8.2 Enteric coating of pellets using Aquateric and DBS

a) Preparation of an enteric coating dispersion

Formulation R8, as shown in Table 2.22 was prepared by accurately weighing all the substances on a digital balance {16,1}. 1.0 g of Tween 80 was added as emulsifier to about 2/3 of total amount of purified water and mixed for 5 min. 35.0 g of DBS was slowly added into the above mentioned solution and further mixed for 15 min. The further procedure is the same as already mentioned in 2.4.8.1.

b) Enteric coating process of pellets containing nicotinamide and subcoats

The formulation R8, Table 2.22, the process number X17, Table 2.23 and the Aeromatic MP-1 with inserted filters were used for the production. The mixture of products as mentioned in 2.4.8.1 was used as loading material. The finished coated pellets were divided into two groups i.e. with and without 0.5 % w/w of Aerosil 200. These finished enteric coated pellets were manually selected in different colours before they were used for further characterizations.

c) Enteric coating process of pellets containing nicotinamide without any subcoats

The formulation R8, Table 2.22, the process number X22, Table 2.24 and the Aeromatic MP-1 with inserted filters were used for the production. The loading material was the mixture of the orange coloured pellets (Product A) and nicotinamide loaded pellets (Product aA). The finished coated pellets were divided into two groups i.e. with and without 0.5 % w/w of Aerosil 200. These finished enteric coated pellets were manually selected in different colours before they were used for further characterizations.

2.4.8.3 Enteric coating of pellets using Aquacoat CPD and DEP

The particular preparing technique of the dispersion and the coating conditions were as follows.

a) Preparation of an enteric coating dispersion

Formulation R10, as shown in Table 2.22 was prepared by moderately mixing the dispersion of Aquacoat CPD with a magnetic stirrer {43} while 2/3 of total amount of water was added. 30.0 g of DEP accurately weighed {16} was slowly added to the dispersion by stirring for about 15 min. This dispersion was stirred over night. Then purified water was added to bring the total solids content to the required concentration of 16.0 % w/w with additional mixing for at least 15 min. The dispersion was filtered through the 100 µm sieve before use as a coating dispersion and the constant stirring of the dispersion during the coating process was performed.

b) Enteric coating process of pellets containing nicotinamide and subcoats

The formulation R10, Table 2.22, the process number X17, Table 2.23, and the Aeromatic MP-1 with inserted filters were used for the production. The mixture of products as mentioned in 2.4.8.1 was the loading material. The finished coated pellets were divided into two groups i.e. with and without 0.5 % w/w of Aerosil 200. These finished enteric coated pellets were manually selected in different colours of subcoats before they were used for further characterizations.

c) Enteric coating process of pellets containing nicotinamide without any subcoats

The formulation R10, Table 2.22, the process number X22, Table 2.24 and the Aeromatic MP-1 with inserted filters were used for the production. The loading material was a mixture of the orange coloured (Product A) and the white coloured nicotinamide loaded pellets (Product aA). The finished coated pellets were also divided into two groups i.e. with and without 0.5 % w/w of Aerosil 200. These finished enteric coated

pellets were manually selected in different colours before they were used for further characterizations.

2.4.8.4 Enteric coating of pellets with Aquacoat CPD, TEC and/or additives

The coating conditions mostly based on the work of Williams and Liu <200> and the recommendation of the specialist of FMC <25>. These details were already mentioned in 1.2.

a) Preparation of an enteric coating dispersion from Aquacoat CPD and TEC

Formulation R11, as shown in Table 2.22 was prepared by moderately mixing the dispersion of Aquacoat CPD with a magnetic stirrer {43} while 2/3 of total amount of water was added. 25.0 g of TEC accurately weighed {16} was slowly added to the dispersion by stirring for about 15 min. This dispersion was stirred over night and then purified water was added to bring the total solid content to the required concentration of 15.0 % w/w with additional mixing for at least 15 min. The further procedure is the same as already mentioned in 2.4.8.1.

b) Preparation of an enteric coating dispersion from Aquacoat CPD, TEC and other additives

If any other additional substances should be added e.g. the following modified formulations number R12 and R13 (Table 2.22) should be used.

For the formulation R12, the first dispersion of Aquacoat CPD was moderately stirred {43} while TEC was slowly added and further stirring of about 15 min was required. The second dispersion was prepared from water and Poloxamer 407 as a medium for dispersing magnesium stearate (Mgst) with a mixer {46}. These two dispersions were mixed together by pouring the Mgst-dispersion to the CAP-dispersion while constantly mixing. Water was added to bring the total solid content to 15.0 % w/w with additional mixing for at least 15 min.

For the formulation R13, the first dispersion containing Aquacoat CPD and TEC was prepared in the same way as aforementioned. The second dispersion containing Mgst and EC, however, was prepared by adding Aquacoat ECD into the Mgst-dispersion

which contained Poloxamer 407 as a wetting agent. These two dispersions were mixed together {43}. Water was added to bring the total solid content to 10.0 % w/w whilst mixing {43} for at least 15 min.

The plasticized dispersions of Aquacoat CPD (Formulations R12 and R13) were sieved through a 100 µm sieve prior to coating and they were continuously mixed {43} during the coating process.

c) Enteric coating process of pellets containing methyl orange

The white coloured placebo pellets (Product P) were mixed with yellow coloured MO-loaded pellets (Product A) to reach a loading weight for the coating process in different trials. The mixture of these pellets was coated with different CAP aqueous dispersions (R11 - R13) as demonstrated in Table 2.22.

The resulted products were demonstrated in Table 2.25. Two different fluidized bed system, i.e. with inserted filters or with a connection to a cyclone, were used to produce the enteric coated products.

If the coating process was performed with interruptions as Process No. X15, Table 2.23, then the intermediate product was dried in the small scale fluidized bed apparatus {19} to avoid sticking of coated pellets during filter changing period.

The finished coated pellets were divided into two groups i.e. with and without 0.5 % w/w of Aerosil 200. These finished enteric coated pellets were manually selected in different colours before they were used for further characterizations.

d) Enteric coating process of pellets containing nicotinamide and subcoats

The formulation R11, Table 2.22 and the different coating conditions were used to produce enteric coated pellets containing nicotinamide and subcoats. Resulted products can be seen in Table 2.26 to 2.29. Both the fluidized bed system i.e. with inserted filters or with a connection to a cyclone served to produce the enteric coated products.

If the coating process was performed with interruptions as Process No. X18, Table 2.23, then the intermediate product was dried in the small scale fluidized bed apparatus {19} to avoid sticking of coated pellets during filter changing period.

The finished coated pellets were divided into two groups i.e. with and without 0.5 % w/w of Aerosil 200. These finished enteric coated pellets were manually selected in different colours before they were used for further characterizations.

- e) Enteric coating process of pellets containing nicotinamide without any subcoats

The formulation R11, Table 2.22 and the process number X23, Table 2.24 using Aeromatic MP-1 connected with a cyclone served for the production. The loading material was the mixture of the yellow coloured pellets (Product A) and nicotinamide loaded pellets (Product aA). Resulted coated pellets can be seen in Table 2.30.

The finished coated pellets were also divided into two groups i.e. with and without 0.5 % w/w of Aerosil 200. These finished enteric coated pellets were manually selected in different colours before they were used for further characterizations.

2.4.8.5 Enteric coating of pellets using Aquacoat CPD, TEC and Aqoat-AS-MF

The combination of two enteric polymers i.e. CAP and HPMC-AS (Aqoat-AS-MF) was tested in order to improve the property of the coating film. The dispersion used for the preliminary test was prepared by modifying the formula as well as the coating conditions from the recommended one <6>. The concentration of a plasticizer was kept to the same level as for the Aquacoat CPD dispersion alone because the content of Aqoat-AS-MF was only 30 parts to 100 parts of Aquacoat CPD solid content. However, the special control of the coating dispersion temperature was carried out to avoid the sedimentation of Aqoat-AS-MF during the coating process.

Before the dispersion containing CAP, TEC and Aqoat-AS-MF was used in the coating process the size and form was determined under a light microscope as mentioned in 2.2.5.2 regarding the quality of the self prepared enteric dispersion. The dispersion was determined both before the beginning of the coating process and after the coating process was ended after about 10 h. The result of ten pictures of each dispersion showed that there was no significant difference between before and after the coating process. Therefore this dispersion was well prepared and the long coating process did not affect the particle size of solid particles.

Result of the particle sizes and form of the dispersion from the microscopic method:

The largest sizes of solid particles expected to be from Aqoat-AS-MF were $50 \pm 5 \mu\text{m}$, $n = 10$ ($p < 0.05$), because the particles sizes of Aquacoat CPD were not larger than $5 \mu\text{m}$.

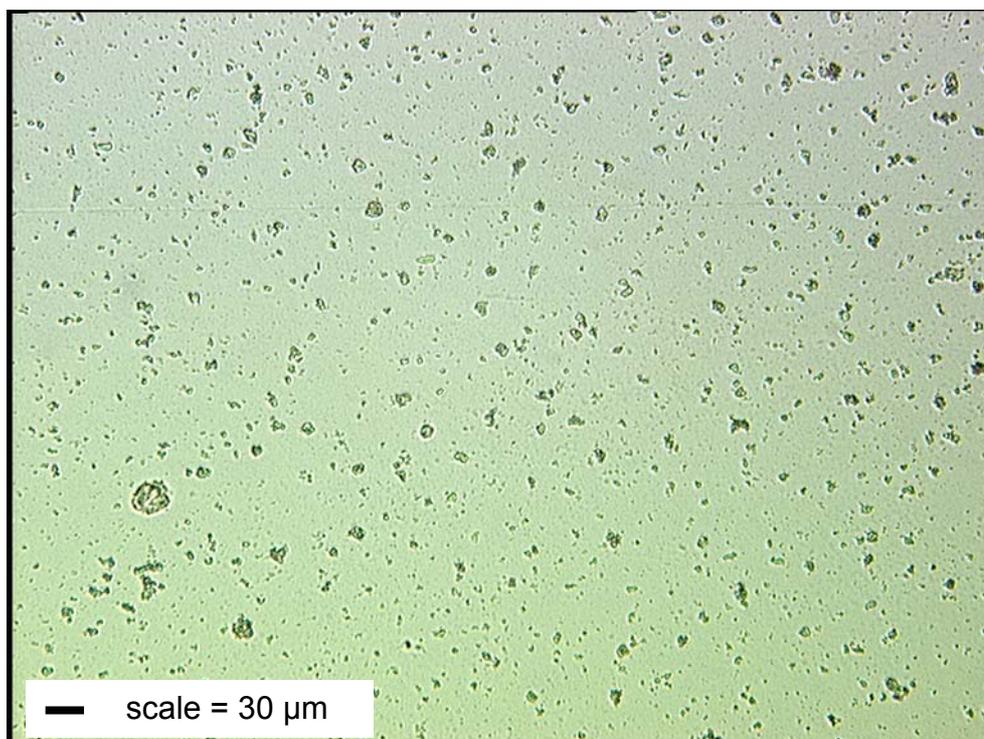


Figure 2.31: Microscopic picture of an aqueous enteric dispersion of Aquacoat CPD, TEC and Aqoat-AS-MF.

a) Preparation of an enteric coating dispersion

Formulation R14, as shown in Table 2.22 was prepared by adding 2/3 of total amount of water to the dispersion of Aquacoat CPD and while constantly stirring 32.5 g of TEC was slowly added to the dispersion. This dispersion was stirred over night {43}. Hereafter the temperature of this homogeneous dispersion containing TEC was kept below $15 \text{ }^\circ\text{C}$ using water-ice-bath and then Aqoat-AS-MF of 30.0 g accurately weighed was slowly added into the cooled dispersion while constantly cooling and stirring for at least 30 min. Purified water was added to bring the total solid content of 15.0 % w/w with additional mixing for at least 15 min. This dispersion was sieved through a $100 \mu\text{m}$

sieve prior to coating and the temperature of the dispersion was kept below 15 °C while continuously stirring during the coating process.

- b) Enteric coating process of pellets containing nicotinamide with a subcoat from a combination of EC and PVA (E&P)

The formulation R14 (Table 2.22), the process number X21 (Table 2.24) and the fluidized bed connected with a cyclone served for the production. The mixture of the white coloured placebo pellets and the green coloured pellets (Product cC) was the loading material. They could be separated from each other after finishing the enteric coating process by manual selection using the different colours.

Formulation Ingredients	R8	R9	R10	R11	R12	R13	R14
Aquateric solid (g)	100	100	-	-	-	-	-
Tween 80 (g)	1	1	-	-	-	-	-
(Aquacoat CPD liquid (g))	-	-	(333)	(333)	(333)	(333)	(333)
~ Aquacoat CPD solid (g)	-	-	100	100	100	100	100
Aquat-AS-MF solid (g)	-	-	-	-	-	-	30
DEP (g)	-	35	30	-	-	-	-
DBS (g)	35	-	-	-	-	-	-
TEC (g)	-	-	-	25	25	25	32.5
Mgst (g)	-	-	-	-	10	10	-
Poloxamer 407 (g)	-	-	-	-	0.1	0.1	-
(Aquacoat ECD liquid (g))	-	-	-	-	-	(67)	-
~ Aquacoat ECD solid (g)	-	-	-	-	-	20	-
Concentration (% w/w)	20	20	16	15	15	10	15

Table 2.22: *Different coating formulations (R8 - R14);*

R8: Aquateric and DBS

R9: Aquateric and DEP

R10: Aquacoat CPD and DEP

R11: Aquacoat CPD and TEC

R12: Aquacoat CPD, TEC, Mgst and Poloxamer 407

R13: Aquacoat CPD, TEC, Mgst, Poloxamer 407 and EC

R14: Aquacoat CPD, TEC and HPMC-AS

Process number / Parameter	X13	X14	X15	X16	X17	X18
Loading weight (g)	1000	250	100	100	280	100
Core material	S	M5	M6	M6	M7	M8
Atomizing pressure (m ³ h ⁻¹)	2.4	2.6	2.6	2.6	2.4	2.6
Orifice diameter (mm) {48}	0.8	1.2	1.2	1.2	1.2	1.2
Distance from bottom to column (mm)	0.8	0.8	0.8	0.8	0.8	0.8
Perforated bottom (% free)	20	13	8	8	13	8
Pre-warming with product (min)	15	15	15	15	15	15
With dehumidified process air	y	n	n	n	y	n
With cyclone instead of filters	n	n	n	y	n	n
Room temperature/humidity (°C, % r.h.)	20, 60	24, 50	24, 50	23, 50	22, 50	24, 50
Inlet temperature (°C)	60	35	35	35	50	35
Product temperature (°C)	54	32	32	32	45	32
Outlet temperature (°C)	52	32	32	32	43	32
Outlet humidity (% r.h.)	18	31	33	35	18	33
Spraying rate (g min ⁻¹)	1.7	0.8	0.8	0.8	1.8	0.8
Initial spray	water	air	air	air	water	air
Process air velocity (m³ h⁻¹)	50-55	95-99	95-99	93-95	55-60	95-100
Drying in Uni-Glatt (°C, min)	-	-	32, 60	-	-	32, 60
Postdrying inside the machine (°C, min)	54,15	32,15	32,15	32,15	45,15	32, 15
Postdrying outside the machine (°C, h)	22, 24	22, 24	22, 24	22, 24	50, 24	22, 24

Table 2.23: Coating conditions of different processes X13 to X18;

S = sugar spheres size range 1000-1180 μm

M5 = mixture of HPMC pellets (Product P) 200 g and MO pellets (Product A) 50 g

M6 = mixture of HPMC pellets (Product P) 50 g and MO pellets (Product A) 50 g

M7 = mixture of Product DD, Product Ee, Product cC, Product bb each 20 g and Product P 200 g

M8 = mixture of Product DD, Product Ee, Product cC, Product bb, Product A each 20 g

y = yes; n = no

Process number Parameter	X19	X20	X21	X22	X23
Loading weight (g)	100	100	100	280	100
Core material	M9	M10	M11	M12	M13
Atomizing pressure (m ³ h ⁻¹)	2.6	2.6	2.6	2.4	2.6
Orifice diameter (mm) {48}	1.2	1.2	1.2	1.2	1.2
Distance from bottom to column (mm)	0.8	0.8	0.8	0.8	0.8
Perforated bottom (% free)	8	8	8	13	8
Pre-warming with product (min)	15	15	15	15	15
With dehumidified process air	n	n	n	y	n
With cyclone instead of filters	y	y	y	n	y
Room temperature/humidity (°C, % r.h.)	22, 32	22, 32	21, 24	22, 50	22, 32
Inlet temperature (°C)	35	35	35	50	35
Product temperature (°C)	32	32	32	45	32
Outlet temperature (°C)	32	32	32	43	32
Outlet humidity (% r.h.)	31	31	15	18	31
Spraying rate (g min ⁻¹)	0.8	0.8	0.8	1.8	0.8
Initial spray	air	air	air	water	air
Process air velocity (m³ h⁻¹)	93-95	93-95	93-95	55-60	93-95
Drying in Uni-Glatt (°C, min)	-	-	-	-	-
Postdrying inside the machine (°C, min)	32, 15	32, 15	32, 15	45, 15	32, 15
Postdrying outside the machine (°C, h)	22, 24	22, 24	22, 24	50, 24	22, 24

Table 2.24: Coating conditions of different processes X19 to X23;

M9 = mixture of Product DD, Product Cc, Product bB, Product bb and Product P each 20 g

M10 = mixture of Product Ee, Product cC, Product A each 20 g and Product P 40 g

M11 = mixture of Product cC 20 g and Product P 80 g

M12 = mixture of Product aA 80 g and Product A 200

M13 = mixture of Product aA 80 g and Product A 20

y = yes; n = no

Product	Formulation	Process number	Weight of dispersion used (g)	Solid content used (g)	Coating level (%w/w)	
					Theoretical	Real
P	R1	X2	400	20.0	2.0	1.8
A	R2	X13	360	18.0	1.8	1.7
B	R11	X14	77	11.5	4.6	4.5
C	R11	X14	137	20.5	8.2	6.0
D	R11	X14	150	22.5	9.0	8.0
E	R11	X14	240	36.0	14.4	11.0
F	R11	X14	330	49.5	19.8	17.5
G	R11	X14	370	55.5	22.2	19.0
H	R11	X15	255	38.3	38.3	31.0
J	R11	X15	381	57.2	57.2	45.0
K	R11	X16	367	55.1	55.1	45.0
L	R11	X16	440	66.0	66.0	56.0
M	R12	X14	287	43.0	17.2	11.0
N	R13	X14	413	41.3	16.5	11.0

Table 2.25: *Products with a thin layer of HPMC containing methyl orange resulting from different combinations of a formulation and process conditions;*
Product P: HPMC-coated pellets (HPMC pellets)
Product A: Methyl orange loaded pellets (MO pellets)
Product B to G: CAP-coated pellets (CAP-MO pellets) prepared by using Aquacoat CPD and TEC, coating process with interruptions
Product H to J: CAP-coated pellets (CAP-MO pellets) prepared by using Aquacoat CPD and TEC, coating process with interruptions and intermediate drying in the Uni-Glatt
Product K to L: CAP-coated pellets (CAP-MO pellets) prepared by using Aquacoat CPD and TEC without interruptions
Product M: CAP-coated pellets (CAP-MO pellets) prepared by using Aquacoat CPD, TEC, Mgst and Poloxamer 407, coating process with interruptions
Product N: CAP-coated pellets (CAP-MO pellets) prepared by using Aquacoat CPD, TEC, Mgst, Poloxamer 407 and EC, coating process with interruptions

Product	Formulation	Process number	Weight of dispersion used (g)	Solid content used (g)	Coating level (%w/w)	
					Theoretical	Real
PP	R1	X7	700	35	3.5	3.2
AA	R3	X8	288	57	11.5	11.3
BB	R4	X9	320	16	8.0	7.5
CC	R4	X9	620	31	15.5	15.0
DD	R4	X9	900	45	22.5	22.0
EE	R10	X17	400	64	23.0	12.0
FF	R9	X17	490	98	35.0	14.0
GG	R8	X17	590	118	42.0	24.0
HH	R11	X18	113	17	17.0	14.0
JJ	R11	X18	133	20	20.0	17.5
KK	R11	X18	167	25	25.0	22.0
LL	R11	X18	253	38	38.0	31.0
MM	R11	X18	380	57	57.0	45.0
NN	R11	X19	367	55	55.0	45.0

Table 2.26: *Products with a subcoat from HPMC resulting from different combinations of a formulation and process conditions;*

Product PP: HPMC-coated pellets (HPMC pellets)

Product AA: Nicotinamide loaded pellets (Nico pellets)

Product BB to DD: Pellets with a subcoat from HPMC (HPMC-Nico pellets)

Product EE: CAP-coated pellets (CAP-HPMC-Nico pellets) prepared by using Aquacoat CPD and DEP, coating process with interruptions

Product FF: CAP-coated pellets (CAP-HPMC-Nico pellets) prepared by using Aquateric and DEP, coating process with interruptions

Product GG: CAP-coated pellets (CAP-HPMC-Nico pellets) prepared by using Aquateric and DBS, coating process with interruptions

Product HH to MM: CAP-coated pellets (CAP-HPMC-Nico pellets) prepared by using Aquacoat CPD and TEC, coating process with interruptions and intermediate drying in the Uni-Glatt

Product NN: CAP-coated pellets (CAP-HPMC-Nico pellets) prepared by using Aquacoat CPD and TEC, coating process without interruptions

Product	Formulation	Process number	Weight of dispersion used (g)	Solid content used (g)	Coating level (%w/w)	
					Theoretical	Real
Pp	R1	X7	700	35	3.5	3.0
Aa	R3	X8	300	60	12.0	9.5
Bb	R5	X10	130	26	13.0	11.5
Cc	R5	X10	320	64	32.0	29.0
Dd	R5	X10	500	100	50.0	48.0
Ee	R5	X10	1000	200	100.0	97.0
Ff	R10	X17	406	65	23.0	12.0
Gg	R9	X17	490	98	35.0	14.0
Hh	R8	X17	590	118	42.0	24.0
Jj	R11	X20	367	55	55.0	45.0
Kk	R11	X19	367	55	55.0	45.0

Table 2.27: *Products with a subcoat from ethyl cellulose resulting from different combinations of a formulation and process conditions;*

Product Pp: HPMC-coated pellets (HPMC pellets)

Product Aa: Nicotinamide loaded pellets (Nico pellets)

Product Bb to Ee: Pellets with a subcoat from EC (EC-Nico pellets)

Product Ff: CAP-coated pellets (CAP-EC-Nico pellets) prepared by using Aquacoat CPD and DEP, coating process with interruptions

Product Gg: CAP-coated pellets (CAP-EC-Nico pellets) prepared by using Aquateric and DEP, coating process with interruptions

Product Hh: CAP-coated pellets (CAP-EC-Nico pellets) prepared by using Aquateric and DBS, coating process with interruptions

Product Jj to Kk: CAP-coated pellets (CAP-EC-Nico pellets) prepared by using Aquacoat CPD and TEC, coating process without interruptions

Product	Formulation	Process number	Weight of dispersion used (g)	Solid content used (g)	Coating level (%w/w)	
					Theoretical	Real
pP	R1	X7	800	40	4.0	3.5
aA	R3	X8	310	62	12.4	11.0
bB	R6	X11	420	84	42.0	36.0
cC	R6	X11	770	154	77.0	67.0
dD	R10	X17	400	64	23.0	12.0
eE	R9	X17	490	98	35.0	14.0
fF	R8	X17	590	118	42.0	24.0
gG	R11	X18	53	8	8.0	6.0
hH	R11	X18	133	20	20.0	17.5
il	R11	X20	233	35	35.0	20.0
jJ	R11	X18	253	38	38.0	31.0
kK	R11	X18	380	57	57.0	45.0
IL	R11	X20	367	55	55.0	45.0
mM	R11	X20	367	55	55.0	45.0
nN	R11	X19	367	55	55.0	45.0
oO	R14	X21	133	28	28.0	20.0

Table 2.28: *Products with a subcoat from a combination of ethyl cellulose and Mowiol 4-98 (100 part + 30 parts) resulting from different combinations of a formulation and process conditions;*

Product pP: HPMC-coated pellets (HPMC pellets)

Product aA: Nicotinamide loaded pellets (Nico pellets)

Product bB to cC: Pellets with a subcoat from EC and PVA (E&P-Nico pellets)

Product dD: CAP-coated pellets (CAP-E&P-Nico pellets) prepared by using Aquacoat CPD and DEP, coating process with interruptions

Product eE: CAP-coated pellets (CAP-E&P-Nico pellets) prepared by using Aquateric and DEP, coating process with interruptions

Product fF: CAP-coated pellets (CAP-E&P-Nico pellets) prepared by using Aquateric and DBS, coating process with interruptions

Product gG to nN: CAP-coated pellets (CAP-E&P-Nico pellets) prepared by using Aquacoat CPD and TEC

Product oO: CAP-coated pellets (CAP-E&P-Nico pellets) prepared by using Aquacoat CPD, HPMCAS and TEC

Product	Formulation	Process number	Weight of dispersion used (g)	Solid content used (g)	Coating level (%w/w)	
					Theoretical	Real
pp	R1	X7	800	40	4.0	3.5
aa	R3	X8	325	65	13.0	11.4
bb	R7	X12	772	54	27.0	20.0
cc	R10	X17	400	64	23.0	12.0
dd	R9	X17	490	98	35.0	24.0
ee	R8	X17	590	118	42.0	14.0
ff	R11	X18	133	20	20.0	17.5
gg	R11	X18	253	38	38.0	31.0
hh	R11	X18	380	57	57.0	45.0
jj	R11	X19	367	55	55.0	45.0

Table 2.29: *Products with a subcoat from a combination of Mowiol 4-98 and ethyl cellulose (100 part + 30 parts) resulting from different combinations of a formulation and process conditions;*

Product pp: HPMC-coated pellets (HPMC pellets)

Product aa: Nicotinamide loaded pellets (Nico pellets)

Product bb: Pellets with a subcoat from PVA and EC (P&E-Nico pellets)

Product cc: CAP-coated pellets (CAP-P&E-Nico pellets) prepared by using Aquacoat CPD and DEP, coating process with interruptions

Product dd: CAP-coated pellets (CAP- P&E -Nico pellets) prepared by using Aquateric and DEP, coating process with interruptions

Product ee: CAP-coated pellets (CAP- P&E -Nico pellets) prepared by using Aquateric and DBS, coating process with interruptions

Product ff to hh: CAP-coated pellets (CAP- P&E -Nico pellets) prepared by using Aquacoat CPD and TEC, coating process with interruptions and intermediate drying in the Uni-Glatt

Product jj: CAP-coated pellets (CAP- P&E -Nico pellets) prepared by using Aquacoat CPD, and TEC without interruptions

Product	Formulation	Process number	Weight of dispersion used (g)	Solid content used (g)	Coating level (%w/w)	
					Theoretical	Real
pP	R1	X7	800	40	4.0	3.5
aA	R3	X8	310	62	12.4	11.0
kk	R10	X22	788	126	45.0	19.0
mm	R8	X22	840	168	60.0	32.0
nn	R11	X23	227	34	34.0	25.0
oo	R11	X23	367	55	55.0	45.0

Table 2.30: Products without a subcoat resulting from different combinations of a formulation and process conditions;

Product pP: HPMC-coated pellets (HPMC pellets)

Product aA: Nicotinamide loaded pellets (Nico pellets)

Product kk: CAP-coated pellets (CAP-P&E-Nico pellets) prepared by using Aquacoat CPD and DEP, coating process with interruptions

Product mm: CAP-coated pellets (CAP- P&E -Nico pellets) prepared by using Aquateric and DBS, coating process with interruptions

Product nn to oo: CAP-coated pellets (CAP- P&E -Nico pellets) prepared by using Aquacoat CPD and TEC, without interruptions

3. Results and discussion

3.1 Pellets with methyl orange

a) Placebo: HPMC-coated pellets (HPMC pellets)

Placebo HPMC-coated pellets were prepared by using the HPMC solution formulation **R1** in Table 2.15. The process number **X2** was chosen as demonstrated in Table 2.11. Therefore the combination of the formulation and the process number gave Product P, as demonstrated in Table 2.25.

b) Model pellets: methyl orange loaded pellets (MO pellets)

Model pellets were prepared in order to optimize the formulation and process conditions of enteric coating. MO pellets were prepared by using the formulation **R2** and the process number **X13** to give Product A, as shown in Table 2.25.

c) Enteric coated pellets: CAP-coated pellets (CAP-MO pellets)

The investigations were concentrated according to the conditions recommended in the three publications <25,200,7>. The small air flow of 50 - 55 m³ h⁻¹ caused a formation of twins and agglomerations as already mentioned in part 2.4.7; therefore a higher air flow was used to perform the coating as seen under the conditions X14 - X16, Table 2.23. The enteric coated pellets have therefore been prepared in different formulations and process conditions (Table 2.25). Products B to J, and Products M and N were produced by using the fluidized bed apparatus with inserted filters, whereas Products K and L were produced by using the apparatus connected with a cyclone.

As reported in the work of Williams and Liu <200>, a high air flow of about 90 m³ h⁻¹ can hinder the agglomeration of pellets. However, this high air velocity caused a high amount of dust as seen in Table 2.25, as the real coating level was much lower than the theoretical one. For example Product G was produced by using 370 g of the CAP aqueous dispersion equivalent to a solid content of 55.5 g. The theoretical coating amount on these pellets should be 22.2 % but the coating amount received was only

19 %. This loss of the coating weight resulted from the formation of dust. This was also confirmed by the blockage of the filters after a short running time of the coating process. It was found that after the coating process (X14) had been performed for about 70 min, the filters inside the coating chamber were blocked with the fine dust. The filters had to be changed before the process could be continued. About 60 min were required for the change of the filters. This process resulted in the different CAP film thicknesses (Products B to G, Table 3.1). The process number X15 (Products H and J) was also performed in an apparatus with filters, but during the phase of filter-change, the coated pellets have been further dried at 32 °C for 60 min in a small fluidized bed apparatus - Uni-Glatt {19} - to control the film formation and to avoid the agglomeration of pellets, because the pellets were not yet completely dried.

To solve the problems regarding the filters, a cyclone {13} as a dust collector was installed. This construction was the process number X16 for preparing CAP-coated pellets. A fluidized bed apparatus {20} connected with a cyclone ensured a continuous process without interruption. The pressure difference from the coating chamber to the outlet of the cyclone was measured to show the resistance of the cyclone. After loading the process chamber with 100 g of cores and setting the highest air velocity position at the control switch, the highest air velocity increased up to about 93 m³h⁻¹ - 95 m³h⁻¹. The cyclone resistance (ΔP) at this highest velocity was 2400 Pa, at which the process can be performed as usual. The resistance remained constant over the whole process. The loading weight was kept low at 100 g in Product H to Product L because a high coating level will be the result within the short processing time.

Williams and Liu <200> prepared the enteric aqueous dispersion by mixing Aquacoat CPD with a propeller mixer, and adding DEP slowly to the dispersion whilst stirring. The dispersion was continuously stirred for 1 h, and then mixed for an additional 23 h using a magnetic stirring bar. The method was comparable to that used in the present study to prepare the aqueous Aquacoat CPD dispersion. The stirring overnight was carried out to ensure a homogenous dispersion of the plasticizer used, because some authors <58> reported about the positive effect of extended dispersing time on the distribution of the plasticizer in the polymer preparation.

Normally, when a Wurster-based bottom spray fluidized-bed technique is employed, it is possible to apply droplets to the substrate surface before evaporation of solvent from the droplets occurs. The solvent on the surface of the pellets should normally

completely evaporate before the solvent can penetrate the core of pellets. Suspending the pellets in air keeps them separated from each other and allows an application of films to the pellets with little or no agglomeration. However, this technique can cause spray drying of the polymer dispersion, which will develop a high amount of dust inside the coating column. This dust will accumulate at the filters because of the high air stream, which is required to suspend pellets. In consequence, the filters may be blocked and the process will have to be interrupted in order to clean the filters.

This part of the present study shows that inserting a cyclone instead of filters seems to be suitable for a coating process that causes a high amount of fine dust because the coating process can be performed without interruption. Moreover, enteric coating of pellets by cellulose acetate phthalate as a film forming agent using a Wurster-based fluidized bed apparatus seems to be problematic. The combination of a process and this polymer needs a special attention. Though some parameters were recommended by the manufacturer and some authors, the optimization should be done for particular formulations. This however, will take a long time until the optimum process parameters would be found.

3.1.1 Film quality, diameter and weight of pellets

The physical properties of the starting pellets (sugar spheres) used for this process and of the finished products (Product A to N) are shown in Table 3.1.

The mean diameter of the raw material was $1095 \pm 40 \mu\text{m}$. This standard deviation was about 2.5 pixel. The thickness of the HPMC layer of Product P was about $8 \pm 2 \mu\text{m}$. The structure of this film was homogenous and did not contain cracks. The mean diameter of Product P as measured by an image analyser was $1120 \mu\text{m}$ with a standard deviation of $32 \mu\text{m}$. This means the standard deviation of the finished product was about 2 pixel which was quite acceptable because it was lower than that of the material. The weight of one HPMC-pellet (Product P) was $1.06 \pm 0.01 \text{ mg}$, which, as expected, was higher than that of sugar spheres, whereas the weight of MO-pellets (Product A) was not significantly different from HPMC-pellets.

Physical properties of the CAP-coated pellets (Product B – N) are also demonstrated in Table 3.1. The pellets showed very high roughness of the surface (Figure 3.1a). The CAP layer contained a porous structure (Figure 3.1b). The SEM photograph of the cross-section shows that some CAP-particles did not melt together (Figure 3.2a).

Moreover, small cracks at the surface of the coated pellets are detected under high magnification of SEM (Figure 3.2b). In spite of a combination of CAP and additives as magnesium stearate (Mgst) and ethyl cellulose (EC), the structure of the films was not improved. They contained small cracks on the surface (Figure 3.3a) and some CAP-particles did not melt together (Figure 3.3b) as well.

It is known that the addition of an additive to a polymer film will alter the permeability characteristics of the film. An example was given by Beckert <16> about tableting of enteric coated pellets. Sugar spheres of the size fraction 800 - 1000 μm were used for layering of bisacodyl. The layering formula consisted of 81.3 g Eudragit L 30 D-55, 244.0 g bisacodyl, 8.1 g TEC, 40.5 g talc and 1305.0 g water. The layering process was performed using a fluidized bed apparatus. This means a high amount of enteric coating polymer and talc was already used for layering the drug. Therefore this combination will protect the release of bisacodyl from the drug-layer. The enteric coating processes were performed by using a fluidized bed apparatus-Uniglatt with a loading weight of 1 kg. The enteric coating formula consisted of 416.7 g Eudragit L 30 D-55 as coating polymer, 12.5 g triethyl citrate as a plasticizer and 62.5 g talc as a separation substance. Two percentages of coating amount were studied i.e. 12.5 and 25.0 % w/w. Beckert found that the release of bisacodyl was 1.6 and 0.1 % after 2 h in 0.1 N HCl and 97.9 and 95.6 % after 45 min in buffer pH 6.8, respectively. This means that the enteric coated pellets had passed the requirement of the USP XXIII . The thicknesses of film coated on the pellets were 20 - 25 μm and 45 - 50 μm at coating amounts of 12.5 % w/w and 25.0 % w/w, respectively. Beckert also found that films from Eudragit L 30 D-55 and talc were very brittle. The stretching level was less than 5 %. This result was also confirmed by Okhamafe and York <119>. Beckert studied a combination of polymers (Eudragit L 30 D-55 and Eudragit NE 30 D) as coating polymers as well. Triethyl citrate was used as a plasticizer and talc as a separating excipient. The coating was applied in two levels i.e. 12.5 and 25 % w/w. Beckert found that the release of bisacodyl in 0.1 N HCl was 4.0 and 0.9 % and the release in buffer pH 6.8 was also low at 33.1 and 2.9 %, respectively. The result implied that the enteric coated pellets had not passed the requirement of the USP. The slow release of bisacodyl in the artificial intestinal fluid may be the effect of talc which in this case may have a sealing effect and additional effect of the low solubility of bisacodyl in the neutral medium <16>.

The effect of two hydrophobic substances on the film formation was studied in this present work. The results were observed with Product M and N. Magnesium stearate

(Mgst) or ethyl cellulose (EC) were used because they may hinder the agglomeration of pellets which happened in the preliminary studies in 2.4.7.3. The results show that the dispersion with Mgst was problematic because of the high tendency of sedimentation of Mgst. This may cause a blockage of the nozzle during the long coating process. Moreover, the release test shows that this incorporation did not give a better resistance to the acidic medium. The structure of the film under SEM was not different from the CAP film without Mgst (Figure 3.3). Some heterogeneous structures could be seen and particles of polymers still existed. This means the coalescence of CAP was not completed.

The reason for the inhomogeneous film was most probably the low product bed temperature, which was 32 °C while the process air temperature was controlled at 35 °C. This product bed temperature was measured in the coating chamber within the streaming air of the product bed but it was not the temperature at the surface of the pellets. The surface temperature of the pellets is supposed to be lower. It is well known that for the coating process the product bed temperature should be higher than the minimum film forming temperature (MFFT). For instance, Frohoff-Hülsmann <58> has investigated recently the film formation from an ethyl cellulose aqueous dispersion and has found that up to 10 °C above the MFFT are necessary to obtain a good coalescence of polymer particles. CAP is also a cellulose derivative and the coating with CAP using an aqueous dispersion at a higher product bed temperature than the respective MFFT may be suitable. In contrast, a specialist of FMC <25> recommended that the product bed temperature should be kept low to avoid stickiness at temperatures above the T_g , which is reported <7> to be about 34 °C as mentioned before in 1.1.2.2.2.1.

Moreover, the use of a higher process temperature, for example up to 60 °C, in order to have a product temperature of 50 - 55 °C, may cause the problem of blockage of the nozzle during the coating process. The reason was that the fluid bed apparatus used, Aeromatic MP-1, had a process air flow from the bottom, as shown in Figure 2.21. The warm air flew from the bottom through the coating chamber and blew out to the outlet air tube. Before the coating of pellets can be performed, the raw materials should be warmed in order to have the suitable product bed temperature. This phase of the process will also heat the nozzle which was inserted in the bottom part. When the dispersion of CAP was pumped into the spraying set in this phase blockage may be caused as the polymer was dried inside the orifice. If there is the possibility to cool the

spraying unit without an affect on the temperature of the air flow it might be possible to coat pellets at high temperatures without any problem. Nevertheless it is very important to consider the stability of the dosage form in case of high temperatures. The high temperature and water which is sprayed onto the surface of the pellets may chemically degrade the drug in the core, at least in regions close to the surface.

The possibility to get more homogenous films is the curing after the initial coating with CAP by using elevated temperature and/or humidity as reported by Williams and Liu <200>. Details were discussed in 3.2.7. Other possibilities to improve the coalescence were mentioned by Obara and McGinity <116,117>. Details were also discussed in 3.2.9.

3.1.2 Colour change of methyl orange of coated pellets

Methyl orange (MO) as a raw material in powder form has a golden colour. After contact with an acidic medium, Methyl orange changes into its protonated form which has pink-red colour. This property provides a fast test of resistance against the diffusion of an acidic medium through the enteric coat.

The use of methyl orange as an indicator for the test on resistance against artificial gastric fluid (0.1 N HCl) was studied in the recent work of Schmidt and Teuber <170>. The percentage of pellets with unchanged color, coated with different enteric polymers was observed and reported. The result was that 100 % of pellets coated with organic solution of Eudragit L100 changed the colour into pink after 2 h exposure to 0.1 N HCl, whereas only 22 % of the pellets coated with organic solution of HPMCP changed the colour into pink. The increasing of a coating amount of polymer Eudragit L100 up to 8.95 mg/cm² could reduce the amount to 55 % of pellets which changed their colour after exposure to 0.1 N HCl for 3 h. This means these pellets were not gastric resistant though the high amount of coating polymer was used. Only HPMCP at a coating amount of about 9.5 mg/cm² brought the result of a gastric resistance against 0.1 N HCl as none of the pellets has changed ist colour.

This study showed cleary that methyl orange is a suitable indicator for determination of gastric resistance. The time until the artificial gastric fluid diffused into the core was demonstrated as the time during which the colour of pellets was changed from yellow or orange to pink. The amount of coated pellets having changed the colour into pink

showed the unsatisfying gastric resistance property. If the coated pellets were gastric resistant then none of the coated pellets would have changed its colour.

The result of the colour change of CAP-MO pellets is illustrated in Figure 3.4. MO Pellets (Product A) coated with CAP had an orange colour instead of gold. This colour change indicated that the pH at the surface of the inner core had already changed during the coating process. After the test for colour changing as described in 2.2.7, the time during which the pink colour was constant was recorded. These data are stated in Table 3.1. The time during which 0.1 N HCl diffused into the inner core increased from 1 min to 10 min when the polymer amount was increased further with an increase of the polymer amount from 2 to 27 mg cm⁻². This time of diffusion was kept constant at 10 min from 27 to 72 mg cm⁻².

The acid resistance test (Table 3.1) by monitoring the colour changing showed that 0.1 N HCl diffused slower into these pellets (Product M and N) than into products without magnesium stearate (Mgst). This resulted probably from the fact that Mgst can be hardly wetted. However, the percentage of release during the first five minutes shows high values which demonstrated the fast release of methyl orange from the core. This means that the polymer film contained porous structures, at least locally. These results confirm that methyl orange incorporated in the core by using HPMC as binder was suitable as an indicator to monitor the resistance against acidic acid of coated films.

Product	Weight gain of total batch (% w/w)	Thickness of the layer ($\mu\text{m} \pm \text{SD}$)	Weight of pellet ($\text{mg} \pm \text{SD}$)	Diameter of pellet ($\mu\text{m} \pm \text{SD}$)	Coating amount (mg cm^{-2})	Time of colour change (min \pm SD)	Release within the first five minutes (% \pm Range)
S	0.0 ^a	1000-1180 ^e	0.96 \pm 0.03	1095 \pm 40	n	n	n
P	0.0 ^b	8 \pm 2 ^f	1.06 \pm 0.01	1120 \pm 32	n	n	n
A	0.0 ^c	8 \pm 2 ^g	1.05 \pm 0.01	1120 \pm 34	n	n	86.3 \pm 2.0
B	4.5 ^d	8 \pm 4 ^h	1.07 \pm 0.01	1140 \pm 30	2 ⁱ	1 \pm 1	21.3 \pm 1.0
C	6.0 ^d	11 \pm 4 ^h	1.11 \pm 0.02	1150 \pm 33	6 ⁱ	3 \pm 1	15.0 \pm 1.0
D	8.0 ^d	15 \pm 2 ^h	1.16 \pm 0.01	1160 \pm 32	11 ⁱ	4 \pm 1	8.0 \pm 0.5
E	11.0 ^d	22 \pm 5 ^h	1.20 \pm 0.01	1180 \pm 31	15 ⁱ	6 \pm 1	7.0 \pm 0.5
F	17.5 ^d	34 \pm 3 ^h	1.32 \pm 0.01	1220 \pm 35	27 ⁱ	10 \pm 1	n
G	19.0 ^d	37 \pm 3 ^h	1.38 \pm 0.02	1230 \pm 37	33 ⁱ	10 \pm 1	4.0 \pm 0.5
H	31.0 ^d	62 \pm 4 ^h	1.50 \pm 0.01	1300 \pm 34	45 ⁱ	10 \pm 1	0.6 \pm 0.2
J	45.0 ^d	90 \pm 5 ^h	1.63 \pm 0.02	1380 \pm 47	58 ⁱ	10 \pm 1	0.0 \pm 0.1
K	45.0 ^d	89 \pm 3 ^h	1.60 \pm 0.02	1380 \pm 40	55 ⁱ	10 \pm 1	0.0 \pm 0.1
L	56.0 ^d	113 \pm 3 ^h	1.77 \pm 0.01	1445 \pm 36	72 ⁱ	10 \pm 1	n
M	11.0 ^d	25 \pm 6 ^h	1.21 \pm 0.01	1170 \pm 38	16 ⁱ	7 \pm 1	11.8 \pm 0.5
N	11.0 ^d	22 \pm 5 ^h	1.16 \pm 0.01	1165 \pm 34	11 ⁱ	5 \pm 1	13.3 \pm 0.5

Table 3.1: Properties of different products showing weight gain of total batch, thickness of the layer, weight of pellet, diameter of pellet, coating amount, release within the first five minutes;

^a = weight gain of total batch of sugar spheres (% w/w), ^b = weight gain of total batch of HPMC pellets to sugar spheres, Product S, (% w/w), ^c = weight gain of total batch of MO pellets to sugar spheres (% w/w), ^d = weight gain of total batch of CAP-MO pellets to MO pellets, Product A, (% w/w), ^e = size of sugar spheres, Product S (μm), ^f = thickness of the HPMC layer (μm), ^g = thickness of the methyl orange and HPMC layer (μm), ^h = thickness of the enteric coating layer (μm), ⁱ = coating amount of the enteric coat on Product A (mg cm^{-2}), n = not measured.

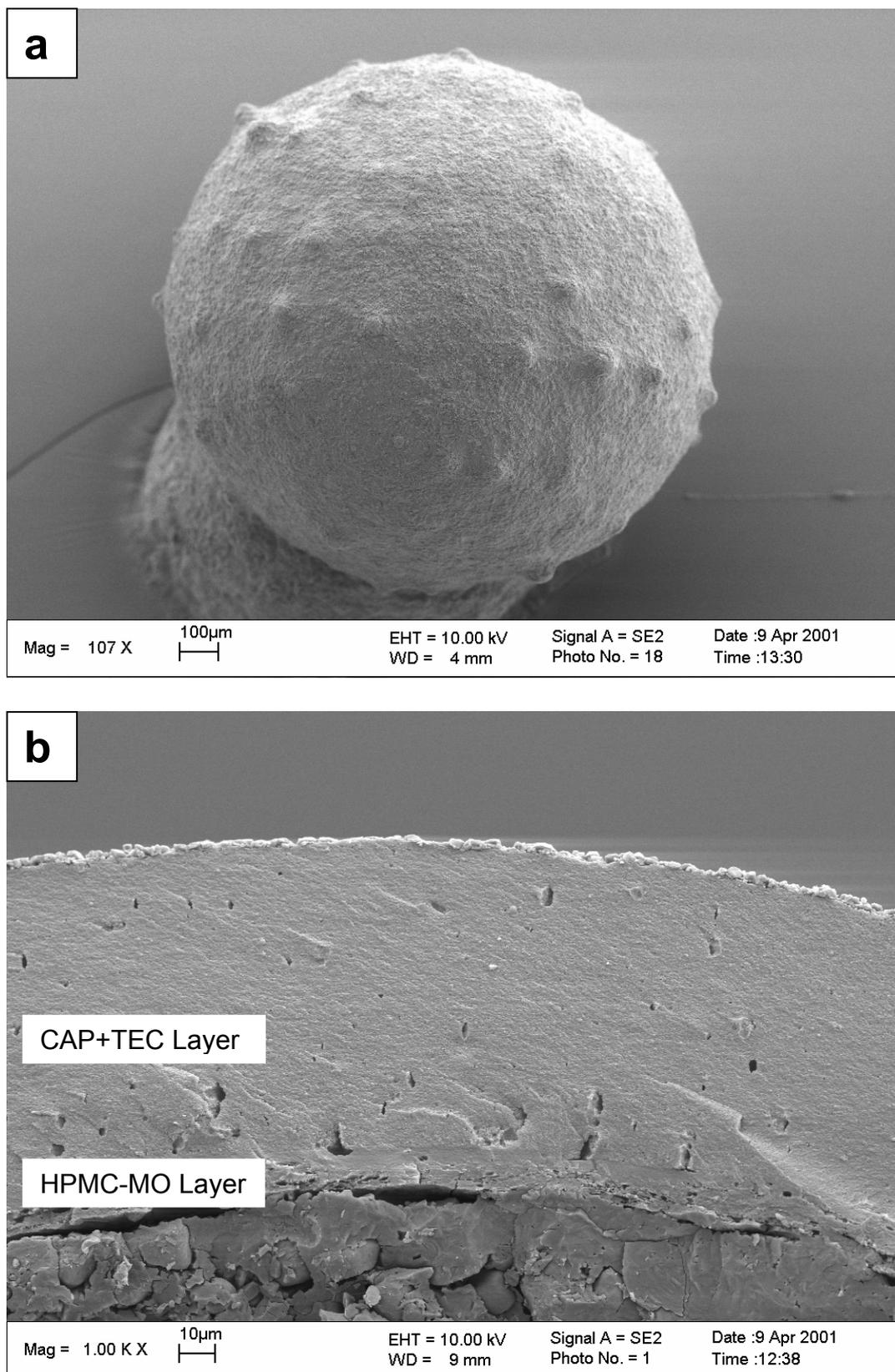


Figure 3.1: SEM pictures of coated pellets; a) the top view of a pellet coated with CAP and TEC (Product K), magnification 110x; b) the cross-section of a pellet coated with CAP and TEC (Product B to L), magnification 1,000x.

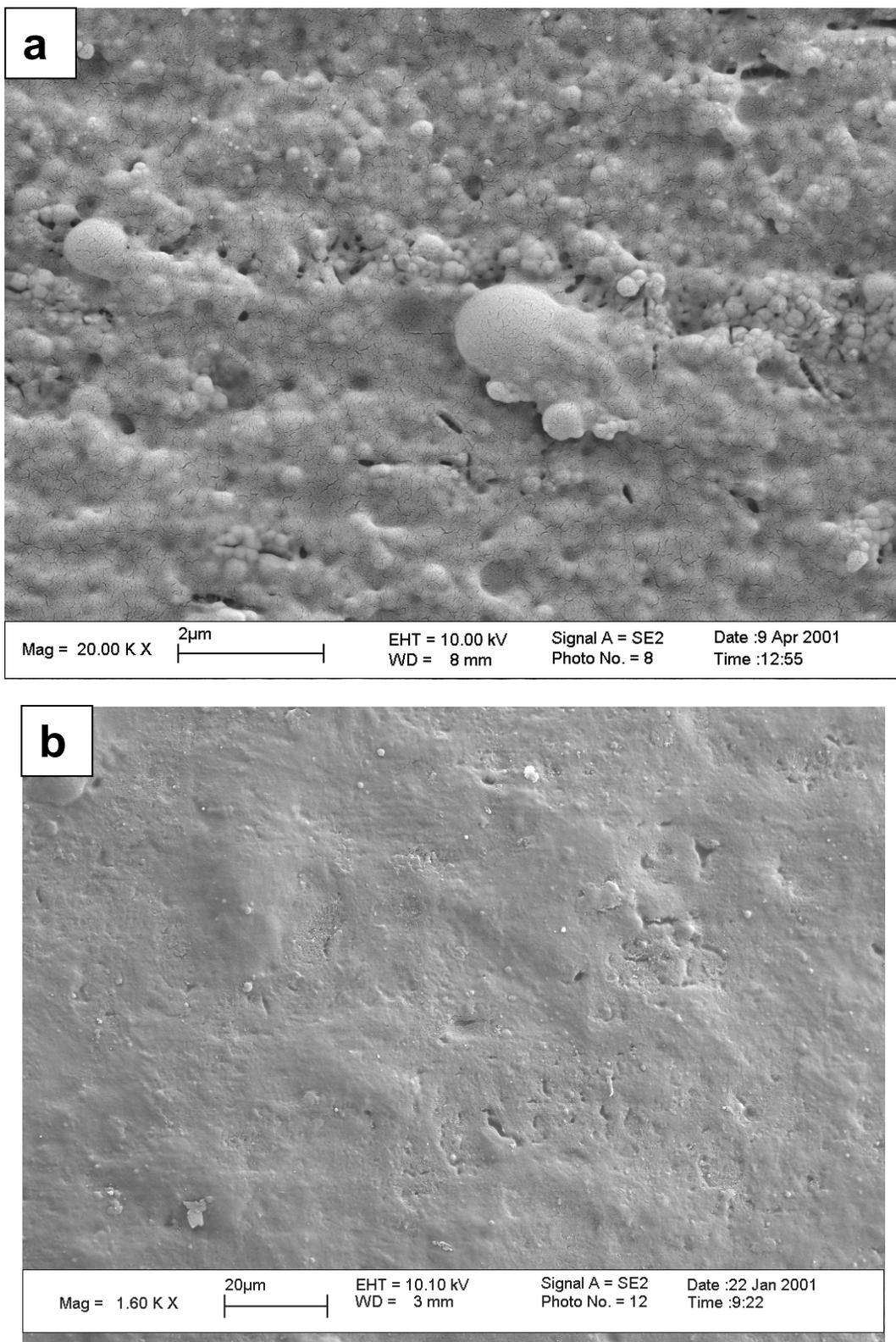


Figure 3.2: SEM pictures of coated pellets; a) the cross-section of a CAP and TEC layer (Product B to L), magnification 20,000x; b) the surface of a pellet coated with CAP, TEC (Product B to L), magnification 1,600x.

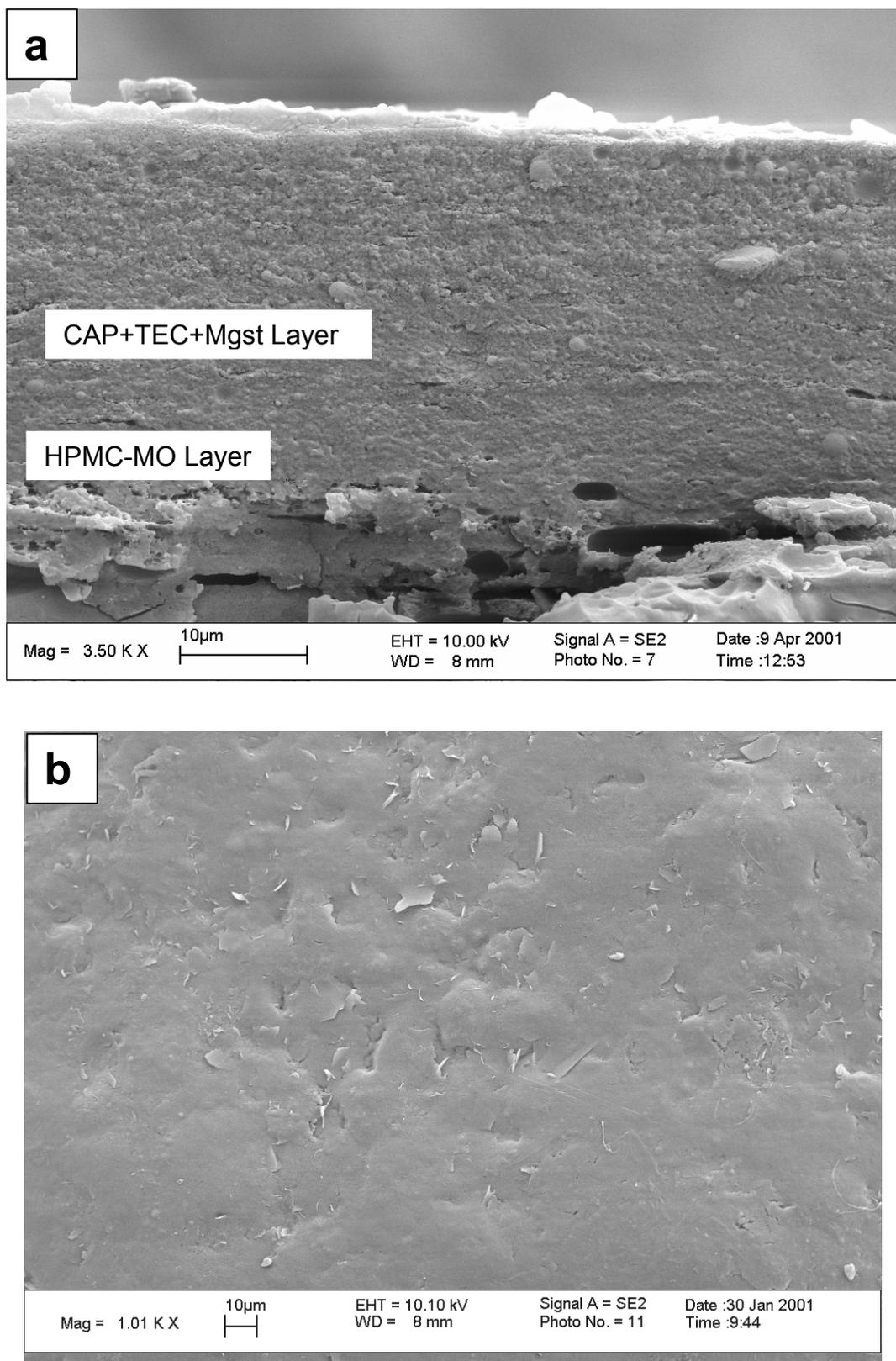


Figure 3.3: SEM pictures of coated pellets; a) the cross-section of a pellet coated with CAP, TEC and Mgst (Product M) magnification 3,500x; b) the surface of a pellet coated with CAP, TEC and Mgst (Product M) or CAP, TEC, Mgst and EC (Product N), magnification 1,000x.

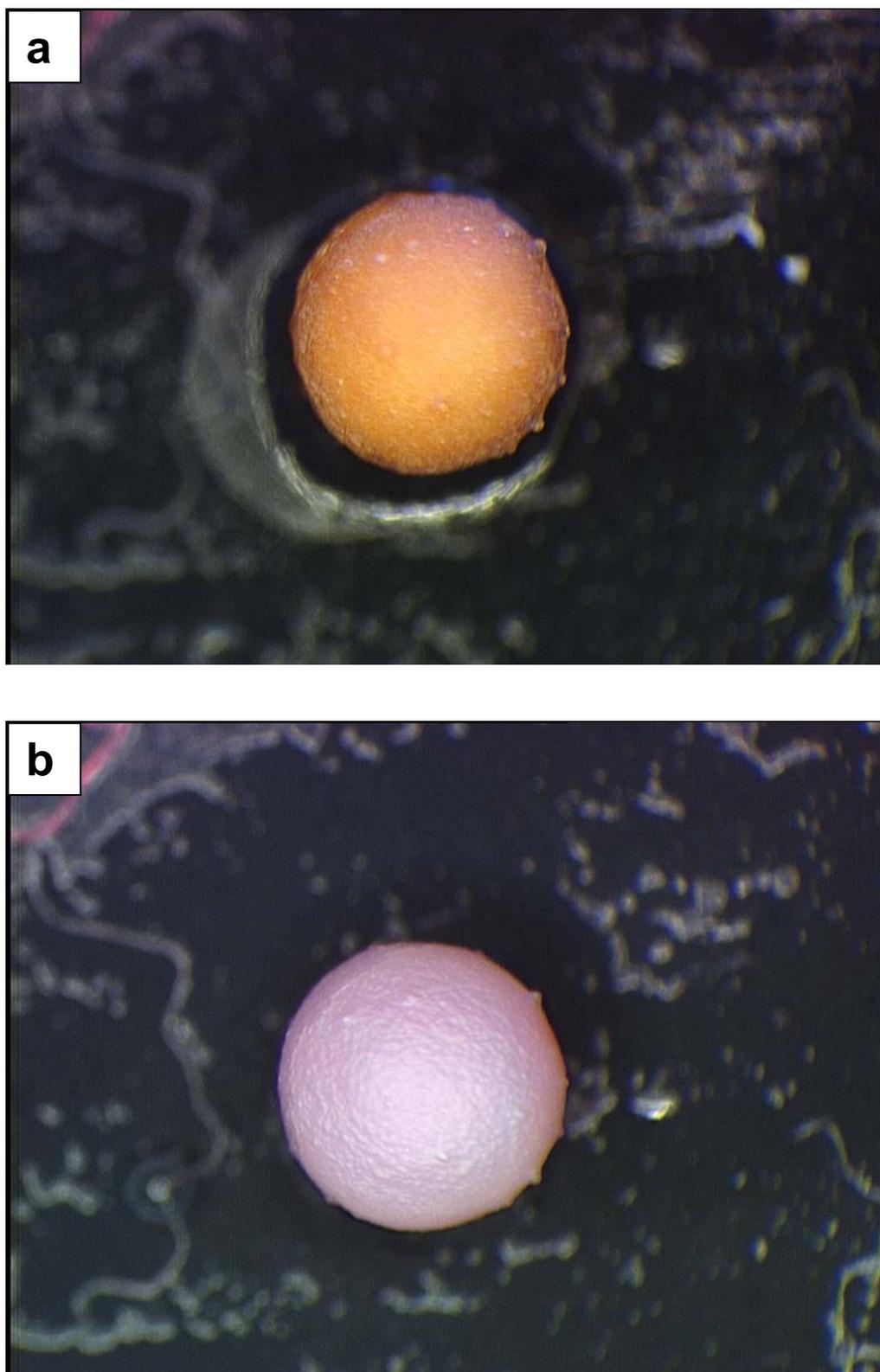


Figure 3.4: Colour changing of a pellet coated with CAP and TEC (Product K) with a primary thin coat of HPMC containing methyl orange in 0.1 N HCl at 22 °C; a) pellet at the start; b) pellet after 10 min.

3.1.3 Swelling

The swelling of HPMC pellets (Product P) was at the high value of 22 %, whereas MO pellets (Product A) had a smaller swelling of 13 % (Table 3.2). The swelling of CAP-MO pellets was performed with Product K. These pellets dissolved partly during 2 h in 0.1 N HCl, detected by a reduction in the diameter of the pellets. This may be due to dissolving both of core material and of the outer layer.

Product	D1 ± SD	D2 ± SD (pixel)	Δ D ± SD	Swelling (%)
P	179 ± 1	218 ± 5	39 ± 4	22
A	185 ± 2	210 ± 4	24 ± 5	13
K	218 ± 3	212 ± 4	-6 ± 2	dissolving

Table 3.2: Swelling property of different products in 0.1 N HCl, 22 °C; D1: diameter before swelling, D2: diameter after swelling, P: HPMC pellets, A: MO pellets, K: CAP-MO pellets

In this present work the percentage of swelling was used because this study can be performed easily by an optical measurement, the details of which were mentioned in 2.2.6.

Thoma and Bechtold, 1999 <185> reported about the minimum thickness of CAP films coated on tablets from an aqueous coating system and an organic system in order to have a swelling of less than 10 % and a resistance to 0.1 N HCl. Their statement was that a high thickness of 110 μm CAP film from an aqueous system was necessary for a resistance to an acidic medium, whereas the thickness of 40 μm was sufficient from an organic system. The recommended percentage of a polymer solid loading onto the pellets from the FMC company <7> is only 10 - 20 % to give a minimum thickness that can resist the acid medium. In the present study the thickness of the CAP film was already high, e.g. Product J: 90 μm, however, after contact with the acid medium the film was broken already after a short time. The swelling test gave negative values,

which means CAP-coated pellets dissolved over a certain time in 0.1 N HCl. Consequently, 0.1 N HCl can diffuse into the coated pellets and therefore dissolves the indicator (methyl orange) which was released slowly from the coated pellets to the outer medium as confirmed by the dissolution test (Figure 3.5). As the swelling of HPMC-coated pellets was very high after contact with 0.1 N HCl (22 %) it may also cause the explosion of the coated pellets because of the swollen layer.

3.1.4 Content of methyl orange in one pellet

The result showed that one methyl orange loaded pellet (Product A), which had a mean weight of 1.05 mg, contained about $0.75 \pm 0.01 \mu\text{g}$ methyl orange. Therefore the content of methyl orange inside one MO pellet was $0.07 \pm 0.001 \%$ w/w, calculated on base of the calibration curve of methyl orange in 0.1 HCl using the UV-method. The content of methyl orange in one pellet was not high. Therefore a high amount of pellets could be used for one release test.

3.1.5 Release of methyl orange from coated pellets

The evaluation of enteric performance of the CAP coated pellets was reported by Williams and Liu <200>. They also used the USP XXIII dissolution Apparatus II (paddle method). The acidic medium was 0.1 N HCl, with is taken as a model for the gastric fluid. The acidic medium was heated to 37 °C and the temperature was held at this temperature. The same condition was also used in this present work but only 400 ml of the acid medium was used because the concentration of nicotinamide can be well determined and only a small amount of coated pellets was necessary for this test.

The dissolution test of pellets was performed to support the results of the test for gastric resistance. If the acid medium diffused through the outer film layer it will not only change the colour of methyl orange inside the core but also dissolve methyl orange which will diffuse outwards through the film layer. The rate of appearance of methyl orange in the release medium will depend on the dissolving rate from inner core and most probably on the diffusion rate from the inner core to the dissolution medium. The total amount of methyl orange dissolved in the dissolution medium will give an

information about the resistance property of the outer film layer. The Pharmacopoeia allows not more than 10 % drug dissolved after testing in acidic medium for 2 h.

The evaluation of the test of delayed-release (enteric-coated) of particles in the USP XXIII <52> is divided into two stages i.e. an acid- and a buffer-stage. The 0.1 N HCl is used as a medium in the acid stage and 0.2 M tribasic sodium phosphate is used as a medium in the buffer stage. After 2 h of operation in 0.1 N HCl the product must be immediately transferred to the buffer stage. The acceptance limit in the acid stage for the total 24 sample-units tested is that the mean dissolution of the active substance should not be more than 10 % based on the percentage of the labeled content and no individual unit, from 24 units, had a dissolution of the active substance greater than 25 %.

The result of the coated pellets in this present study shows that the cumulative percentage of release during the first five minutes from MO-pellets, which were not coated with CAP, was the highest one as expected (Table 3.1). The percentage of release was reduced after coating with CAP. The dissolution profiles of different products containing methyl orange can be seen in Figure 3.5. The maximum range of deviation observed for any product was not more than 2 %. Therefore, error bars were not included in the dissolution profiles to avoid visual complexity of the several dissolution curves in individual graphs. The CAP-MO pellets were not resistant to 0.1 N HCl over 2 h, although different thicknesses and combinations of different additives were used. After 2 h, every kind of CAP-MO pellets (Products B to N) released more than 20 % of MO. The smallest percentage of release appeared from Products J and K. The delay of MO release from these two types of pellets may be due to the effect of the CAP layer which, in this case, had a thickness of about 90 μm . At this thickness the coating amount was very high i.e. at about 56 mg cm^{-2} . The release result of these coated pellets did not pass the requirement of USP XXIII. The failure in gastric resistance of coated pellets containing methyl orange may be due to the formation of inhomogeneous films. The bad coalescence was confirmed by SEM (Figure 3.1-3.3).

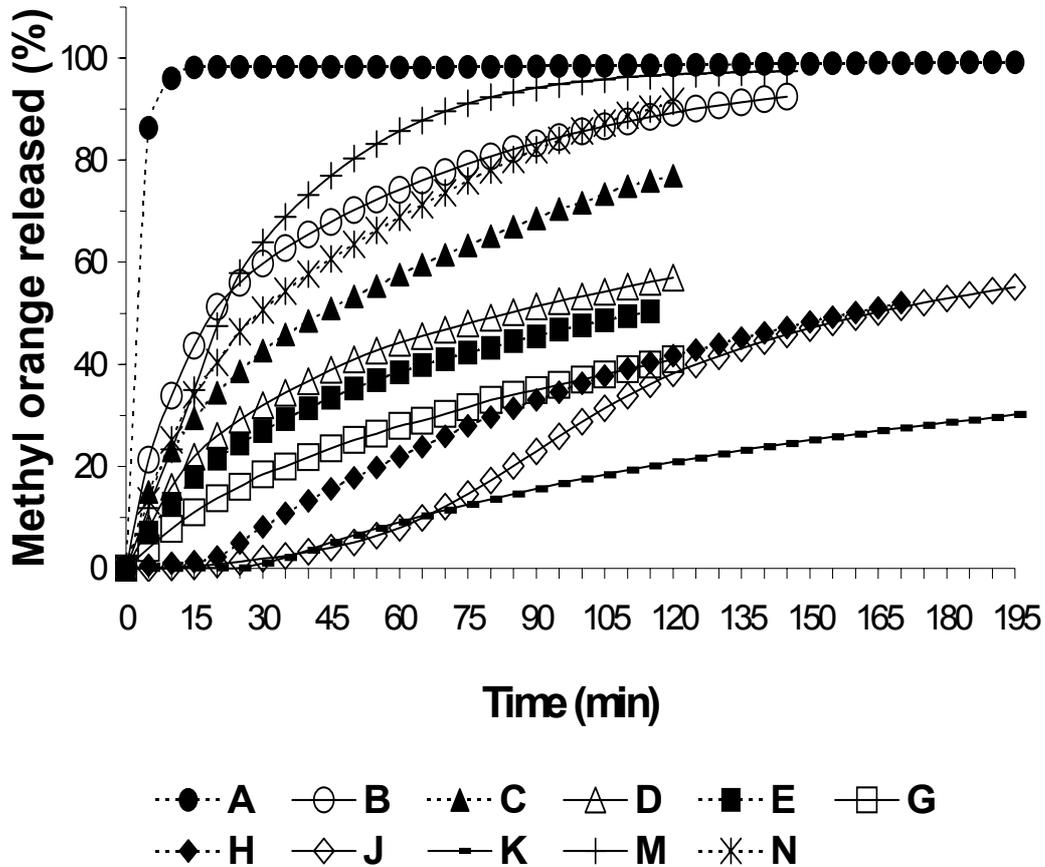


Figure 3.5: Dissolution profiles of differently coated pellets containing methyl orange in 0.1 N HCl at 37 °C without (Product A) and with enteric coats containing TEC as a plasticizer (Product B to N); increasing thickness of enteric coat in mg cm^{-2} ;
 Product B:2, C:6, D:11, E:15, G:33; H:45, J:58, K:55; Product J: production with intermediate drying phase; Product K: similar to Product J, but with cyclone instead of filter; Product M: containing 10 parts of magnesium stearate in CAP, M:16; Product N: similar to Product M, but with addition of 20 parts of EC in CAP, N:11

The unsatisfying acidic gastric resistance and the release of drug from the CAP-coated pellets were also reported by many authors <200,207,117,121>.

Williams and Liu <200> varied the different parameters to determine the effect on the release. The plasticizer level was 30 and 35 % of DEP based on latex solids. The outlet temperature was varied between 36 and 48 °C. The spray rate and the air velocity were also varied between 2 and 3.2 g/min and 50 and 90 m³/h, respectively. The release rate of all coated pellets was first order. They have found that all pellets coated at 48 °C released about 80 % of theophylline within 30 min in the acidic medium and that all these coated pellets lost their integrity after 15 min, indicating that the film was not acid-resistant. The SEM pictures showed that the polymeric latex particles did not melt together. This indicated that the high temperature caused drying of the atomized droplets before they could spread and coalesce on the surface. The high processing temperature may cause a loss of plasticizer from the polymer structure as well. This can result in a bad coalescence of the polymer because of too low concentration of a plasticizer.

Pellets that were coated at 36 °C showed lower drug-release rates compared to the same conditions but with higher outlet temperature. The pellets that were coated with a dispersion containing 30 % DEP at the outlet temperature of 36 °C, both with air flow of 50 or 90 m³/h, showed cracks on the surface of pellets which implied that the polymer coating was under-plasticized.

The smallest release rate resulted from pellets coated with a dispersion containing 35 % DEP. The coating conditions were an outlet temperature of 36 °C, a spray rate of 3.2 g/min and an air velocity of 50 m³/h. The SEM picture of these pellets demonstrated the improvement of the coalescence of the film and no cracks occurred. However, these pellets had the highest degree of agglomeration. This may be due to the overwetting of product inside the coating chamber because water that was sprayed onto the pellets could not evaporate fast enough from the surface. However, on the other hand, an agglomeration can also occur from the high processing temperature. If the processing temperature was higher than the T_g. This should lead to a rubbery state of polymer, which will cause sticking of pellets resulting in agglomerates.

Normally, if agglomeration occurred in the process, the coated pellets will have defect films. Sieving in order to eliminate twin-pellets cannot be performed with sufficient precision. Some pellets that have agglomerated would be separated from each other by

mechanical stress but they will have defect films. These pellets with defective films will give higher dissolution rate of drug because of drug-diffusion through the defect holes. Williams and Liu <200> reported that the MFFT of CAP dispersion containing 35 % DEP based on latex solids was about 29 °C. This means the temperature of 48°C was well above the MFFT and within the normal coating range of 10 - 20 °C above the MFFT. However, the SEM picture revealed that coalescence had not taken place under this coating temperature.

In summary they showed that the release rate was significantly decreased when the pellets were coated at 36 °C compared to those pellets coated at 48 °C. Higher coating efficiencies and better coalescence of films were obtained at the lower coating temperature. They mentioned that the drug release in acid was decreased as the coating temperature, which was above the MFFT, was decreased.

The unsatisfying result after using a high process temperature was also reported by Yang and Ghebre-Sellassie <207>. They have studied the effect of product bed temperature on the microstructure of aqueous dispersion of ethyl cellulose. They used the bed temperature of 50 °C which was well above the T_g. They found that the films did not form because the evaporation rate of water may have overcome the diffusion of water existing inbetween the polymer particles and the surface, and prevented the development of capillary forces required for particle deformation.

Williams and Liu <200> have also studied the effect of a process temperature on the release behaviour. They used three different outlet temperatures at 32, 36 and 40 °C in the study. These temperatures were all above the MFFT. The plasticizer level was at 35 % DEP, the spray rate was 3.2 g/min and the air velocity was 90 m³/h. They reported that as the temperature was decreased, the release rate was also decreased. However only the pellets that coated at 32 °C had the release of theophylline lower than 15 % in 0.1 N HCl after 2 h. Other pellets that coated at the outlet temperatures up from 36 °C released more than 20 % theophylline after 2 h. They mentioned that the outlet temperature of 32 °C was not low enough to resulting the complete coalescence. However, the result implied that the lowering of the coating temperature will enhance the coalescence. The low water evaporation rate possibly gave more opportunities for the polymer particles to coalesce before the film was dried. The polymer particles were able to move freely, which led to the formation of a continuous and well-packed film.

Since moisture was present in the film and water molecules could function as a plasticizer. The release of the drug may vary when moisture that remained in the coating layer was gradually evaporated. The temporary plasticization with water may lead to increase the release when water is moved, but if the coalescence was continued during the water evaporation the drug release will decrease further.

All these data reveal that the temperature was a critical parameter which affects the drug release. The condition that represented a wet environment for the coating will result in better coalescence. This means the temperature and air velocity should be low, the spraying rate should be high so that the overall drying rate was low which led to better film formation. This finding was consistent with the studies of free films reported by Obara and McGinity <117>.

The other example of enteric coated products that did not pass the requirement of the Pharmacopoeia were shown by the work of Oschmann <121>. He studied the property of resistance against acid medium or the disintegration in the buffer of marketed products and he showed that about 25 % of total 181 tested products were not in the requirement of the Pharmacopoeia. Especially the capsule preparations have more problems to reach the above mentioned requirement. Most of the marketed products that had CAP as a coating polymer lost their resistance against acid and the time of disintegration in the buffer increased after a period of storage. Most of the marketed products containing pancreatin as an active drug lost their resistance against acid and the time of disintegration in the buffer increased after a period of storage. Perhaps this problem came from the chemical interaction between pancreatin and CAP. The enzymatic splitting of CAP because of pancreatin was not the case. Products containing bisacodyl, phenylbutazon or digitoxin did not have the above mentioned problems. This could result from the non-ionic property of these drugs. The small amount of drugs incorporated in the tablets may also be the reason that interaction between the drug and the enteric polymer did not exist.

On the other hand, the satisfactory acidic gastric resistance of CAP-coated products was reported by Oschmann <121> in formulations based on organic or ammonia system. Oschmann used both the formulations to coat tablets and the mean thickness of film coated on tablets was 48 μm . The alcoholic formulation consisted of 8 parts CAP, 1.5 parts DEP, 42.25 parts ethyl acetate and 42.25 parts iso-propanol, whereas the

ammonia based formulation contained 8 part of CAP and 1.5 parts of triacetin. Oschmann showed that both tablets coated with the alcoholic and ammonia salt solution were resistant against acid medium over 4 h. However, tablets coated with the ammonia salt solution were swollen after 2 h. The disintegration times of these two products were less than 20 min.

3.1.6 Optical appearance after the release study

The optical appearance of pellets in the acidic dissolution medium was observed with CAP-MO pellets (Product K). It was found that the greatest portion of the CAP-MO pellets was broken within 30 min (Figure 3.6). The inner core of the pellets had now a pink colour, because methyl orange had changed to its protonated form. Only the outer CAP layer was broken. However, since the pellet below the CAP film was not destroyed but swollen and/or partly dissolved, it cannot be the CAP film layer, which hindered the release of methyl orange from the pellets. Therefore further investigations were carried out to elucidate the delay of the release of methyl orange.

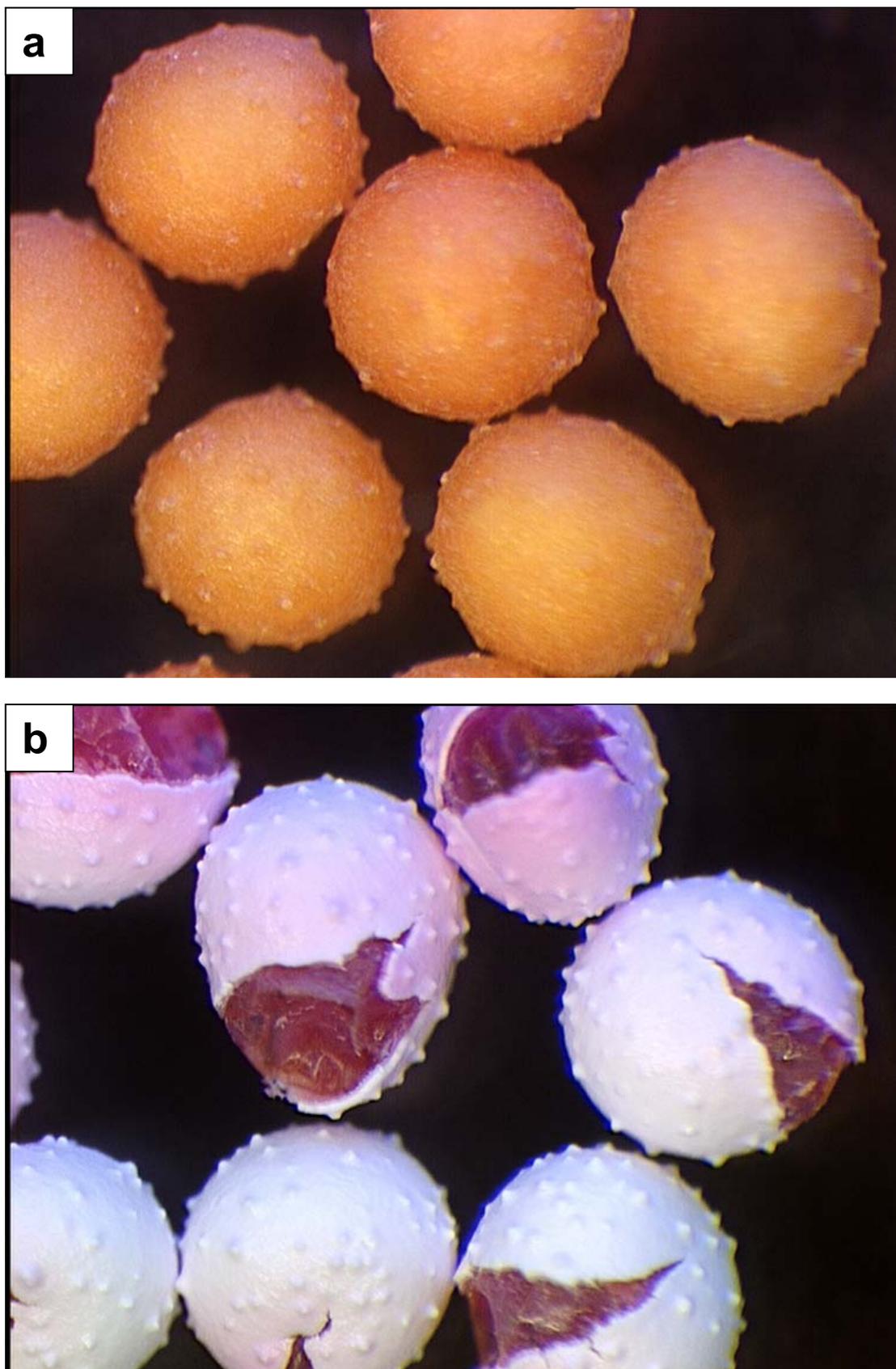


Figure 3.6: Optical appearance of CAP-coated pellets containing methyl orange (Product K); a) before and; b) after exposure to 0.1 N HCl, 37 °C for 30 min.

3.1.7 Content of phthalyl in coated pellets

The data of calculated contents of phthalyl groups based on different products are demonstrated in Table 3.3. The amount of methyl orange in one pellet was already determined and the mean value was 0.75 μg or 0.002 μmole . The amount of phthalyl in different enteric coated pellets was calculated both in μg and μmole . The mole ratio of phthalyl and methyl orange can be calculated as follows; For example Product L had phthalyl of 0.43 μmole . Therefore the mole ratio between phthalyl and methyl orange was $0.43/0.002 = 215$. This ratio was the highest one compared to all enteric coated pellets. This means that the content of methyl orange incorporated in one pellet was very low compared to the content of phthalyl groups. The mole ratio of the samples used for determination by FTIR and NMR was $0.003/0.015 = 0.2$. This means the mole ratio of phthalyl groups and methyl orange in the FTIR and NMR technique was lower than that in the released study, but the content of methyl orange incorporated into the mixture was higher. This may make it possible for determination of salt bonding which may happen.

Product	Weight gain of total batch (% w/w)	Weight of pellet (mg)	Amount of coated solid (mg)	Amount of Aquacoat CPD (mg)	Amount of CAP (μg)	Calculated phthalyl content (μg)	Calculated phthalyl content (μmole)	Mole ratio of phthalyl and methyl orange ($\mu\text{mole}/\mu\text{mole}$)
B	4.5	1.07	0.05	0.04	9	3	0.02	10
C	6.0	1.11	0.07	0.05	12	4	0.03	15
D	8.0	1.16	0.09	0.07	17	6	0.04	20
E	11.0	1.20	0.13	0.11	24	8	0.06	30
F	17.5	1.32	0.23	0.19	43	15	0.10	50
G	19.0	1.38	0.26	0.21	48	17	0.11	55
H	31.0	1.50	0.47	0.37	86	30	0.20	100
J	45.0	1.63	0.73	0.59	135	47	0.32	160
K	45.0	1.60	0.72	0.58	133	47	0.31	155
L	56.0	1.77	0.99	0.79	182	64	0.43	215
M	11.0	1.21	0.13	0.11	25	9	0.06	30
N	11.0	1.16	0.13	0.11	24	8	0.06	30

Table 3.3: Phthalyl content in one pellet of different products containing methyl orange (MO) and the ratio between the phthalyl content and methyl orange.

3.1.8 Hypothesis of salt formation between methyl orange and CAP

The delay of the release of methyl orange from CAP coated pellets (Figure 3.5, Products J and K) cannot be caused by the thickness of the CAP layer alone because the CAP film layer was broken after exposure to 0.1 N HCl for a certain time as already mentioned in 3.1.6. The other mechanism such as chemical bonding may be responsible for the delay of release as well. If the chemical structure of methyl orange (MO) in 0.1 N HCl is considered, it is supposed that the protonated nitrogen atom of methyl orange could form salt with oxygen atom of the dissociated carboxylic groups in CAP (Figure 3.7). Therefore two spectroscopic methods i.e. FTIR- and NMR-technique were used to determine the extent of a possible salt bonding between methyl orange and the carboxylic groups of CAP.

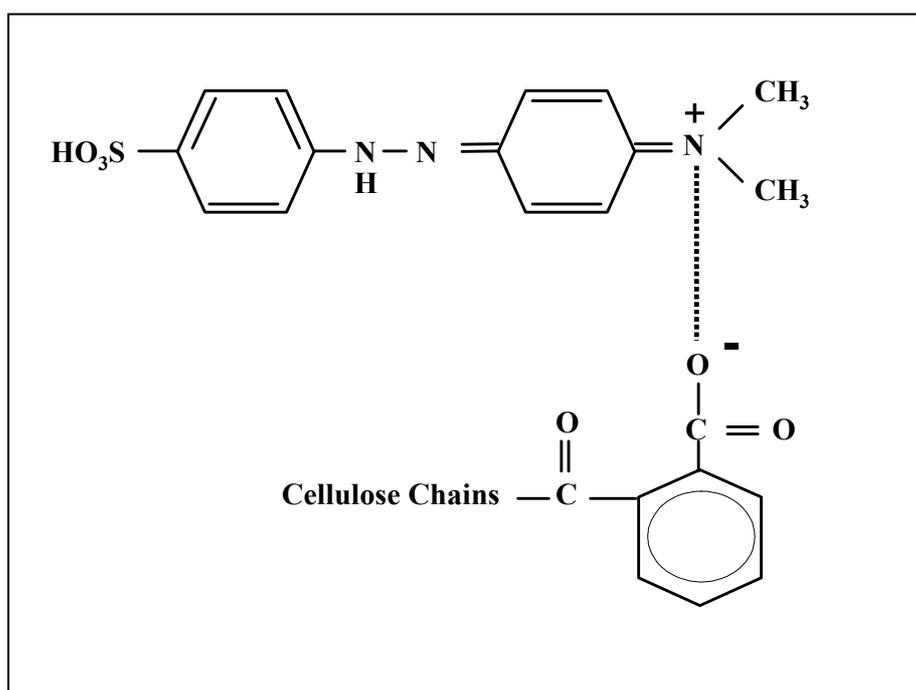


Figure 3.7: A scheme shows a possible salt formation between the positively charged nitrogen atom of methyl orange and the oxygen atom of the phthalyl group of CAP due to an association of the proton from the carboxylic group with anionic sulfonyl group of methyl orange.

3.1.7.1 FTIR

The interpretation of different bands was performed by using the table of absorption of different chemical groups demonstrated in the literature <201,72,66>. The comparison of the spectra of four samples i.e. methyl orange powder as a sodium salt (a), methyl orange as a protonated form by dispersing powder in 1 N HCl and subsequent drying at r.t. (b), the dried film of CAP and TEC (c) and the dried mixture of CAP, TEC and MO (d) was performed. Figure 3.8 shows the characteristic sharp bands of these four samples. The broad band at the region 3450 cm^{-1} in Figure 3.8a and Figure 3.8b indicates the valency vibration of the CH – groups and bands at the region of 2800 cm^{-1} - 2900 cm^{-1} indicate the N – CH₃ groups in the samples of methyl orange. However, the broad band in the region of $3450 - 3500\text{ cm}^{-1}$ and $2800 - 2900\text{ cm}^{-1}$ in Figure 3.8c indicates the associated OH - group of CAP. The carbonyl of ester groups shows a sharp band at 1738 cm^{-1} and also bands at 1600 , 1580 , 1490 cm^{-1} . The aromatic band is at 1450 cm^{-1} . The absorption bands of ester are in the finger print region of 1370 cm^{-1} and 1230 cm^{-1} . A vibration of valancy of C – O group shows a strong band at 1100 cm^{-1} . The bands of absorption of aromatic groups are at the regions of 800 cm^{-1} and lower. Figure 3.8d shows the combination of specific bands from methyl orange and CAP. Figure 3.9 shows the higher magnification of the spectra between $700 - 1700\text{ cm}^{-1}$. The typical bands of the chemical group N = N of the sodium salt of methyl orange can be seen clearly at peaks 1518 , 1444 , 1421 , 1390 , 1366 , 1313 , 1217 , 1185 , 1119 , 1038 and 1007 cm^{-1} in Figure 3.9 a. The sharp band at 1605 cm^{-1} indicates the aromatic groups. The bands lower than 900 cm^{-1} indicate substituents at the benzene ring. Figure 3.9b shows the typical bands of the chemical group N - N or N = N of the protonated form of methyl orange i.e. 1404 , 1385 , 1262 , 1235 , 1183 , 1163 , 1114 , 1026 and 1006 cm^{-1} . The bands in the region of $1500 - 1650\text{ cm}^{-1}$ indicate the aromatic groups and the bands below 900 cm^{-1} indicate substituents at the benzene ring of methyl orange as well. Figure 3.10 shows the difference of bands in the region between 1000 and 1200 cm^{-1} . The new band can be seen at 1069 cm^{-1} in Figure 3.10d, demonstrated by an arrow, because the spectra of the samples of methyl orange (Figure 3.10a and Figure 3.10b) and CAP with TEC (Figure 3.10c) does not contain this band. The new band may correspond to the change of the carbonyl group of CAP as it was known that the band in the region of $1040 - 1150\text{ cm}^{-1}$ demonstrates the vibration of a valancy of C – O in the C - OH group <201,72>. Normally the N - CH₃ group shows

a medium sharp band in the region of $2820 - 2780 \text{ cm}^{-1}$ and the - OH group of the carboxylic groups normally shows a broad band in the region of $3200 - 2500 \text{ cm}^{-1}$. The ammonium salt shows band in the region of about 3000 cm^{-1} . However, the difference of bands in the region of $2700 - 3500 \text{ cm}^{-1}$ and $3300 - 3500 \text{ cm}^{-1}$ was not clearly seen in the above mentioned four spectra which may be due to the interference of chemical bonding of - OH and N - CH_3 groups.

The possibility of using FTIR technique to determine the chemical bonding was also demonstrated in many works [121,165,155]. For example: Oschmann [121] showed the possibility of using the FTIR technique in studying the stability of films from CAP. He found that after storing films at $40 \text{ }^\circ\text{C}$ for 1 year, the intensity of bands was increased especially at the region of $3500 - 2500 \text{ cm}^{-1}$ which may be due to the increase of the content of free hydroxyl groups. No significant new bands could be detected after this storage condition. However, after storage at the higher stress condition of $60 \text{ }^\circ\text{C}$ and 80 % r.h. for 1 year, two double bands at 2550 and 2750 cm^{-1} , represented the carboxylic acid groups, could be clearly seen. Moreover there was a shifting of band of the carbonyl group to lower wavelength numbers which indicated that there was a high degree of free acid instead of ester groups. This phenomenon was also confirmed by the presence of a single band at 1580 cm^{-1} instead of double bands in this region and double bands at 800 cm^{-1} also changed into a single band. Oschmann concluded that the result from the IR technique showed clearly that films from CAP after exposition to stress conditions contained a higher amount of free phthalic acid which occurred from the splitting of the ester groups of CAP.

Schierz [165] has used IR technique to determine the ammonium salt, which has bands in the region of 1500 to 1600 cm^{-1} , in different coating formulations and coating techniques. Schierz also used the IR technique to find out the suitable method to remove ammonia from the polymer because ammonia contained in the film layer after finishing the coating process was not desired. For this reason films from the fluidized-bed technique and from the casting technique were used as samples. Both the aqueous and alcoholic formulations were observed in comparison.

Roxin, Karlsson and Singh [155] studied the stability of CAP by using IR technique. They showed the differences in infrared spectra of the fresh powder of CAP and the CAP powder after storage under a stress condition at $40 \text{ }^\circ\text{C}$, 89 % r.h., for 15 weeks. The spectra of the stored sample showed characteristic bands in the region of 2600 , 1700 , 1400 , $1000 - 400 \text{ cm}^{-1}$ of phthalic acid that were not present in the fresh sample.

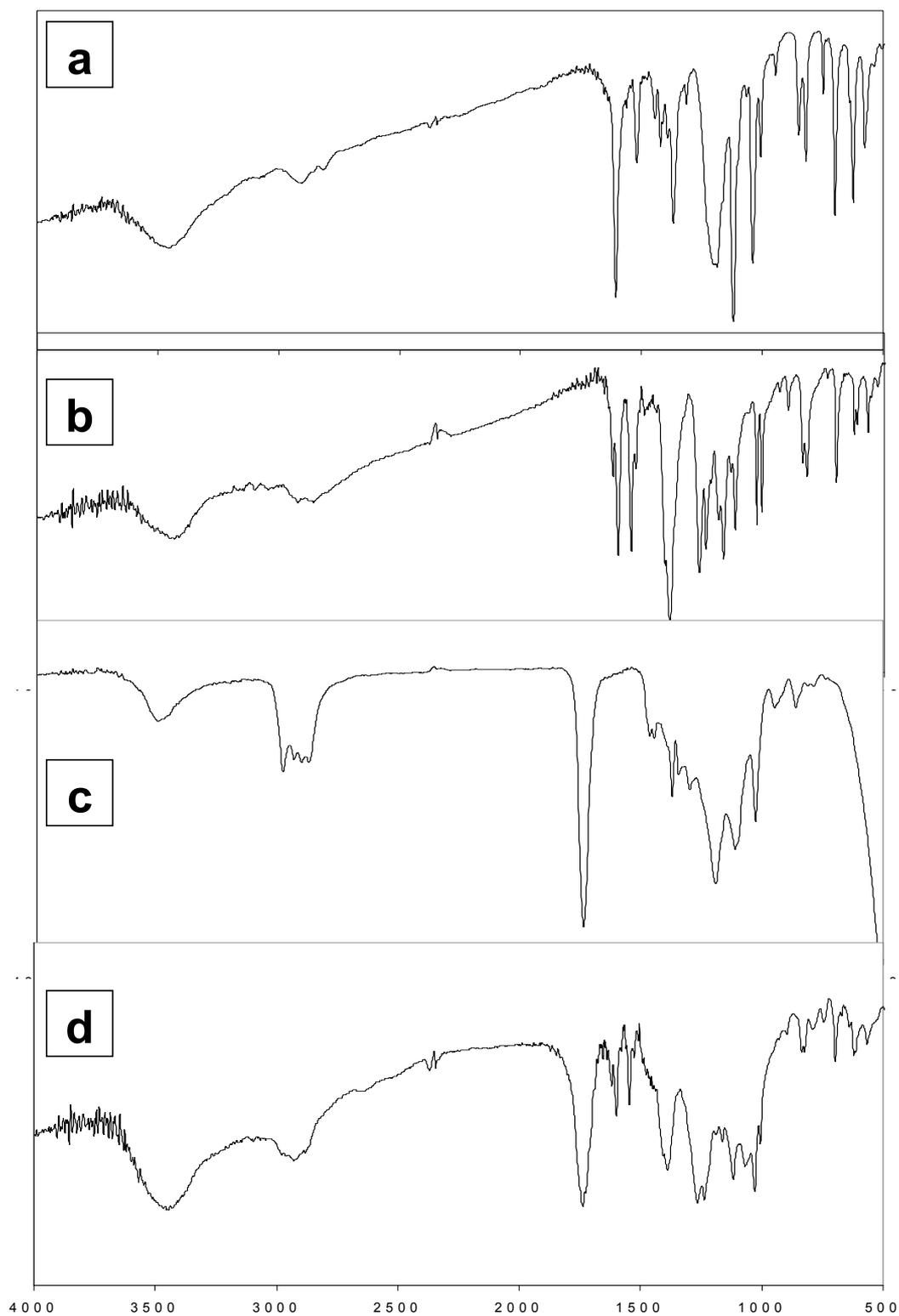


Figure 3.8: FTIR spectra of four samples; a) methyl orange (MO) powder in KBr; b) MO-protonated by dispersing powder in 1 N HCl and subsequent drying at r.t., in KBr; c) film from CAP and TEC in dichloromethane on NaCl disc; d) dried mixture from CAP, TEC and MO, in KBr.

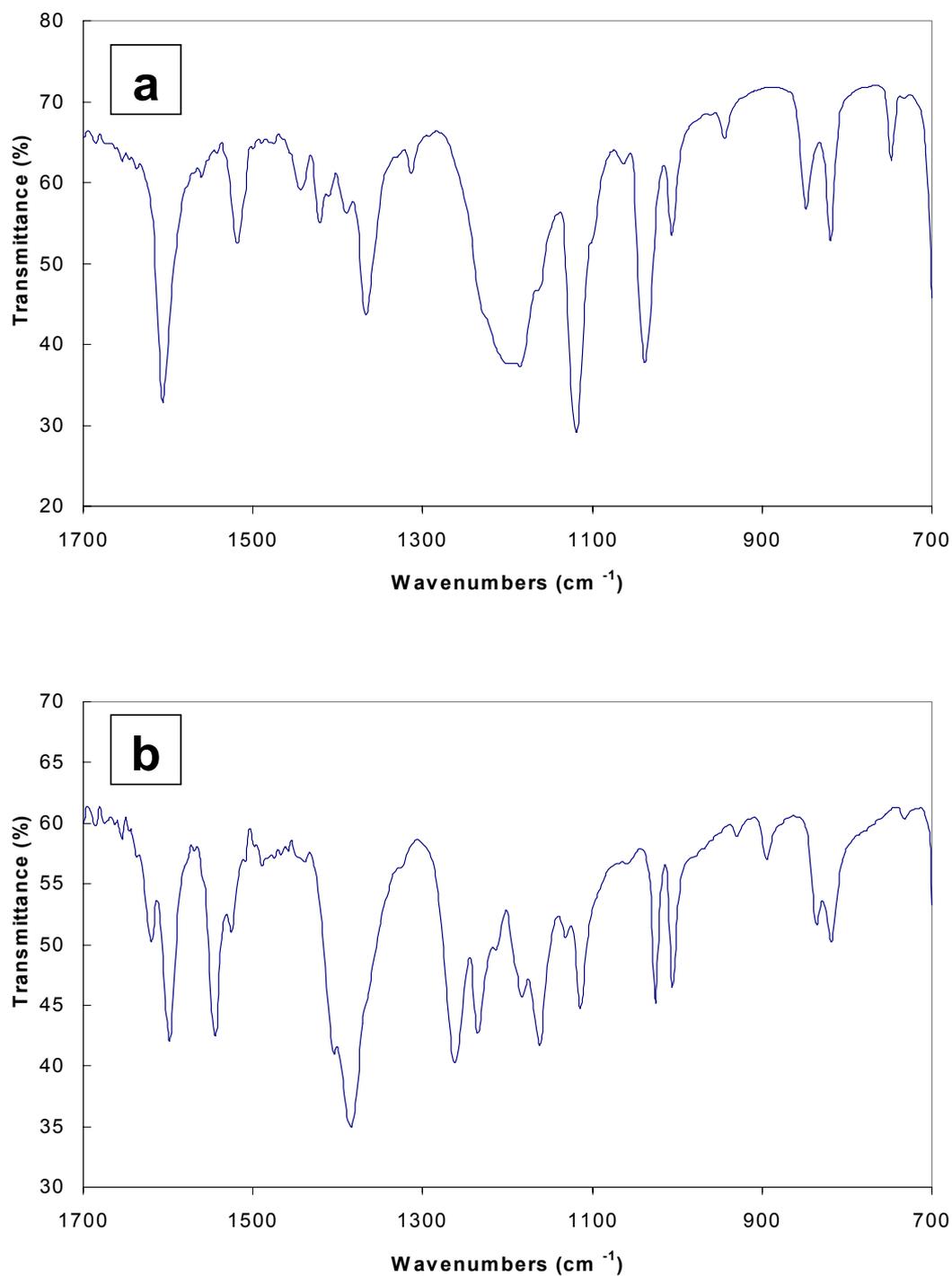


Figure 3.9: FTIR spectra of substances; a) methyl orange (MO) powder in KBr; b) MO-protonated by dispersing powder in 1 N HCl and subsequent drying at r.t., in KBr.

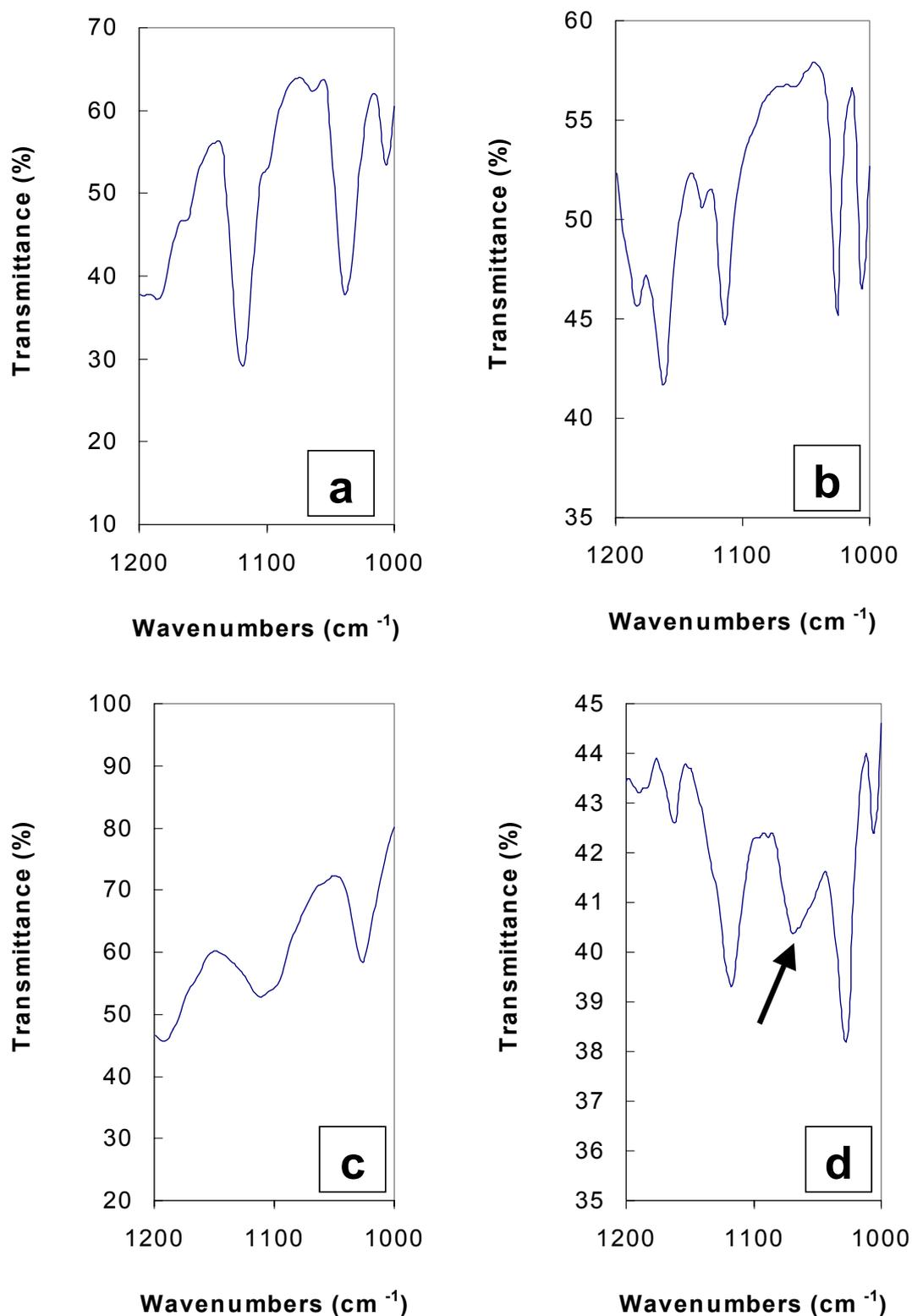


Figure 3.10: FTIR spectra of four samples; a) methyl orange (MO) powder in KBr; b) MO-protonated by dispersing powder in 1 N HCl and subsequent drying at r.t., in KBr; c) film from CAP and TEC in dichloromethane on NaCl disc; d) dried mixture from CAP, TEC and MO, in KBr; the arrow shows new band.

3.1.7.2 NMR

The residual solvent signal of the deuterated dimethyl sulfoxide (DMSO- d_6) is shown at 2.50 ppm and the signal of the internal reference tetramethylsilane (TMS) appears at 0.0 ppm. Only the results from the ^1H -NMR spectra are presented because information from the ^{13}C -NMR was very limited.

Figure 3.11 to 3.14 show the results from ^1H of NMR. Only the region from 0 to 8 ppm is demonstrated because there are no bands in the region from 8 to 16 ppm. The NMR spectra of methyl orange as a sodium salt and a protonated form are shown in Figure 3.11 and 3.12, respectively. A shift of one band at 3.35 (Figure 3.11) to 3.42 ppm (Figure 3.12) and a double bands at 3.18 and 3.17 ppm (Figure 3.11), shown by arrows, may indicate the change in the nitrogen atom connected to methyl groups at the periphery. However, the result from ^{13}C of NMR method showed no significant difference between methyl orange sodium salt form and its protonated form. Both of them show the same bands at 126.4, 124.7, 121.1, 111.5 and 39.7 ppm.

Figure 3.13 shows the characteristic bands of a CAP film containing TEC. Figure 3.14 shows the spectrum of a dried mixture of CAP, TEC and methyl orange. After comparing the four ^1H NMR spectra (Figure 3.11 - 3.14) a new group of bands can be found in the region of 7.65 - 7.68 ppm, as demonstrated by an arrow. The other bands in Figure 3.14 originated from methyl orange (normal type letters) and from CAP+TEC (italic letters).

In the literature concerning the NMR spectroscopy, the chemical shifting in the region of 7 - 9 ppm is mostly caused by the aromatic groups $\langle 72 \rangle$. If the aromatic group does not contain any substituents the ^1H signal will be at 7.26 ppm. If the aromatic group contains a substituent such as COOH or N(CH₃) there may be a shifting. For example: if the substituent is COOH the ^1H signal, calculated by addition of the maximum value of (+ 0.8) to the value of non-substituent one (7.26), will be at the higher region i.e. 8.06 ppm. However, if the substituent is N(CH₃) the ^1H signal, calculated by addition of the maximum value of (- 0.67) to the value of non-substituent one (7.26), will be at the lower region i.e. 6.59 ppm. This present study shows that the new bands of ^1H NMR appear at the region of 7.65 - 7.68 ppm, which lay in the region of the aromatic group with a substituent. The new bands possibly resulted from the change of the substituents at the aromatic groups of methyl orange and the phthalyl group of CAP.

The possibility of determination of the phthalyl groups of CAP by NMR technique was also studied by Roxin, Karlsson and Singh <155>. Both the ^1H -NMR and ^{13}C -NMR have been employed to determine the degradation products (acetic acid and phthalic acid) from the powder of CAP polymer. DMSO was used as a solvent. They showed that this technique can be used to determine the amount of acetyl and phthalyl groups in relation to the polymer by using specific shifts at 2.2 - 1.8 ppm and 7.9 - 7.2 ppm, respectively, though there were several overlaps in the proton signals from cellulose. Roxin, Karlsson and Singh have also stored the powder of CAP at various conditions; partial pressure of 22.1 to 65.6 mbar and/or temperatures of 20 to 60°C, a loss in the degree of substitution was found. The acetyl content was reduced from 19.4 % w/w in a fresh sample to 9.2 % w/w after storage at a stress condition of 65.6 mbar and 40 °C and the phthalyl contents was reduced in the same manner i.e. from 33.5 % w/w to 19.6 % w/w. They mentioned that the storage humidity was a major parameter influencing the rate of hydrolysis of the CAP polymer. It can be seen from the work of Roxin, Karlsson and Singh that the signal of phthalyl groups (7.9 – 7.2 ppm) was almost in the same region as in this present study with a shift in the region of about 7.6 ppm.

The determination of the substances by using the two techniques (FTIR and NMR) has given the opinion that the new band in FTIR spectrum and the shifting of ^1H NMR signals may be due to the salt bonding between the nitrogen atom of methyl orange and the oxygen atom of phthalyl group.

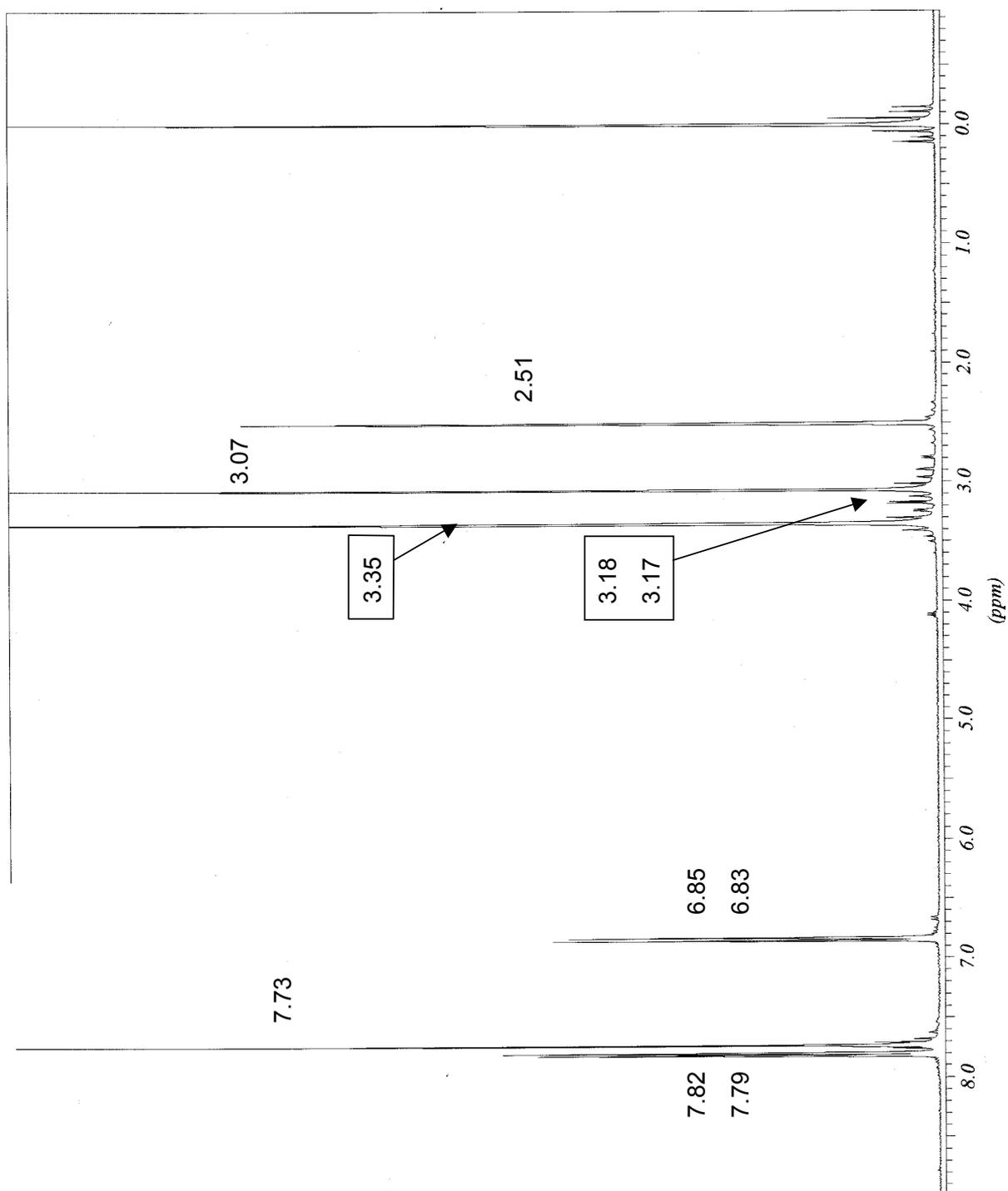


Figure 3.11: $^1\text{H-NMR}$ spectrum of methyl orange (MO) yellow coloured powder in DMSO.

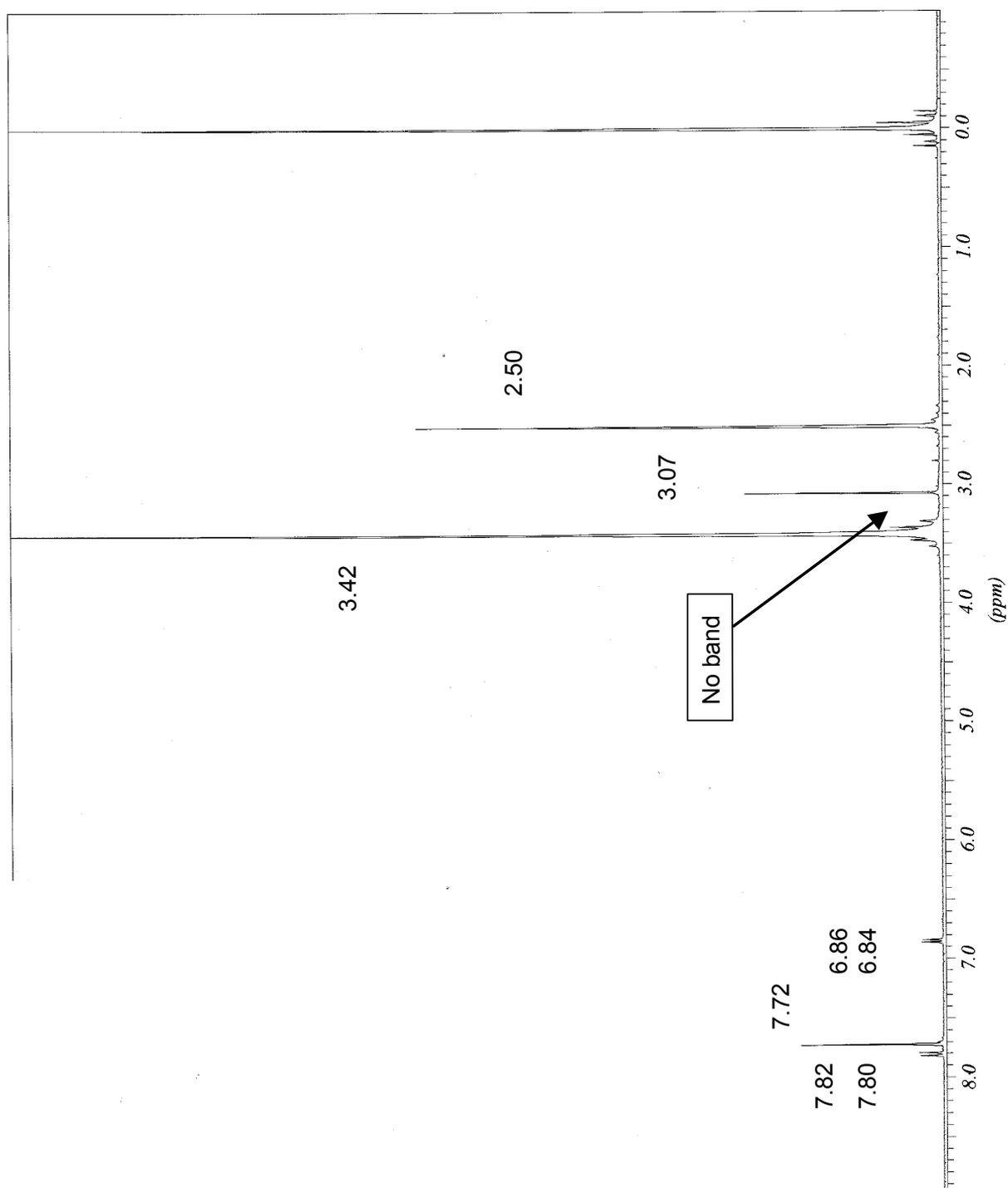


Figure 3.12: $^1\text{H-NMR}$ spectrum of MO - protonated by dispersing powder in 1 N HCl and subsequent drying at r.t., red coloured powder in DMSO.

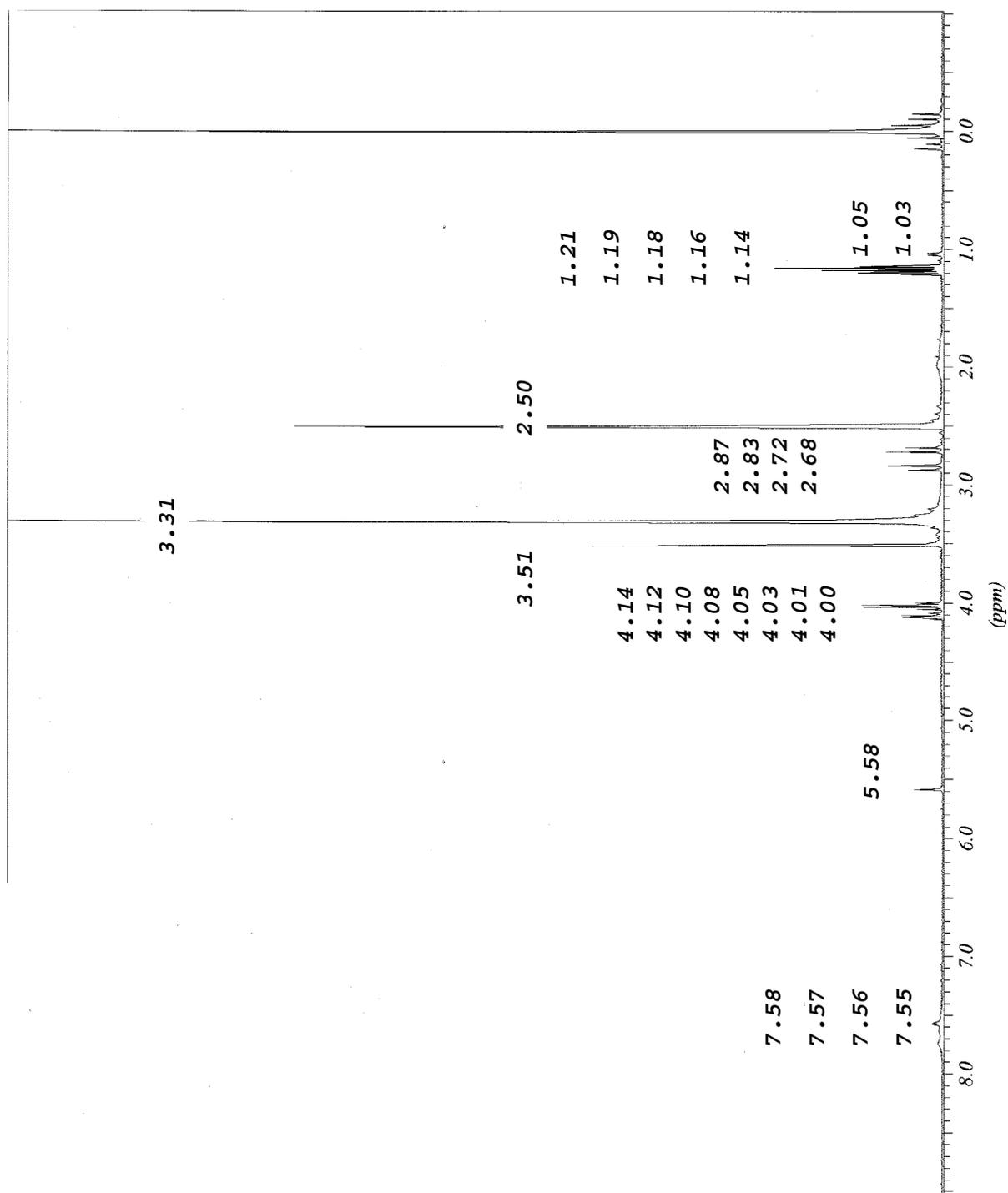


Figure 3.13: $^1\text{H-NMR}$ spectrum of film from CAP and TEC in DMSO.

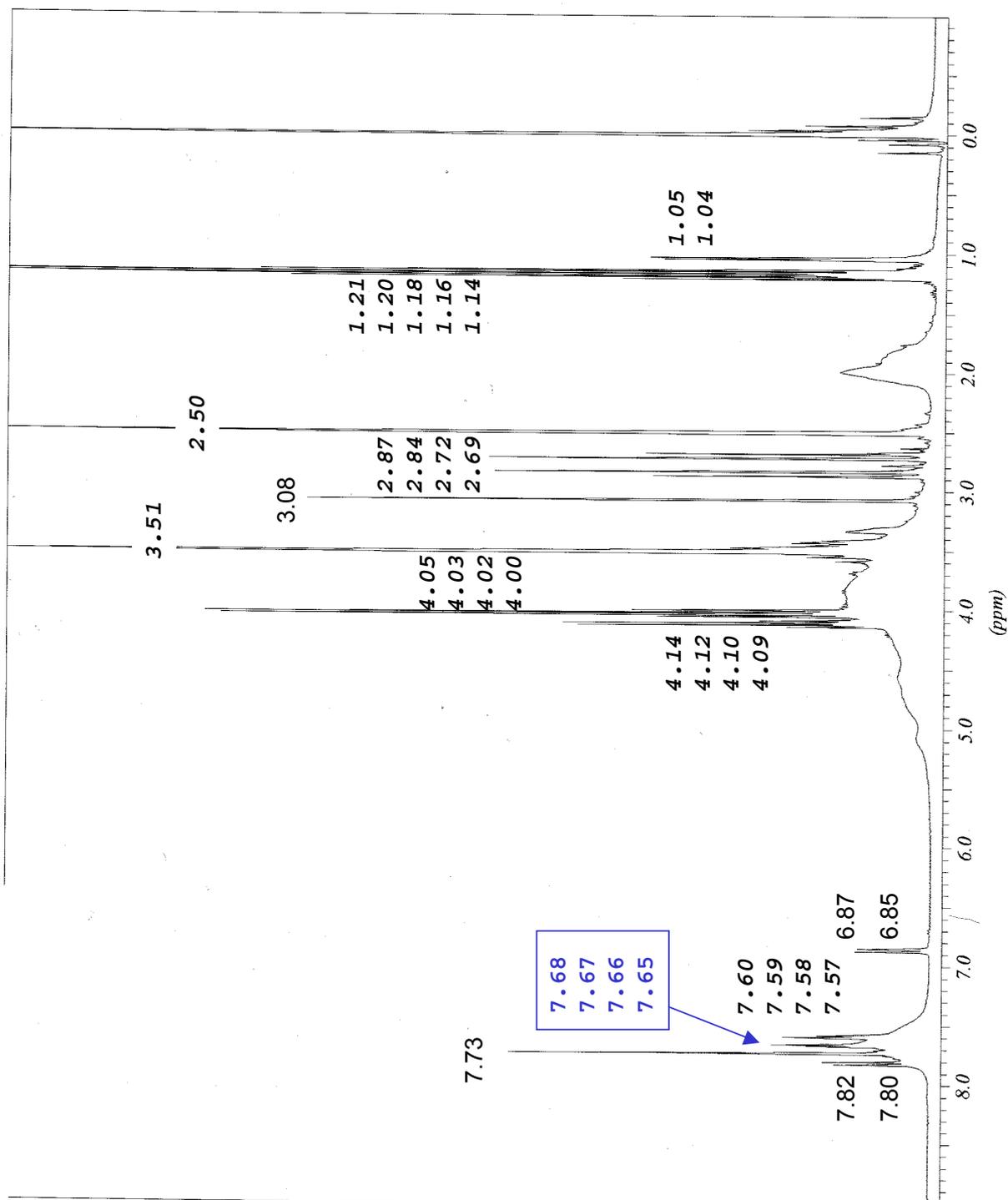


Figure 3.14: $^1\text{H-NMR}$ spectrum of a dried mixture from CAP, TEC and MO in DMSO.

3.2 Pellets with nicotinamide and HPMC as a subcoat

a) Placebo: HPMC-coated pellets (HPMC pellets)

The dissolution of sugar from the surface of the spheres may happen especially if the coating process with an aqueous base solution required a long time and the spraying rate was slow so that it took a long time to coat all the surface of the sugar spheres. The seal coat with HPMC can hinder the high dissolution of the surface because less time was necessary to coat all the surfaces with HPMC than to layer with nicotinamide and HPMC as a binder. The HPMC coated pellets (Product PP) later-on had a white colour because of the clear film layer. These pellets were achieved from the combination of a formulation **R1** and a process number **X7**, as demonstrated in the Table 2.26.

b) Nicotinamide loaded pellets: Nico pellets

The Nico pellets (Product AA) had also a white colour because HPMC was used as a binder. These pellets were achieved from the combination of a formulation **R3** and a process number **X8**, as demonstrated in the Table 2.26.

Williams and Liu <200> used pellets, which were prepared by the extrusion-spheronization method, as core materials. These pellets contained theophylline, Avicel PH 101 and lactose in a ratio of 1:2:1. The size of core pellets was 16 - 20 mesh. The preparation method of pellets is an extrusion-spheronization which contained a lot of insoluble substances (microcrystalline cellulose and lactose), i.e. 3 parts of fillers and one part of drug. The insoluble drug can hinder the diffusion of the drug from the core. In the present study the drug was layered in a thin layer with only a little binding substance, HPMC. This layer of drug can directly contact the adjacent film layer. This model was used in order to observe the effect of outer film layer on the inner core which contained water soluble drug and was a weak base. The physical and chemical effects were observed. The 16 - 20 mesh size of pellets prepared from Williams and Liu <200> is comparable to the size of 1000 µm of sugar spheres used in this present study.

c) HPMC as a subcoat: HPMC-Nico pellets

The HPMC-Nico pellets (Product BB to DD) had an orange colour as a marker was used. These pellets were achieved from the combination of a formulation **R4** and a process number **X9**, as demonstrated in the Table 2.26.

HPMC was applied in this work in order to achieve the non-ionic polymer layer. This layer will be used as a subcoat or intermediate coat to separate the layer of drug and the enteric polymer layer.

d) Enteric coated pellets: CAP-HPMC-Nico pellets

The CAP-HPMC-Nico pellets (Product EE to NN) still had an orange colour caused by the marker. Therefore these finished CAP-coated pellets could be well selected from the other pellets, which have the colour of pink (EC as a subcoat), blue (PVA+EC as a subcoat), green (EC+PVA as a subcoat) and white (Placebo). The same coating conditions were well performed by mixing different loading materials. The CAP-HPMC-Nico pellets were achieved from different combinations of a formulation (R8 - R11) and a process number (X17 - 19), as demonstrated in the Table 2.26.

A specialist, Mr. Carlin <25>, recommended that the plasticizer content should be 20 % – 24 % and the dispersion should be stirred after adding for 30 min. On the other hand, in the work of Williams and Liu <200>, a high plasticizer content of 35 % was used and stirred for 24 h because droplets of the plasticizer were still observed after 1 h. Dibutyl sebacate (DBS) is not a recommended plasticizer for Aquacoat CPD <25>. However, Mr. Carlin does not give further details about unsuitable properties of DBS.

3.2.1 Film quality, diameter and weight of pellets

The physical properties of raw materials used for this process and for the finished products are shown in Table 3.4. The mean diameter of the raw material (sugar spheres with a size fraction of 800 - 1000 μm , SS) determined by an image analyser was $970 \pm 37 \mu\text{m}$. The mean diameter of the HPMC-coated pellets (Product PP) was $970 \pm 34 \mu\text{m}$. According to 2.2.2 the standard deviation of 34 - 37 μm was equivalent to about 2 pixel which was quite acceptable. The comparison between the mean diameter of the raw material (SS) and the HPMC-coated pellets (Product PP) showed that the diameter was not significantly different. Consequently, the coating process was well carried out and homogeneously coated pellets resulted.

The thickness of the HPMC layer (Product PP) as measured by the SEM was about $9 \pm 3 \mu\text{m}$. The structure of the film was homogeneous and did not contain cracks. This means that these pellets can be well used for the layering of nicotinamide.

The mean weight of one HPMC pellet (Product PP) was $0.66 \pm 0.01 \text{ mg}$, which was negligibly lower than that of sugar spheres. This may be due to the dissolving of the sugar from the surfaces of the spherical cores. After layering the HPMC pellets with nicotinamide and applying HPMC as a binder the Nico pellets resulted. One Nico pellet (Product AA) had a mean weight of $0.75 \pm 0.02 \text{ mg}$ and a mean diameter of $1010 \pm 35 \mu\text{m}$. The thickness of the nicotinamide layer (Product AA) was $22 \pm 3 \mu\text{m}$ and the weight gain of these Nico pellets were 11.3 % w/w. Nicotinamide was recrystallized again as rod-crystals on the surface of HPMC pellets after water was evaporated. The structure of this nicotinamide layer was loose. Details were discussed in 2.4.3.

The subcoat from HPMC has been achieved in three different thicknesses; i.e. 12 ± 2 , 26 ± 3 and $38 \pm 5 \mu\text{m}$ with amounts of HPMC of 7.5, 15 and 22 % w/w respectively. The SEM photograph in Figure 3.15a shows the thickness of HPMC layer of Product BB and that the layer was homogeneous. The mean weight and the mean diameter of one pellet compared between cores (Product AA) and HPMC-Nico pellets (Product BB to DD) allowed to calculate amounts of HPMC-polymer coated per pellet, namely from 7.5 to 21.2 mg cm^{-2} .

Table 3.4 shows the physical properties of CAP-coated pellets. As expected, as the amount of CAP coated onto the HPMC-Nico pellets increased, the CAP film layer also

increased in the thickness. The layer of CAP and DEP as a plasticizer showed big cracks with a length of about 20 μm on the surface (Figure 3.15b). From the top view of the whole pellet, the porous regions can also be well demonstrated (Figure 3.16a). This may be due to the high drying rate so that the CAP particles did not have enough time to fuse together. On the other hand if the drying capacity was not high enough local wetting might have occurred, which would cause sticking of the CAP coated pellets. There was no difference between the CAP film layer from Aquateric or Aquacoat CPD as judged from physical properties of the products. Therefore, further trials were made by using only Aquacoat CPD as a source for CAP. Because the preparation method of the dispersion of Aquacoat CPD required less steps than of Aquateric which in addition needed Tween 80. The preferable use of Aquacoat CPD rather than Aquateric was also recommended by a specialist of FMC, Mr. Carlin <25>.

In this present work before the coating process was performed the dispersion containing CAP and DBS (R8, Table 2.22) was dried in a hot air oven at the temperature of 45 °C up to a constant weight but the resulted films were only partially transparent. However, the drying process in a hot air oven was not the same process as it appeared in the coating process in a fluidized-bed apparatus. Therefore the coating process at the product temperature of 45 °C was performed to observe the film formation.

The result shows that the surface of the layer of CAP and DBS as a plasticizer under SEM is very rough. The whole pellet shows uneven regions (Figure 3.16b). This result may be due to the inhomogeneous distribution of DBS. The SEM photograph of the cross-section shows that many particles did not melt together (Figure 3.17a). The structure of CAP layer is very porous. Already during the cutting of the pellets for the SEM test, the pellets were crumbled without control. This present work shows that DBS seems not to be well distributed between the polymer chain and therefore resulted in the uneven film structure. However, DBS can hinder the formation of twins or agglomerates during the coating process. This may be due to the greasy property (water insoluble) of DBS.

The MFFT of CAP in combination with DBS was not reported. Therefore it may be necessary to determine the MFFT especially by the spraying technique. The casting method may not be suitable because of the sedimentation of the solid content or the cohesion of the plasticizer during the drying process.

It seems based on this present work that, if DBS should be used, the higher coating temperature may be necessary to receive the MFFT in order to bring the CAP particles to melt together. The best CAP film was achieved by using TEC as a plasticizer at the defined process conditions, however this film was not resistant to 0.1 N HCl. A cross-section of the CAP layer shows almost homogeneous film structure (Figure 3.17b) but there are small cracks of about 3 μm on the surface (Figure 3.18a). The big particles on the surface of CAP-HPMC-Nico pellets are Aerosil 200 particles, added to hinder the sticking of pellets during storage. Figure 3.18b shows the uneven position on the surface of a whole pellet. This means pellets coated with CAP and TEC, and HPMC as a subcoat, showed very clear uneven regions. This result appeared especially when a subcoat came from the hydrophilic polymer, e.g. HPMC or PVA. The following part (Part 3.5) confirms this again.

The film layer prepared from CAP and TEC was increased from 27 to 90 μm in order to observe whether the higher CAP thickness can resist the artificial gastric fluid or not.

The mean weight of one pellet was increased up to 1.51 ± 0.02 mg while the mean diameter of one pellet was 1395 ± 43 μm at the highest coating amount of 62 mg cm^{-2} .

In general, the standard deviations of all products in Table 3.4 have a range of only 32 to 44 μm , which demonstrates a well-controlled course of the coating processes, even when different materials are used for coating.

Product	Weight gain of total batch (% w/w)	Thickness of the layer ($\mu\text{m} \pm \text{SD}$)	Weight of pellet ($\text{mg} \pm \text{SD}$)	Diameter of pellet ($\mu\text{m} \pm \text{SD}$)	Coating amount (mg cm^{-2})	Release within the first five minutes (% \pm Range)
SS	0.0 ^a	800-1000 ^f	0.68 \pm 0.01	970 \pm 37	n	n
PP	3.2 ^b	9 \pm 3 ^g	0.66 \pm 0.01	970 \pm 34	n	n
AA	11.3 ^c	22 \pm 3 ^h	0.75 \pm 0.02	1010 \pm 35	n	n
BB	7.5 ^d	12 \pm 2 ⁱ	0.81 \pm 0.02	1040 \pm 32	7.5 ^k	n
CC	15.0 ^d	26 \pm 3 ⁱ	0.87 \pm 0.02	1070 \pm 40	15.0 ^k	n
DD	22.0 ^d	38 \pm 5 ⁱ	0.92 \pm 0.01	1100 \pm 41	21.2 ^k	99.0 \pm 1.0
EE	12.0 ^e	21 \pm 3 ^j	1.07 \pm 0.01	1190 \pm 42	15.8 ^l	80.5 \pm 1.0
FF	14.0 ^e	24 \pm 4 ^j	1.09 \pm 0.01	1200 \pm 37	17.9 ^l	n
GG	24.0 ^e	68 \pm 13 ^j	1.14 \pm 0.02	1230 \pm 44	23.1 ^l	96.0 \pm 1.0
HH	14.0 ^e	27 \pm 4 ^j	1.09 \pm 0.02	1200 \pm 33	17.9 ^l	14.0 \pm 1.0
JJ	17.5 ^e	34 \pm 3 ^j	1.13 \pm 0.02	1220 \pm 42	22.1 ^l	10.0 \pm 1.0
KK	22.0 ^e	44 \pm 3 ^j	1.19 \pm 0.01	1250 \pm 38	28.4 ^l	8.0 \pm 0.5
LL	31.0 ^e	62 \pm 4 ^j	1.32 \pm 0.01	1310 \pm 44	42.1 ^l	7.0 \pm 0.5
MM	45.0 ^e	90 \pm 5 ^j	1.51 \pm 0.02	1395 \pm 43	62.0 ^l	5.0 \pm 0.5
NN	45.0 ^e	89 \pm 7 ^j	1.50 \pm 0.02	1390 \pm 42	61.0 ^l	1.8 \pm 0.5

Table 3.4: Properties of different products showing weight gain of total batch, thickness of the layer, weight of pellet, diameter of pellet, coating amount, release within the first five minutes;

^a = weight gain of total batch of sugar spheres (% w/w), ^b = weight gain of total batch of HPMC pellets to sugar spheres, Product SS, (% w/w), ^c = weight gain of total batch of Nico pellets to HPMC pellets, Product PP, (% w/w); ^d = weight gain of total batch of HPMC-Nico pellets to Nico pellets, Product AA, (% w/w), ^e = weight gain of total batch of CAP-HPMC-Nico pellets to HPMC-Nico pellets, Product DD, (% w/w), ^f = size of sugar spheres, Product SS (μm), ^g = thickness of the HPMC layer (μm), ^h = thickness of the nicotinamide and HPMC layer (μm), ⁱ = thickness of the HPMC-subcoat layer (μm), ^j = thickness of the enteric coating layer (μm), ^k = coating amount of the HPMC-subcoat on Product AA (mg cm^{-2}), ^l = coating amount of the enteric coat on Product DD (mg cm^{-2}), n = not measured.

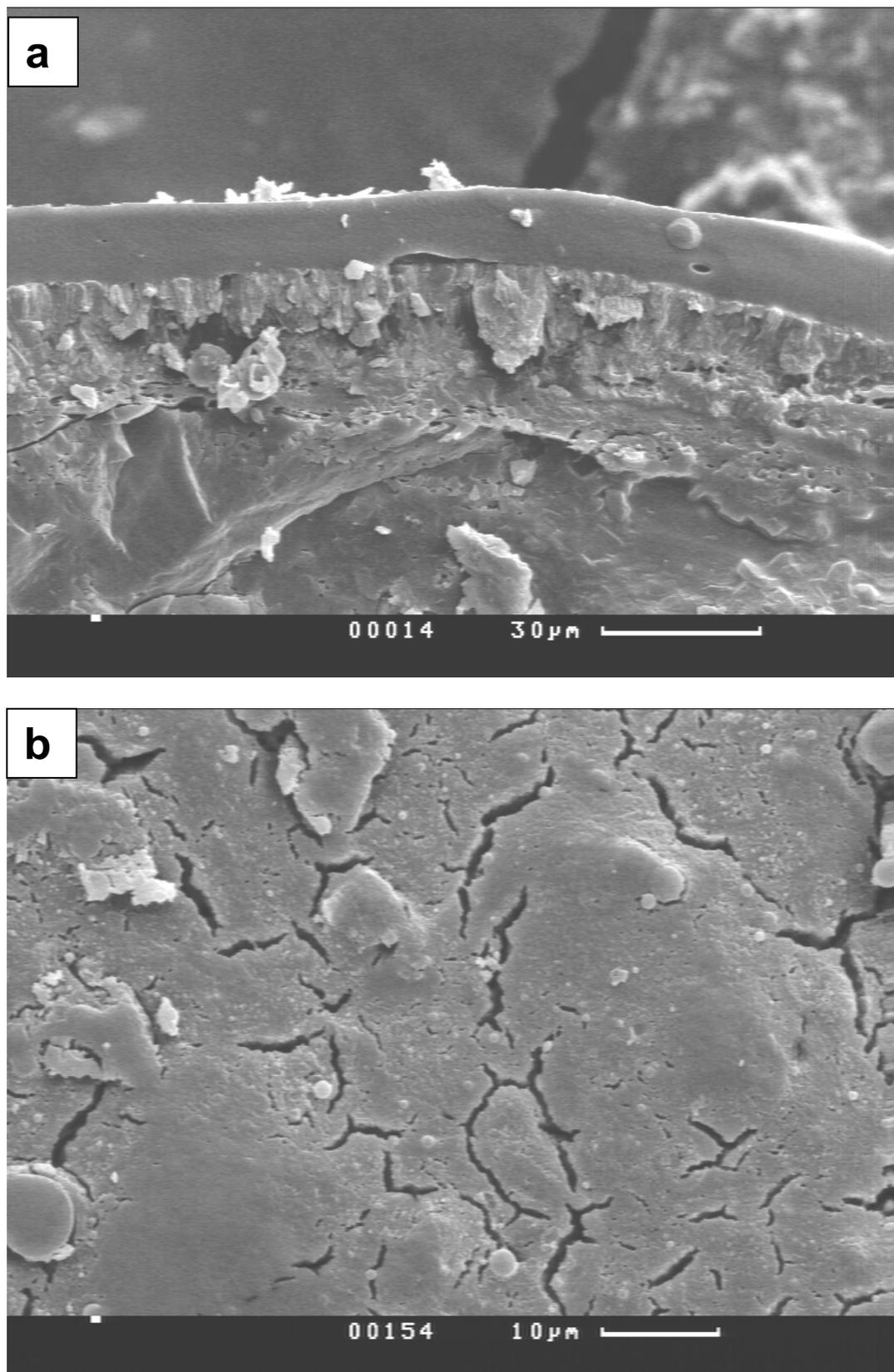


Figure 3.15: SEM pictures of coated pellets; a) the cross-section of a HPMC-Nico pellet (Product BB), magnification 680x; b) the surface of a pellet coated with CAP and DEP (Product EE), magnification 1,570x.

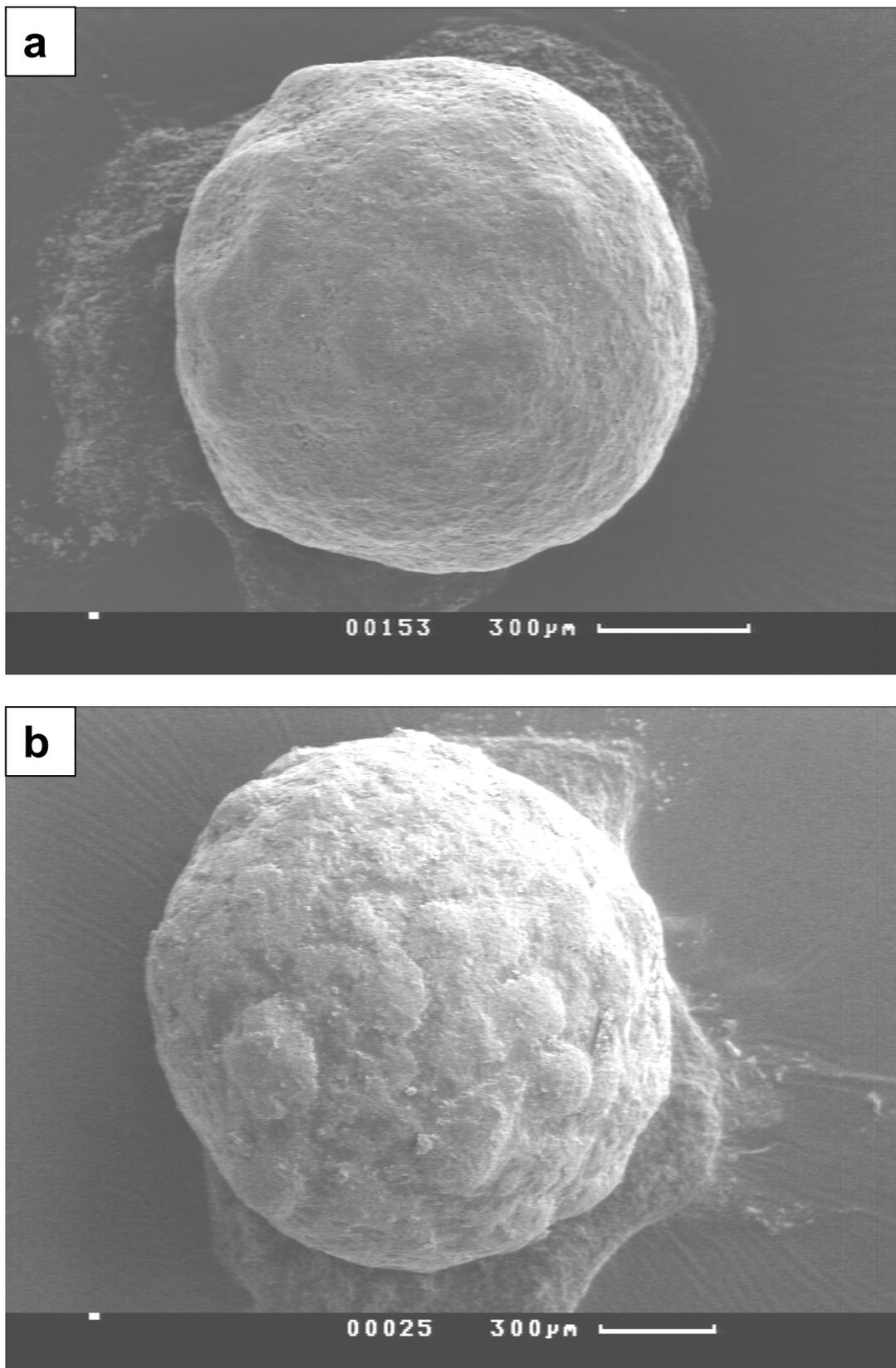


Figure 3.16: SEM pictures of enteric coated pellets; a) the top view of a pellet coated with CAP and DEP (Product EE), magnification 65x; b) the top view of a pellet coated with CAP and DBS (Product GG), magnification 49x.

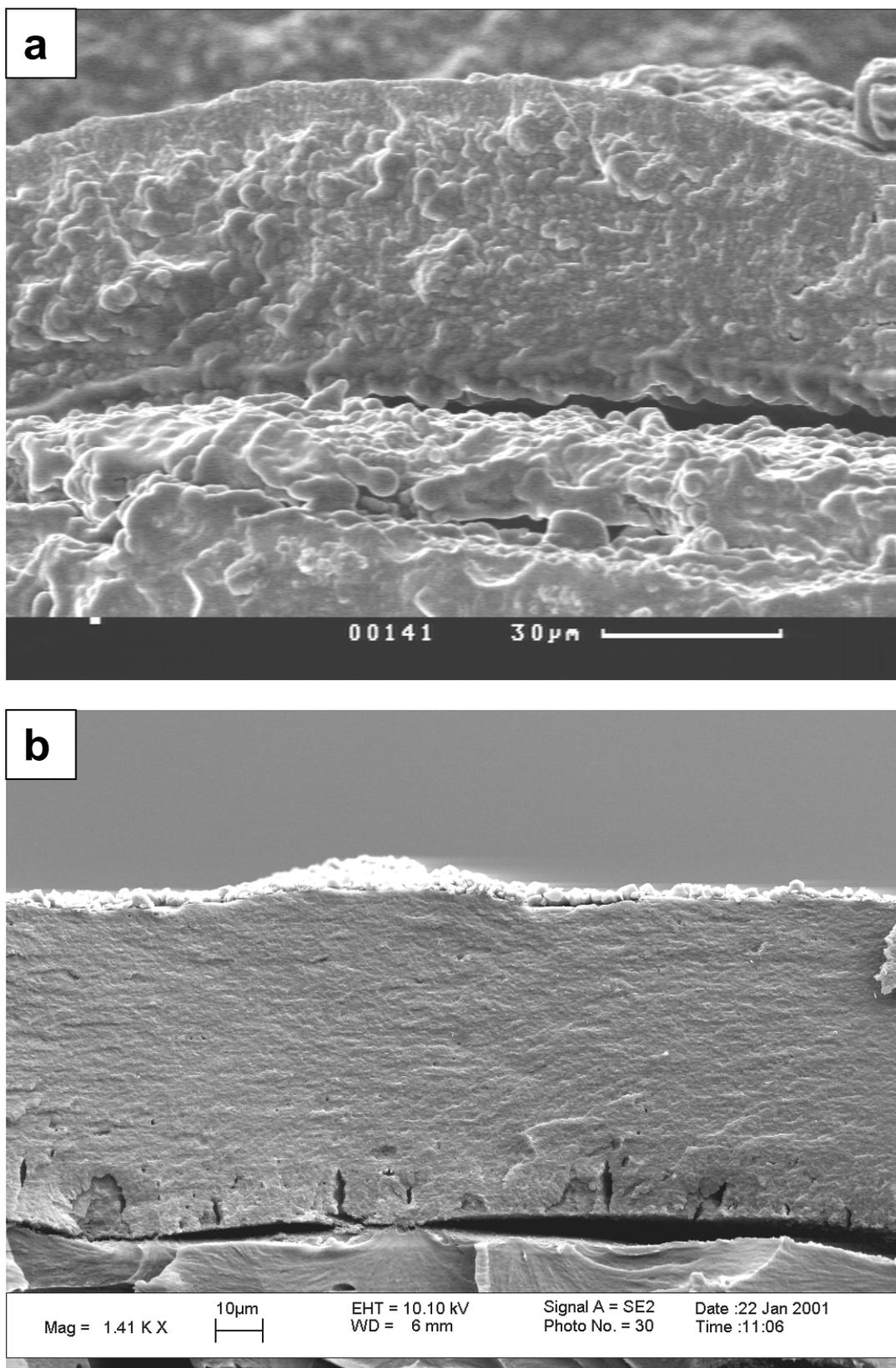


Figure 3.17: SEM pictures of coated pellets; a) the cross-section of a pellet coated with CAP and DBS (Product GG), magnification 740x; b) the cross-section of a pellet coated with CAP and TEC (Product NN), magnification 1,400x.

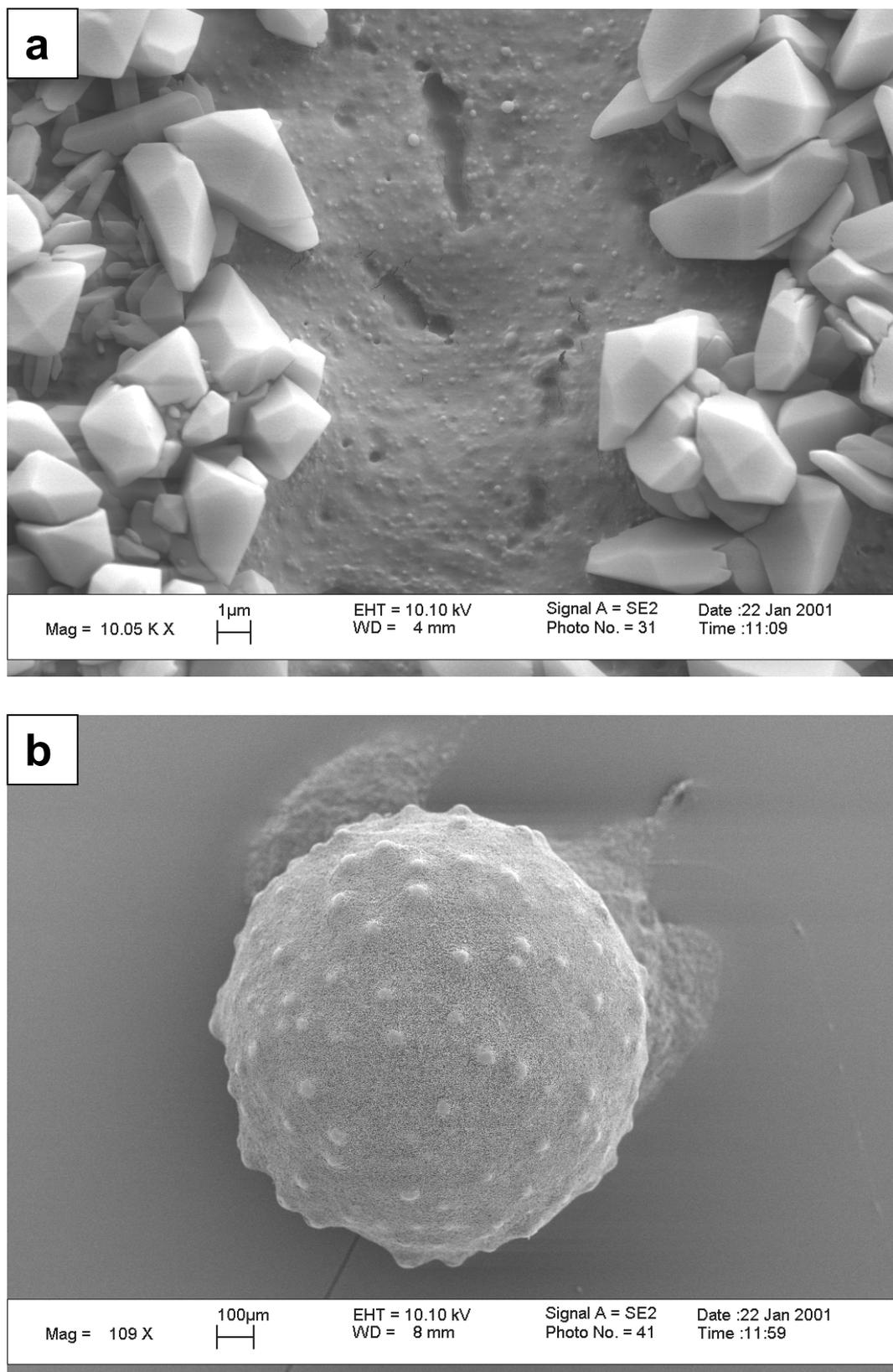


Figure 3.18: SEM pictures of pellets coated with CAP and TEC (Product NN); a) the surface of a pellet, magnification 10,050x; b) the top view of a pellet, magnification 109x.

3.2.2 Sieving

The content of each product (% w/w) was distributed in the size range which is comparable to the mean diameter measured by the image analyser. For example: Product NN has the highest amount (92.4 % w/w) in the size fraction of 1250 - 1400 μm , the mean diameter from Table 3.4 was $1390 \pm 42 \mu\text{m}$. This means that the diameter of pellets measured by the sieving technique was comparable with the measurement by an image analysing method. The sieving method was faster compared to the image analysing method but with the last method the pellets received a mechanical treatment by the vibration of the sieving apparatus. Therefore the undestructive method as image analysis was preferred for the determination of the diameters of pellets.

Size fraction (μm)	Type of product (%w/w)								
	SS	PP	AA	BB	CC	DD	EE	GG	NN
< 800	0.5	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
800-1000	95.3	57.3	47.4	42.3	26.6	0.0	0.0	0.0	0.0
1000-1120	4.2	42.3	52.6	57.7	73.4	66.2	12.1	0.0	0.0
1120-1250	0.0	0.1	0.0	0.0	0.0	33.8	87.9	95.4	1.2
1250-1400	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.6	92.4
> 1400	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6.4

Table 3.5: Sieve analysis of different products;

SS: Sugar spheres, PP: HPMC pellets, AA: Nico pellets,

BB to DD: HPMC-Nico pellets, EE to NN: CAP-HPMC-Nico pellets

3.2.3 Swelling

The swelling in 0.1 N HCl of HPMC-Nico pellets was investigated with Product DD. A high swelling of 25 % is shown in the Table 3.6. CAP-HPMC-Nico pellet (Product EE) has a swelling of 12 %. This smaller value may be due to the small resistance of the layer of CAP and DEP as a plasticizer, which is almost insoluble in water. The artificial gastric juice may diffuse slower into the core so that the HPMC cannot swell well. On

the other hand, the swelling of Product NN cannot be measured because the pellet dissolved in 0.1 N HCl. This may come from the effect of TEC which was a water soluble plasticizer. If the plasticizer was dissolved in 0.1 N HCl, it will diffuse out of the CAP film layer and cause a high diffusion of 0.1 N HCl into the core. If HPMC is swollen it will also dissolve out of the core later-on. Nicotinamide, under the subcoat of HPMC, can also well dissolve in 0.1 N HCl. This dissolving of the different layers and also the inner core of sugar spheres may be the result of the reduction of the diameter.

Product	D1 ± SD	D2 ± SD (pixel)	ΔD ± SD	Swelling (%)
DD	187 ± 2	234 ± 4	47 ± 2	25
EE	207 ± 1	232 ± 3	24 ± 3	12
NN	218 ± 1	212 ± 1	-6 ± 2	dissolving

Table 3.6: Swelling property of different products in 0.1 N HCl, 22 °C; D1: diameter before swelling, D2: diameter after swelling, DD: HPMC-Nico pellets, EE: CAP-HPMC-Nico pellets (CAP+DEP), NN: CAP-HPMC-Nico pellets (CAP+TEC)

The subcoat from HPMC gives a very high swelling so that this can cause a breakage of the outer layer. It was then confirmed that the film from CAP and TEC was not elastic enough to tolerate this high swelling property of HPMC subcoat.

Another method to quantitatively determine the swelling was mentioned. Li and Peck <90> have studied the swelling property of free films. They observed and determined the water uptake of free films for this purpose. If the percentage of water uptake is high then it will indicate that the free films were swollen. The effect of the concentrations of the coating liquid was demonstrated. When a concentrated coating liquid is used the extent of its spreading is much less than that one attained by a diluted liquid because of its relatively high viscosity and the resulting reduced fluidity. The low water content of the concentrated liquid also effects a much faster drying rate which further limits the degree of spreading. In some cases this concentrated liquid may produce the more

discontinuous film structure. In some regions thinner film layers will result, which cause a higher drug permeability. The comparison between the side-vented pan coating and the air suspension coating (fluidized bed technique) was performed.

Potassium chloride tablets were used as the core material. A dispersion containing silicone elastomer and 25 % w/w PEG 8000 was used as a coating liquid. Li and Peck <90> found that the tablets coated in the fluidized bed apparatus exhibited a much faster drug-release rate and the microstructure of the coating film was less compact than that one coated in the coating pan. This result may be due to the difference in the dynamic of the coating equipment. In a pan coating process the contact and friction between tablets is more pronounced and thus promotes shearing and spreading of the coating dispersion on the tablet surface. This action probably facilitates the formation of a more compact and less permeable coat. By comparison, in a coating column tablets are suspended to some extent in the air stream and therefore able to slide fast with minimal contact to each other and to the wall of the column. Hence tablet-to-tablet contact and the consequent spreading of the coating dispersion are minimized, leading to the formation of a less compact films. The loading weight was reported to affect the coating property. It was mentioned that higher, intense friction was produced at the higher loading weight which would give the more compact and less permeable coating film <90>.

Thoma and Kräutle <187> reported about applying of a barrier coat of HPMC prior to the enteric coating produced from an aqueous dispersion of the coating agent CAP. This model can reduce the swelling of the coated tablets. The percentage of swelling of pancreatin tablets coated with an aqueous dispersion of Aquateric without any barrier coat was very high, up to 35 %. The barrier coat prepared from HPMC at a coating amount of 3 mg cm^{-2} reduced the swelling to 10 %. However, after storage at 35 °C for 12 months, the swelling of the coated tablets with a barrier coat increased again to about 35 %.

Teuber <184> has studied the swelling of gelatine by the weighing technique. A dosage form of gelatine prepared by a casting technique was exposed to different media at 23 °C for 96 h. The weight increase after this time period was determined after the rest of the medium was removed from the dosage form by using the filter paper. The weight before and after the swelling process facilitates the calculation of the degree of swelling.

3.2.4 Content of nicotinamide in one pellet

The content of nicotinamide inside one pellet of different products was varied. Product AA or Nico pellet without further coatings contained 9.0 ± 0.2 % w/w of nicotinamide based on q total weight of one pellet. One pellet after coating with the subcoat HPMC (Product DD) contained 8.3 ± 0.3 % w/w of nicotinamide. The reduction of nicotinamide after coating with HPMC may be due to the dissolving at the surface of Nico pellets during the first step of the coating process.

3.2.5 Release of nicotinamide from coated pellets

The cumulative percentage of nicotinamide release during the first five minutes from HPMC-Nico pellets, which were not coated with CAP, was 99 % (Table 3.4). The cumulative percentage of release reduced after the coating, especially with CAP and TEC as a plasticizer. As shown in Table 3.4, the percentage of nicotinamide release reduced from 14 to 1.8 % as the coating amount increased from 17.9 to 61 mg cm⁻². The dissolution profiles of different products containing nicotinamide can be seen in Figure 3.19. The maximum range of deviations from the mean between two curves in repeated determinations of release observed for any product was not more than 2 %. Therefore, error bars were not included in the dissolution profiles to avoid visual complexity of the several dissolution curves in individual graphs. It was found out that the CAP-HPMC-Nico pellets were not resistant to 0.1 N HCl over 2 h, although different thicknesses and combinations between CAP and plasticizers were used. After 2 h, every kind of CAP-HPMC-Nico pellets (Products EE to NN) released almost 100 % of nicotinamide. The release from Product MM and Product NN was not significantly different over 2 h, only small differences appeared during the first 20 min. This shows that the film property may not differ between coating by using filters or cyclone as a fine dust collector. By inserting a cyclone, the total processing time was reduced as a filter-change was not necessary. The release of nicotinamide from Product GG in the first five minutes was extremely high, 96.0 %, which was almost the same as without enteric coat as with Product DD (99.0 %). This may be due to the highly porous structure of CAP and DBS as a plasticizer which was also confirmed by SEM. Product EE had also a high release of nicotinamide (80.5 %). The wide cracks on the surface of pellets coated with CAP and DEP as a plasticizer may be responsible for this result.

The release of nicotinamide from the CAP-coated pellets with HPMC as subcoat was very fast. Especially in the case of CAP-coated pellets, by using DEP or DBS, the percentage of nicotinamide release within the first five minutes was more than 80 %. When the thickness of the CAP became higher, the protection against the gastric fluid was also higher, which is demonstrated in the result of the nicotinamide release within the first five minutes by using CAP and TEC as a plasticizer (Productc HH to NN in Figure 3.19).

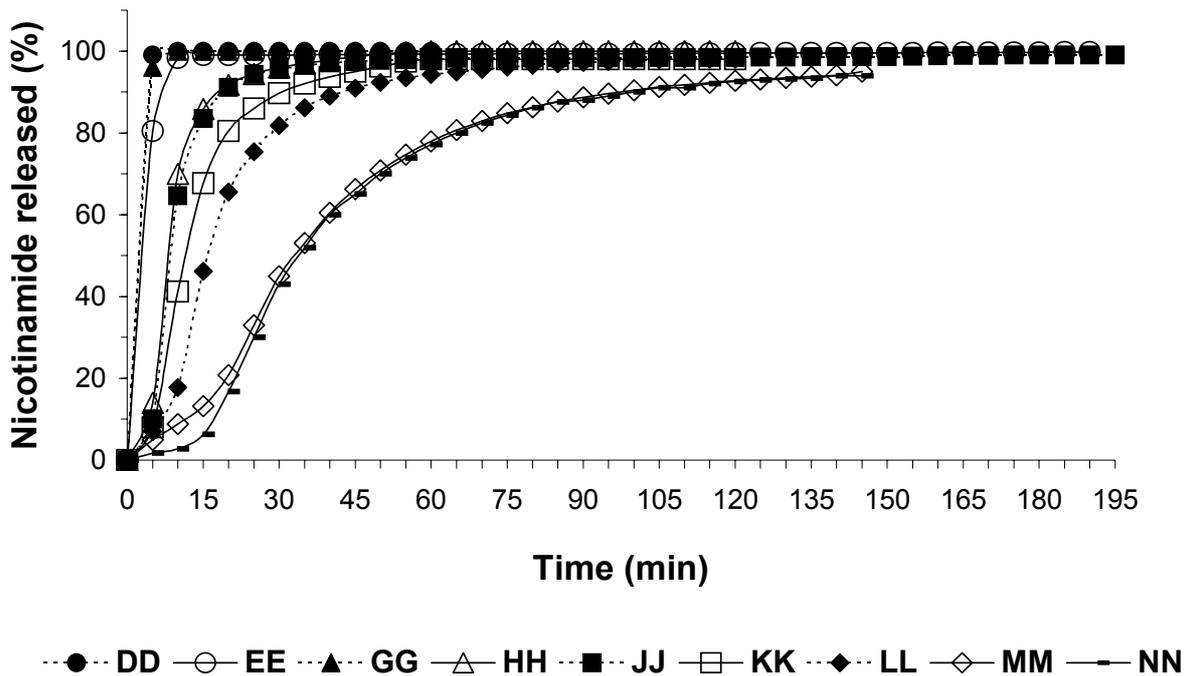


Figure 3.19: Dissolution profiles of differently coated pellets containing nicotinamide in 0.1 N HCl at 37 °C without (Product DD) and with enteric coats containing different plasticizers (Products EE to NN);

EE: CAP with DEP at a coating amount of 15.8 mg cm^{-2} ; FF: CAP with DEP at a coating amount of 17.9 mg cm^{-2} ; GG: CAP with DBS at a coating amount of 23.1 mg cm^{-2} ; HH to NN: CAP with TEC with increasing thicknesses of the enteric coat in mg cm^{-2} ; HH:17.9, JJ:22.1, KK:28.4, LL:42.1, MM:62; NN:61; MM: production with intermediate drying phase, NN: similar to MM, but with cyclone instead of filters set.

As mentioned before in 3.1.1, the failure in gastric resistance may be due to the formation of inhomogeneous films. The incomplete coalescence or the formation of cracks can be well confirmed by SEM, 3.2.1. The physically best CAP film was achieved by using TEC as a plasticizer at the defined process conditions, but this film was not resistant to 0.1 N HCl.

Gumowski, Doelker and Gurny <65> have investigated the different formulations of CAP as an organic system and as an aqueous redispersible system for coating of tablets. The loading product were tablets containing 88 % w/w acetylsalicylic acid which were prepared by direct compression. Tablets were coated in a lab-scale rotary drum coater. The pan had four perforated zones, and drying air was pulled through the bed of tablets under slight negative pressure. They used a higher pan revolution for the organic system than for the aqueous system, but the drying air temperature (70 - 75 °C), the spraying rate of the dispersion (2.5 ml/min), the exhaust air temperature (35 - 40 °C) and the final drying time (10 min) of the aqueous system were higher than those of the organic system. The weight of the coating materials was varied from 1 to 11 % w/w. They found that tablets coated with an aqueous system, after 1 h in 0.1 N HCl showed a higher loss by diffusion of active drug (maximum 2.1 %) than tablets coated with an organic system (maximum 0.5 %). Nevertheless, at all coating levels (5 - 11 %) the percentage of drug release was less than 2.1 % on the average which met the requirements of the USP. The possibility of replacing diethyl phthalate (DEP) with glyceryl triacetate, triethyl citrate or glycerol polyethylene glycol oxystearate in aqueous systems at various levels was investigated. The amount of about 25 % of DEP, glyceryl triacetate and triethyl citrate, respectively to the solid content of CAP has been used successfully. These formulations were gastric resistant. The combination of propylene glycol and DEP or glyceryl triacetate was also suitable for use as a plasticizer. Scanning electron micrographs of cross sections of the two systems revealed no obvious differences, and no individual polymer particles were evident in the films. They concluded that these films were completely coalesced and therefore functionally stable. However, it should be considered that this early study <65> was performed with tablets and a perforated pan coater was used as a coating apparatus. The movement of a loading product inside the coating chamber was different from the fluidized bed apparatus. The density of the tablets compared to pellets was also different and this will also affect the movement inside the coating chamber. The aqueous enteric coating

formulation, however, was prepared almost in the same way. Only the stirring over night in our study was different from their study. The differences in the coating apparatus and dosage form may be the reason that these coated tablets were resistant against 0.1 N HCl and therefore meet the requirement of the USP. Moreover acetylsalicylic acid is a drug which is less soluble in water. The release test of uncoated tablets in 0.1 N HCl and phosphate buffer showed that this drug was completely dissolved (100 % release) only after 50 min. The slow release of the drug itself may additionally hinder the release after coating with enteric coating formulations. Nicotinamide, which was used in our work, however is highly soluble in water. This property may induce the release of nicotinamide from the coated pellets after 0.1 N HCl had diffused into the inner side.

3.2.6 Optical appearance after the release study

The optical appearance of CAP-HPMC-Nico pellets (Product EE and NN) after contact with the acidic dissolution medium was observed under a light microscope. It was found that all pellets were damaged within 30 min (Figure 3.20 and 3.21). Product NN showed after this time the inner core of the pellets which was orange in colour. Only the outer CAP layer was broken. This may be due to the high swelling property of HPMC-Nico pellets as demonstrated before. Product EE, however, showed only the broken outer layer of CAP and DEP. This means the inner core was completely dissolved within 30 min. This test showed that films from CAP and DEP or TEC as a plasticizer may not be elastic enough to tolerate the high swelling of the subcoat.

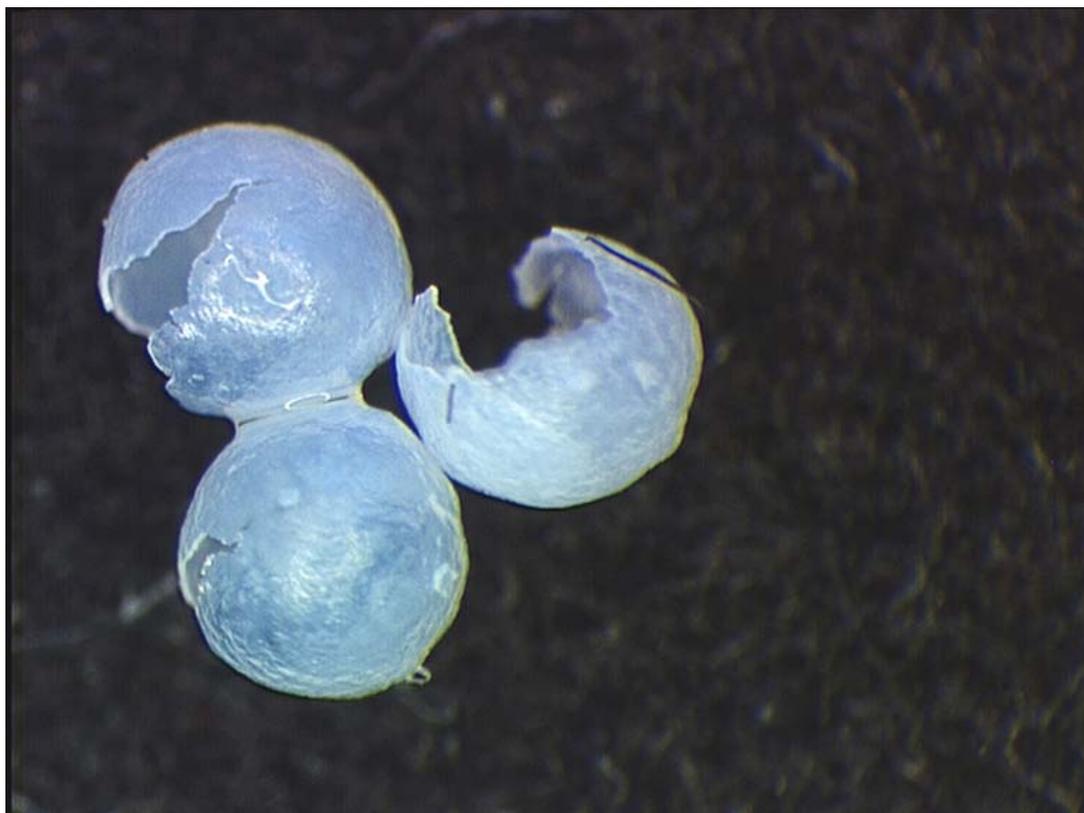


Figure 3.20: Optical appearance of CAP-coated pellets containing nicotinamide and HPMC as a subcoat (Product EE) after exposure to 0.1 N HCl, at 37 °C for 30 min.

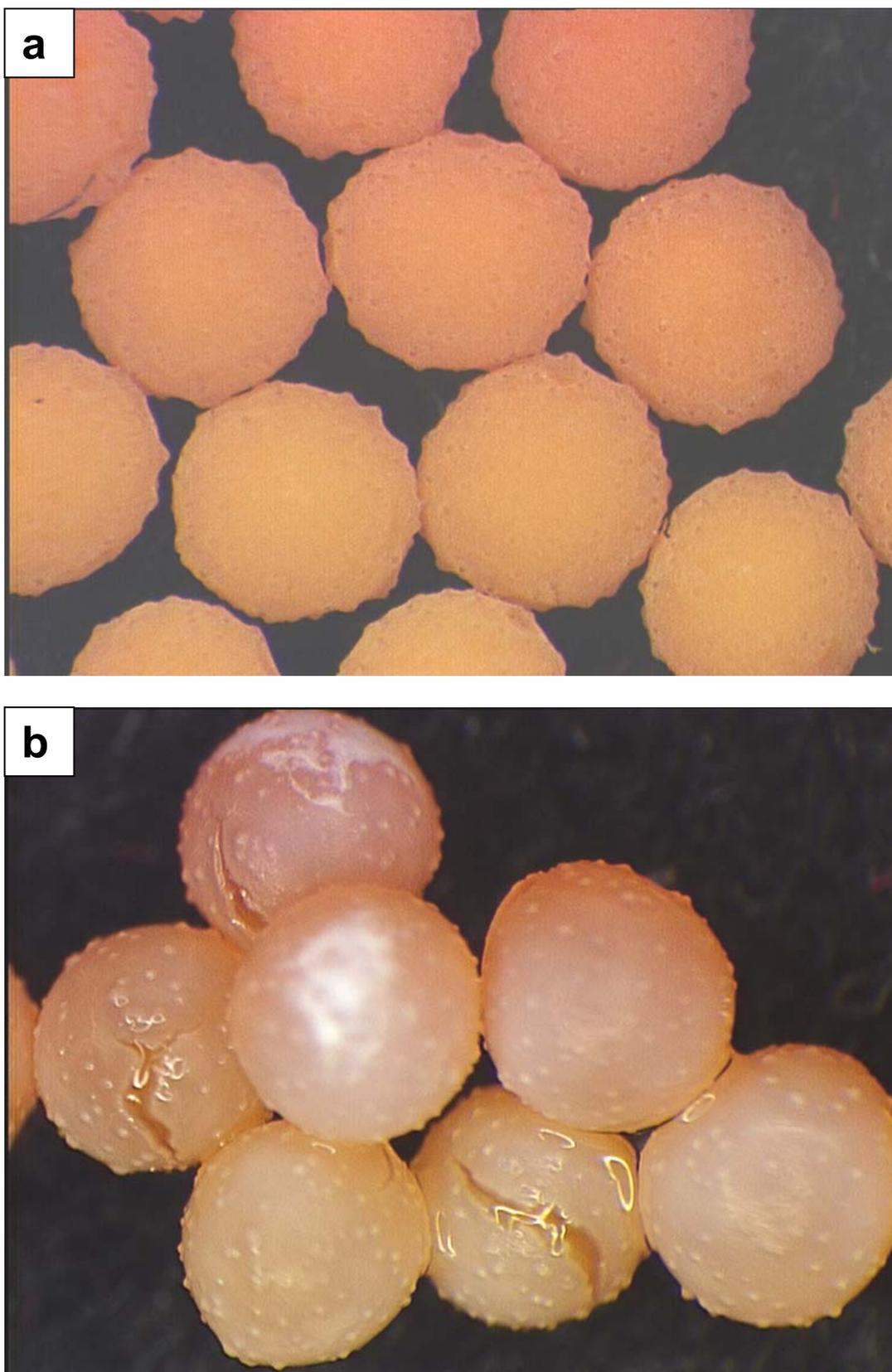


Figure 3.21: Optical appearance of CAP-coated pellets containing nicotinamide and HPMC as a subcoat (Product NN); a) before and; b) after exposure to 0.1 N HCl, at 37 °C for 30 min.

3.2.7 Postdrying (curing) of enteric coated pellets

Postdrying or curing is the thermal treatment after coating to provide additional heat for further coalescence, and has been suggested for use with polymers with a high T_g , such as CAP <200>.

Only two types of CAP-HPMC-Nico pellets were used for this test, CAP with DEP (Product EE) and CAP with DBS (Product GG). The film structure of Product EE contained a high amount of big cracks before the postdrying. After the postdrying under different conditions (40 - 80 °C and up to 75 % r.h., details in part 2.2.12) the film structure was not improved. This was the similar case as with Product GG, which contained porous structure instead of cracks. This means when cracks happened in the structure of the film, it may indicate that the film was overdried. Therefore, further drying during the postdrying phase may not improve the structure. On the other hand, if the structure was highly porous, it may indicate that the plasticizer was not well distributed at the intermolecular level of the CAP-polymer.

However, the successful postdrying for films prepared from CAP was demonstrated by Williams and Liu <200>. They have studied the curing effect with pellets coated with Aquacoat CPD and 35 % DEP at the outlet temperature of 32 °C and then cured at 60 °C for 12 h. They found that these pellets have less than 10 % release after 2 h in acidic media. The percentage of release of pellets without curing was more than 10 %. However, these coated pellets were found to be aggregated after the curing step. Therefore 2 % talc was added before placing them into the oven. However, they found that pellets coated at the outlet temperature of 36 - 48 °C and then cured at the same condition, had no significant difference in the percentage of release after 2 h compared to the pellets without curing. They showed that the curing was dependent on the coating temperature. The residual moisture retained in the coating layer of pellets coated at 32 °C may play a role in the coalescence during the curing. They mentioned that heat was not the only factor required for the coalescence of CAP films and that the curing was not able to proceed without sufficient moisture present in the film coating.

The effect of different humidities in the curing phase to the CAP-coated pellets were also studied by Williams and Liu. They used pellets that were coated at the outlet temperature of 48 °C and 90 m³/h and then the curing at 40 and 50 °C with humidities of 51, 65 and 75 % r.h. for 24 h was performed. In comparison pellets coated at the lower outlet temperature of 32 °C and the air flow of 90 m³/h were cured at 40 and 50 °C at 75 % r.h.. The result showed that the humidity of 51 % r.h. at two temperatures had no effect to the release of pellets coated at the higher outlet temperature (48 °C). Only the combination of 40 °C and 75 % r.h. or 50 °C with the humidity up from 65 % r.h. can reduce the release of theophylline. The release of theophylline from pellets coated at the lower outlet temperature (32°C) in acidic media can be also reduced to less than 10 % by using the curing with temperatures up from 40 °C and 75 % r.h..

Williams and Liu mentioned that without sufficient moisture in the coating layers, capillary forces were not able to deform the polymer particles, leaving dried particles on the surfaces of the polymer coating. The semi-transparent appearance of the free film may be the result of some uncoalesced polymer particles formed during spraying. When these dried particles were exposed to heat with sufficient moisture, water molecules will interact with polymer chains by competing for bonding sites such as hydroxyl groups. Therefore the mobility of the polymer would be increased. After the heat-moisture treatment a plasticizer such as DEP, which did not distributed between the CAP chains, might be associated with CAP chains and with the sufficient heat provided the coating layer became soft. The polymer particles were mobilized and can be coalesced to form a continuous film. When absorbed moisture was removed from the cured pellets, DEP still remained in the film and it will maintain the integrity of the film.

Williams and Liu concluded that the coating temperature was found to be a critical parameter. Above the MFFT, the lower the coating temperatures, the better the enteric film was formed. The heat-only curing did not have a significant effect on the reduction of the drug release, except for the batch coated at the lowest temperature. The exposure of pellets to the elevated humidity during curing seemed to enhance the coalescence and the mechanical strength of the film. The degree of improvement was dependent on the history of coating conditions. These results therefore supported the importance of controlling the processing and curing conditions to enhance the coalescence of the CAP polymer from aqueous formulations. However, in order to maintain the stability of the drug and CAP, it is preferred to conduct the curing process at a lower temperature and humidity for shorter periods of time.

In conclusion Williams and Liu recommended to use the following coating conditions to coat pellets; outlet temperature 32 °C, 35 % DEP, spray rate 3.2 g/min and air velocity 90 m³/h with curing.

In this present study, however, the coating process X17 (Table 2.23) was performed with the low spray rate of 1.8 g/min to avoid agglomeration because the air velocity was low at 55 – 60 m³/h. The relative humidity measured inside the coating chamber was low at about 18 % r.h., which may have also resulted from the dehumidifying of the inlet air. This almost dry coating condition may cause the fast drying so that polymer particles did not have enough time to move near to each other and fuse together. The possible solving method for this problem is to hinder the evaporation of water. The addition of hydrophobic substances may solve this problem. However, the results of an addition of these substances as shown in 3.1 did not satisfy because the film formation was not improved. This may be due to the fact that an addition of these substances will cause an increase of the T_g and the MFFT. The higher temperature and humidity in the curing process can sometimes increase the mobility of the plasticizer <200>, but in this present study, it seems that DBS could not easily be mobilized, although a combination of a high temperature and a high humidity was used.

In conclusion the postdrying by using different combinations of temperature and humidity did not improve the film structure. If the drying condition was extremely high, it caused a liquidation of the film and a change of the physical property of the enteric film which could not anymore be used for the further investigation.

3.2.8 Optical characterization of pellets after storage

The following storage conditions demonstrated the highest humidity at each temperature that still allowed the placebo pellets or enteric coated pellets to flow freely after 30 days of storage.

Conditions \ Samples	Placebo pellets (Product P)	Enteric coated pellets (Product EE)
Temperature (°C)	Relative humidity (% r.h.)	
25	80.9	57.5
30	56.0	56.0
35	54.0	30.2
40	53.1	30.0
45	52.0	29.8
50	50.9	29.7

Table 3.7: The highest humidity at each temperature that still allowed the placebo pellets (Product P) and the enteric coated pellets and a HPMC as a subcoat (Product EE) to flow after 30 days of storage.

In summary it was found that the placebo pellets (Product P) were more stable to the temperature and humidities than the CAP-coated pellets (Product EE), which had HPMC as a subcoat. The HPMC-coated pellets (Product P) could freely flow when the relative humidity did not exceed 60 % r.h.. Only at the low temperature of 25 °C the high relative humidity of 80 % r.h. still allowed the Product P to flow and did not stick together. However, the CAP-coated pellets (Product EE) can tolerate a high temperature up to 50 °C but the relative humidity should not exceed 30 % r.h. It is obvious that if pellets contained more layers e.g. nicotinamide, subcoat, and CAP then they would be more sensible to the temperatures and humidities compared to the placebo pellets only coated with a thin layer of HPMC.

Moreover, it was also found that Product EE stuck together after 7 days of storage when the temperature was above 45 °C and the relative humidities were higher than 70 % r.h. At the highest stress condition of 50 °C and 80 % r.h., the CAP-coated pellets and HPMC as a subcoat (Product EE) liquefied. This means, if an accelerated chemical degradation test should be performed with CAP-coated pellets the temperature should neither exceed 40 °C nor the relative humidity the limit of 60 %. In this range of temperatures and humidities, the physical property of the CAP-film was still acceptable and the chemical degradation of the coated pellets may then be observed and not the physical damage.

3.2.9 Discussion of results of related coating experiments in the literature

HPMC

It was reported that film coating from HPMC has become popular because of its solubility in water, stability in presence of heat, light, air and moisture and ability to coat using a fully aqueous system. A transparent, tough, flexible and nontacky film can be formed from an organic or aqueous solution of HPMC. The HPMC film can be dissolved readily in the gastrointestinal tract at 37 °C. When granules or beads coating is carried out it was important to prevent adhesion of them during coating. Therefore it is recommended that the low viscosity coating solution is more effective. Thus the 3 cps type of HPMC is most suitable. Generally the coating quantity of 3 - 4 % w/w was sufficient for the masking effect. It was reported that the water vapor permeability of HPMC films tended to decrease as the viscosity of HPMC solution was decreased. For example; it was reported that if HPMC of low viscosity (e.g. 3 cps) was used both the tensile strength and elongation decreased. These properties would create a cracking of the coating product. The possible optimization to receive the acceptable mechanical properties and water-vapor permeability was to blend the low and high viscosity grades of HPMC together <106,107>.

It was reported that the uniform wetting of cores with coating solution and good adhesion between a coating film and the core surface are desirable properties in a film coating process. The wettability of cores can be predicted by using contact angle measurement. Lehtola, Heinämäki, Nikupaavo and Yliruusi <89> have studied the

adhesion between aqueous based HPMC films and tablet surface. They showed that the contact angle between aqueous – based HPMC solutions and the tablet surface increased with increasing compression pressure because the roughness of the tablets was decreased. The contact angle also increased with increasing concentration of magnesium stearate in the tablet formulation. The tablet containing microcrystalline cellulose had the highest contact angle (up to 80 °) to aqueous – based HPMC solution compared to lactose and a combination of lactose and cellulose as an excipient. The adhesion of HPMC-film to the cores surface was influenced by the composition, the polarity and roughness of the cores. The addition of a hydrophobic lubricant such as magnesium stearate was found to decrease the adhesion. It is mentioned that the adhesion of a film to tablet-core is due to the formation of hydrogen bonds between the polar groups of the film former and the tablet-core constituent. Both HPMC and microcrystalline cellulose (MCC) contain hydroxyl groups and therefore can form strong bonding which results in a high adhesion between HPMC film and tablets containing MCC. The tablets coated with aqueous based HPMC solution had a higher mechanical strength than those without coats of three excipients (MCC, lactose, Cellactose) used. The increase of mechanical strength may be due to an action as a padding material and also as a filler to irregularities on the surface. It is expected that the film adhesion to the tablet-surface increases in accordance with a decrease in the contact angle because the solution can spread more readily on the tablet-surface. In this recent study they have found that the adhesion between tablet-cores and aqueous based HPMC film increased with higher compression pressure which gave an increasing smoothness of the tablet-surface. The increasing of contact area between the aqueous based HPMC solution, with a relatively high viscosity of 218 mPas, and the tablet surface is the reason for higher adhesion values.

Heinämäki, Lehtola, Nikupaavo and Yliruusi <71> have studied the mechanical and moisture permeability properties of aqueous based HPMC coating systems plasticized with polyethylene glycol. Different types of PEGs (400, 1500 and 4000) were studied with HPMC films prepared by using a pneumatic spraying technique. They have found that over the range of concentrations tested (0 – 30 %) the moisture permeability of the films decreased slightly as compared to unplasticized control films with increasing molecular weight of the PEG-plasticizer. The mechanical strength of the films was shown to be more dependent on the concentration incorporated in the coating

formulations than on the molecular weight of the PEGs, while the ductility of the films was mainly dependent on the molecular weight of the PEGs. The aqueous-based HPMC free films plasticized with PEG 400 had the higher weight increase after storage for about 5 days which means that they have higher moisture permeability compared to HPMC free films plasticized with PEG 1500 and PEG 4000. This appearance may be explained by a less enhanced chain mobility and smaller diffusion pathways of the higher molecular weight plasticizers resulting in a lower diffusion rate in the film matrix. It was discussed that the unplasticized aqueous HPMC films were brittle and hard. The addition of a plasticizer at the lowest concentration of 10 % resulted in relatively hard and strong films with moderate elongation especially when lower molecular weight plasticizers (PEG 400 or 1500) were used <71>.

HPMC was not only used as a moisture barrier coat but also as a subcoat to hinder the interaction between a drug and an enteric polymer. For example; Bengtsson and Loevgren <17> have developed the oral pharmaceutical formulation containing a magnesium salt of omeprazole. They used a formulation containing HPMC as a subcoat before enteric coating with methacrylic acid polymer.

CAP films from aqueous dispersions

Some publications reported about the enteric coating by using of CAP and different plasticizer. The physico-chemical properties of CAP such as solubility, T_g and the content of free acids were mentioned in some literatures <15,166,155,83>. Details were discussed in 3.1.

Heinämäki, et al <70> studied the permeability and mechanical properties of free films prepared from the ammoniated aqueous or organic-solvent based system containing CAP. The ammoniated aqueous coating solutions contained CAP, ammonium hydroxide, magnesium carbonate, triacetin and water. The organic solvent systems contained CAP, triacetin, acetone and water. These two solutions were used to prepared free films by pouring the solution into glass petridishes. They showed that enteric films prepared from the organic-solvent based solutions had a lower permeability to basic drug (caffeine) and hydronium ions compared to films prepared from ammoniated aqueous based solutions. The ammoniated aqueous enteric films were

reported to be weaker and more brittle than corresponding films prepared from organic-based systems.

Raffin, Dura and Jacob <147> found that films prepared from the aqueous dispersion of Aquateric were more permeable than those prepared from the organic solutions.

Obara and McGinity <116,117> have studied the properties of free films prepared from aqueous dispersions of CAP by a spray method and a cast method. They found that the casting of a CAP dispersion resulted in transparent films. On the other hand poor film formation was observed with the spraying method. A powdered aggregate was obtained even though the surface temperature was maintained higher than the MFFT. The experimental conditions may have provoked rapid drying and prevented the coalescence of latex particles. Satisfactory CAP films were only formed when using a high spraying rate with slow postdrying to provide sufficient moisture content. The moisture content in the coating chamber can be increased by using higher spraying rates or diluting the dispersion in order to have more water at the same spraying rate so that a higher relative humidity can be formed. However, the spraying rate cannot be increased unlimitedly because a too high spraying rate may cause overwetting in some part of a product bed. A compromise should be found between sufficient moisture to allow a better coalescence and a good evaporation of water to dry the coated product by adjusting to a suitable spraying rate. In conclusion, Obara and McGinity suggested that TEC would be an ideal plasticizer for Aquateric based on the data of MFFT which can form clear films at lower temperatures than with DEP or DBS. Apart from this the water soluble plasticizer can well distribute into the polymeric dispersion and therefore can rapidly reach the equilibrium. The water insoluble such as DEP or DBS were often emulsified into the dispersion and the equilibrium time can sometimes be quite longer.

Scheiffele, Kolter and Schepky <164> have studied different products (free films and coated tablets) prepared from Aquateric pseudolatex. The aqueous dispersion of unpigmented Aquateric composed of Aquateric powder, triacetin (43.3 % to CAP), Tween 80, and water. The aqueous dispersion of pigmented Aquateric composed of Aquateric powder, colour, titanium dioxide, triacetin, Tween 80, and water. The coating apparatus Accela Cota 24 inch was used to coat the caffeine tablets. The coating of tablets with Aquateric dispersion was performed by using air inlet temperature of 78 °C,

product temperature of 32 - 33 °C, spraying rate was 60 g/min and postdrying at 60 °C for 60 min. The resistance to gastric juice was reached at a coating amount of 11 mg/cm² for Aquateric. Irregularities were recognized in the films obtained from Aquateric. The MFFT of Aquateric dispersion without pigment but containing triacetin (43 % w/w to CAP) was less than 52 °C, and the value of MFFT of this dispersion with pigment (Sicovit and titanium dioxide each 3.4 % w/w to CAP) was 36 °C. The MFFT of the liquid preparation was considerably reduced by the addition of pigments. The T_g of unpigmented Aquateric was 48 °C and after adding pigments the T_g was reduced to 56 °C. In the test for coagulation under shear and heat it could be seen that the dispersion of Aquateric did not cause any coagulation. The particle size distribution of the unpigmented dispersion of Aquateric was 20 µm. It was reported that the water vapor permeability and proton permeability of free films from Aquateric was high. This may come from the high mean particle size of these polymers. It was found that the weight of enteric-coated tablets especially tablets coated with Aquateric was increased up to 25 % during the resistance tests in artificial gastric fluid after 2 h at the coating level of 8 mg/cm². This may be due to the swelling of the films. After increasing the coating amount of Aquateric to 11 mg/cm² the weight increase of the coated tablets was reduced to about 22 % after 2 h. It was mentioned that tablets coated with Aquateric were not resistant to 0.1 N HCl until the thickness reached 8 mg/cm². The resistance to artificial gastric fluid of tablets coated with the aqueous dispersion of Aqoat-MF was higher than that of Aquateric.

Chang <31> has studied the rheological and enteric properties among organic solutions, ammonium salt aqueous solutions, and latex systems of some enteric polymers. The organic solution coating formulation composed of 88.2 g CAP, 13.2 g DEP, 441 g isopropyl alcohol and 441 g acetone. The neutralized solution coating formulation composed the same amount of CAP and DEP but instead of organic solvents 16.8 g of ammonia hydroxide and 882 g of water were used as solvent. The pseudolatex coating formulation composed of 88.2 Aquateric, 22.1 g DEP, 2.7 g Tween 80 and 640 g water. The lab-scale fluidized bed coating apparatus- Uniglatt was used to produce the enteric coated pellets. Spherical theophylline pellets, which were manufactured by slurry layering onto sucrose seeds in a fluidized bed, were chosen as model core substrates for this purpose. After the coating process the pellets were dried in the coating chamber for another 15 min at the same temperature and air flow. The

coating conditions were set so that the inlet air temperatures for the organic, ammonium salt and aqueous systems were 50 °C, 60 °C and 60 °C, the spraying rates were 14.7, 10.1 and 12.7 g/min, respectively. It was found that because of the larger surface area of the pelletized dosage forms a relatively high coating weight is needed to impart enteric properties. Consequently a prolonged batch cycle time may result. To build up film thickness in a reasonable time a coating system having a high polymer content must be used. The concentration of polymer is often limited by solution viscosity. As viscosity increases, there is an increasing strain on the pumping unit, increasing difficulty in atomization, decreasing spreadability of the coating solution, increasing tackiness during coat formation and increasing possibility of substrate agglomeration. The viscosity-concentration relationships among the enteric materials in organic solvent solution, in ammonium salt solution and in pseudolatex form were presented. As expected, the viscosity of the polymer solution or dispersion increased with the polymer concentration. The solutions of ammonium salts of the enteric materials tested exhibited markedly higher viscosity than the respective enteric polymer in organic solutions did. For example the viscosity of the 15 % w/w CAP organic solution was about 250 cP whereas the viscosity of the ammonium solution at the same concentration was about 1800 cP. As the carboxyl groups on the enteric polymers become ionized with the aid of ammonia water, the polymer chains are extended due to mutual charge repulsion and the viscosity increased. This charge interaction may be one of the reasons for the marked difference between the viscosity of these two formulations. The viscosity of the 15 % w/w aqueous dispersion of Aquateric was very low i.e. about 60 cP. It is difficult to use a spray solution having a viscosity higher than approximately 200 cP to coat pellets in a fluidized bed apparatus. The use of ammonium salts is inferior to the use of organic solution or pseudolatex systems when viscosity is considered. However, the viscosity of 11.3 % CAP ammonium salt solution was about 200 cP and therefore it can be used as a coating formulation. To investigate the enteric quality of the coatings, dissolution testing was performed in simulated gastric fluid without enzyme at pH 1.2 for 4 h. The rotating-paddle method with a stationary basket was used. Pellets were placed into this basket which was positioned closely to the paddle which rotated at 100 rpm. The result showed that films prepared from CAP organic solution and ammonium solution had a good protection from gastric juice. The release of theophylline was lower than 5 % over 4 h. Surprisingly the Aquateric film gave no gastric-fluid resistance. The release of theophylline arrived 100 % within 1 h. The substantial quantities of Pluronic F-68

presented in Aquateric may have an adverse effect on the enteric properties. The surface structure performed by using SEM showed the crater-like texture of pellets coated with a neutralized CAP formulation. The aqueous based Aquateric showed a rough and wrinkle surface which indicated the incomplete coalescence <31>. However, another report concluded that Aquateric provided enteric performance was similar to the organic systems <65>.

Stability of products coated with CAP

Thoma and Kräutle <187> have studied the influence of pancreatin on the stability of gastroresistant coatings. They have found that after storage period of 12 months the pancreatin tablets with a CAP-coat no longer disintegrate within 60 min as stipulated in the Pharmacopoeia. The disintegration time of tablets coated with Aquateric kept constant at about 10 min after storage at 25 °C for up to 12 months. The disintegration time was increased up to 30 min after storage at 35 °C for 12 months and if the tablets contained barrier coat the disintegration time was about 15 - 20 min after 12 months. The increasing of the disintegration time was mentioned to depend on the decreasing of the solubility of the polymer e.g. CAP which was hydrolysed after long-term storage. It was mentioned that a stable coat cannot be produced by Aquateric in a fluidized bed apparatus. Aquateric caused the problem of stability already after storage at the room temperature.

Thoma and Bechtold <185> studied the influence of aqueous coatings on the stability of enteric coated pellets and tablets. Pancreatin pellets and tablets containing riboflavine were coated with various aqueous and organic enteric polymers such as CAP, HPMCAS, HP, Eudragit L, etc. The stability after storage was comparatively investigated. They reported that a higher amount of coating materials were needed to achieve gastro-resistance when using aqueous coating compared to organic formulations. The disintegration time of CAP-coated tablets at a storage of 40 °C after 6 months increased to more than 60 min which may be due to the hydrolysis of the phthalic ester groups and formation of insoluble cellulose acetate.

Heckenmüller <69> has compared the differences in the test methods for enteric coated dosage forms in many Pharmacopoeia such as USP, BP, DAB, Eur.Ph, etc. He found

that there were differences for example; test media, the dimension of the test apparatus, temperature of test media, mechanical stress to the dosage form and the analysis of the outcome data. Tests of the disintegration and the resistance against gastric fluid were compared. He tried to find out the suitable guideline based on the different Pharmacopoeia for use in the technological development, quality control and stability test of enteric dosage form. The comparison between data from in-vitro and in-vivo test was carried out by applying the particular model dosage form containing an indicator for the resistance and disintegration test. The stability of enteric dosage forms was performed by observing the disintegration and resistance test. The temperatures used were 20 and 40 °C for a period of up to 2 years. Many marketed enteric dosage forms lost their acid resistance and disintegration properties after storage at 20°C after 1 year. Many products prepared by using CAP showed problems of acid resistance and disintegration properties. The indicator used for the in-vitro and in-vivo acid resistance test is composed of a resin from chinin hydrochloride and Amberlite IRC 50. It is a weak acid-cationic-change based on polyacrylate. It is very sensitive to acid media. This indicator can be well determined in the urine after in-vivo test. The indicator used for the in-vitro and in-vivo disintegration test was riboflavin-5-phosphate because the resorption of this drug was depending on the location of the dissolution. This drug can be absorbed only at the upper part of the intestinal <69>.

3.2.10 Present conclusions

In conclusion, many works have reported about the problematic of coated dosage form prepared from dispersions containing CAP. In this present work, HPMC can be successfully used as a subcoat and it can hinder the interaction between a basic drug and the outer acid polymer. However, HPMC causes a high swelling which may have an additional effect on a breakage of the CAP-coated pellets.

The film quality of the outer layer prepared from Aquacoat CPD and different plasticizers was ranged as follows; TEC gave the best film quality compared to DEP and DBS. DEP was a better plasticizer than DBS. However, the CAP-coated pellets containing nicotinamide and HPMC as a subcoat were not resistant to 0.1 N HCl up to 2 h.

3.3 Pellets with nicotinamide and EC as a subcoat

a) Placebo: HPMC pellets

As mentioned before, the seal coat with HPMC can hinder the dissolution of core material at the surface because it takes a shorter time to coat all the surfaces with HPMC than to layer them with nicotinamide and HPMC as a binder. The HPMC coated pellets (Product Pp) were achieved from the combination of a formulation **R1** and a process number **X7**, as demonstrated in the Table 2.27.

b) Nicotinamide loaded pellets: Nico pellets

The Nico pellets (Product Aa) were achieved from the combination of a formulation **R3** and a process number **X8**, as demonstrated in the Table 2.27.

c) EC as subcoat: EC-Nico pellets

The EC-Nico pellets have a pink colour as a marker was used. These pellets (Product Bb to Ee) were achieved from the combination of a formulation **R5** and a process number **X10**, as demonstrated in the Table 2.27.

d) Enteric coated pellets: CAP-EC-Nico pellets

The CAP-EC-Nico pellets still have a pink colour caused by the marker. These pellets (Product Ff to Kk) were achieved from different combinations of a formulation and a process number, as demonstrated in the Table 2.27.

3.3.1 Film quality, diameter and weight of pellets

The physical properties of raw materials used for this process and of the finished products are shown in Table 3.8. The mean diameter and standard deviation of the raw material (sugar spheres as sieve fraction 800-1000 μm) by image analysis were $970 \pm 37 \mu\text{m}$. The thickness of the HPMC layer (HPMC pellets) as measured from SEM was about $7 \pm 2 \mu\text{m}$. The mean diameter of these pellets measured by an image analyser was $970 \pm 40 \mu\text{m}$. The comparison between the raw material and HPMC pellets shows that there is no significant difference between these two products. Consequently, the coating process with HPMC was carried out well and homogeneously coated pellets resulted.

The mean weight of one HPMC pellet (Product Pp) was $0.65 \pm 0.01 \text{ mg}$, which was lower than that of sugar spheres. This may be due to dissolution of the sugar from the surfaces of the spheres as mentioned before. One Nico pellet has a mean weight of $0.80 \pm 0.01 \text{ mg}$ and a mean diameter of $990 \pm 36 \mu\text{m}$. The thickness of the nicotinamide layer of Product Aa was $20 \pm 5 \mu\text{m}$ and the weight gain from nicotinamide and HPMC was 9.5 % w/w.

The subcoat from EC has been achieved in four different thicknesses; i.e. $19 \pm 5 \mu\text{m}$, 48 ± 6 , 80 ± 4 , $160 \pm 10 \mu\text{m}$ with amounts of EC of 11.5, 29, 48 and 97 % w/w respectively. The SEM photograph in Figure 3.22a shows the thickness of the EC layer of Product Jj and that the layer was homogeneous. The mean weight and the mean diameter of one pellet compared between cores (Product Aa) and EC-Nico pellets (Product Bb to Ee) allowed to calculate the amounts of EC-polymer coated per pellet, namely from 10 to 88 mg cm^{-2} .

Physical properties of CAP coated pellets are also stated in Table 3.8. Product Ff shows the layer of CAP and DEP with cracks distributed around the surfaces with a length of about 5-10 μm (Figure 3.22b). This may be due to the high drying rate so that the CAP particles have not enough time to fuse together as mentioned before. There is no difference between the CAP film layer from Aquateric (Product Gg) or Aquacoat CPD (Product Ff) as judged from physical properties as mentioned before. The SEM photograph of the cross-section of Product Hh shows the inhomogeneous layer of CAP and DBS and that many particles did not melt together (Figure 3.23a). This may be due to the distribution of DBS. The best enteric layer from CAP can be achieved from TEC as a plasticizer. The whole surface of cores (Product Ee) was well covered by the CAP

layer, as in the Figure 3.23b. A cross section of the CAP layer (Product Jj) shows an almost homogeneous film structure with cracks dispersed in the CAP-layer, which may be due to the sample preparation for SEM study but not due to the coating process (Figure 3.24a). The surface of these pellets shows also small cracks of about 5 - 7 μm (Figure 3.24b). The white particles of about 1 - 2 μm on the surface of CAP-EC-Nico pellets are Aerosil particles, added to hinder the sticking of pellets during storage.

The mean weight of one CAP-EC-Nico pellet (Product Kk) from Product Cc as cores was 1.37 ± 0.03 mg while the mean diameter of these pellets was 1245 ± 46 μm at the coating amount of 39 mg cm^{-2} . However, the mean weight of one CAP-EC-Nico pellet (Product Jj) from Product Ee as cores was increased up to 2.15 ± 0.03 mg while the mean diameter of one pellet was 1455 ± 50 μm at the coating amount of 50 mg cm^{-2} .

In general, the standard deviations of the diameter of all products in Table 3.8 have a range of 35 to 61 μm . The Product Hh has the highest standard deviation, which resulted from CAP and DBS. This may be due to the highly porous structure of the CAP film layer which will cause a high friability during a coating process which then results in the thickness variation of the finished product.

Product	Weight gain of total batch (% w/w)	Thickness of the layer ($\mu\text{m} \pm \text{SD}$)	Weight of pellet ($\text{mg} \pm \text{SD}$)	Diameter of pellet ($\mu\text{m} \pm \text{SD}$)	Coating amount (mg cm^{-2})	Release within the first five minutes (% \pm Range)
SS	0.0 ^a	800-1000 ^g	0.68 \pm 0.01	970 \pm 37	n	n
Pp	3.0 ^b	7 \pm 2 ^h	0.65 \pm 0.01	970 \pm 40	n	n
Aa	9.5 ^c	20 \pm 5 ⁱ	0.80 \pm 0.01	990 \pm 36	n	n
Bb	11.5 ^d	19 \pm 5 ^j	0.88 \pm 0.02	1030 \pm 35	10.0 ^l	n
Cc	29.0 ^d	48 \pm 6 ^j	1.01 \pm 0.03	1085 \pm 40	27.0 ^l	1.6 \pm 0.5
Dd	48.0 ^d	80 \pm 4 ^j	1.14 \pm 0.01	1145 \pm 38	44.0 ^l	n
Ee	97.0 ^d	160 \pm 10 ^j	1.48 \pm 0.01	1305 \pm 52	88.0 ^l	1.5 \pm 0.5
Ff	12.0 ^e	25 \pm 3 ^k	1.65 \pm 0.02	1335 \pm 52	13.0 ^m	51.6 \pm 1.0
Gg	14.0 ^e	28 \pm 3 ^k	1.68 \pm 0.01	1350 \pm 45	15.0 ^m	n
Hh	24.0 ^e	28 \pm 7 ^k	1.81 \pm 0.04	1450 \pm 61	25.0 ^m	74.9 \pm 1.0
Jj	45.0 ^e	76 \pm 5 ^k	2.15 \pm 0.03	1455 \pm 50	50.0 ^m	6.1 \pm 0.5
Kk	45.0 ^f	75 \pm 5 ^k	1.37 \pm 0.03	1245 \pm 46	39.0 ⁿ	24.4 \pm 1.0

Table 3.8: Properties of different products showing weight gain of total batch, thickness of the layer, weight of pellet, diameter of pellet, coating amount, release within the first five minutes;

^a = weight gain of total batch of sugar spheres (% w/w), ^b = weight gain of total batch of HPMC pellets to sugar spheres, Product SS, (% w/w), ^c = weight gain of total batch of Nico pellets to HPMC pellets, Product Pp, (% w/w), ^d = weight gain of total batch of EC-Nico pellets to Nico pellets, Product Aa, (% w/w), ^e = weight gain of total batch of CAP-EC-Nico pellets to EC-Nico pellets, Product Ee, (% w/w), ^f = weight gain of total batch of CAP-EC-Nico pellets to EC-Nico pellets, Product Cc, (% w/w), ^g = size of sugar spheres, Product SS (μm), ^h = thickness of the HPMC layer (μm), ⁱ = thickness of the nicotinamide and HPMC layer (μm), ^j = thickness of the EC-subcoat layer (μm), ^k = thickness of the enteric coating layer (μm), ^l = coating amount of the EC-subcoat on Product Aa (mg cm^{-2}), ^m = coating amount of the enteric coat on Product Ee (mg cm^{-2}), ⁿ = coating amount of the enteric coat on Product Cc (mg cm^{-2}), n = not measured.

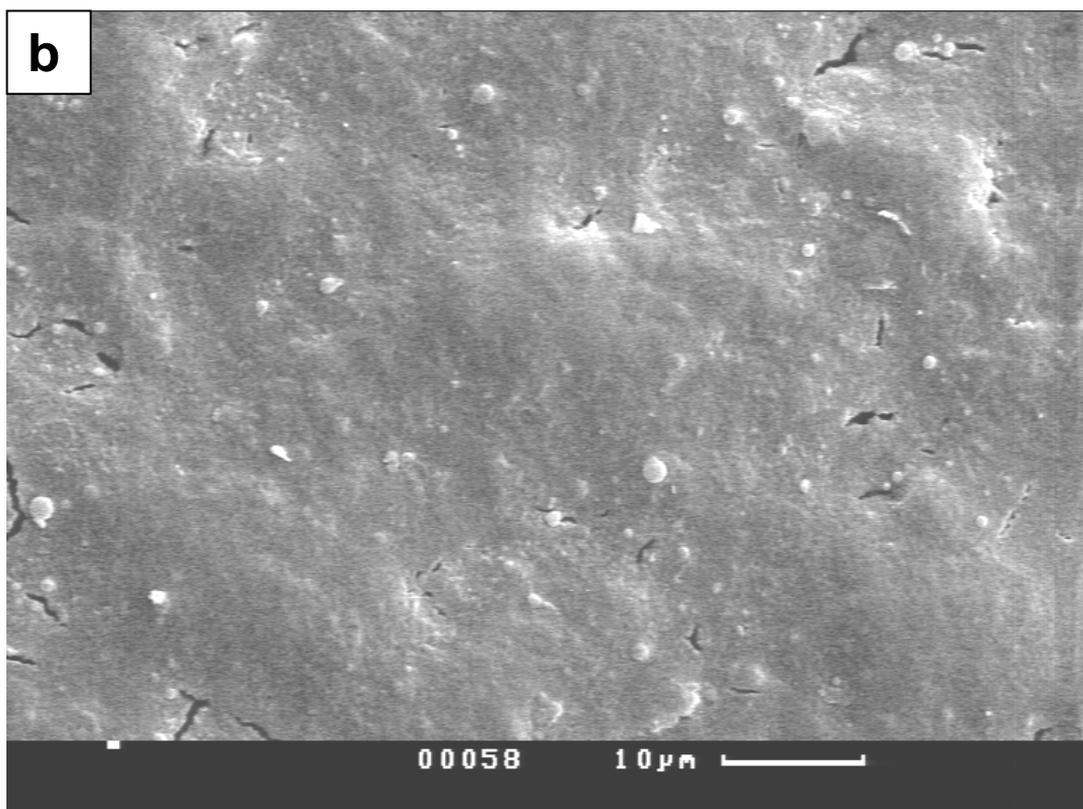
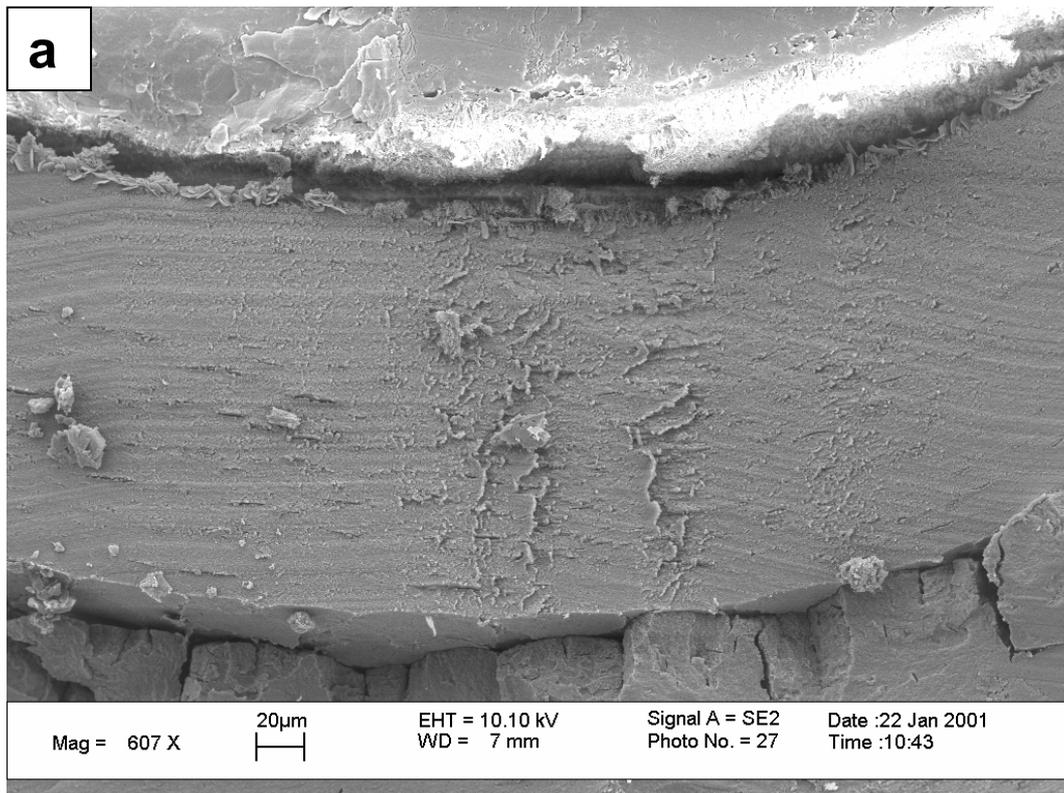


Figure 3.22: SEM pictures of enteric coated pellets; a) the cross-section of a pellet coated with CAP and TEC (Product Jj), magnification 607x; b) the surface of a pellet coated with CAP and DEP (Product Ff or Gg), magnification 1,540x.

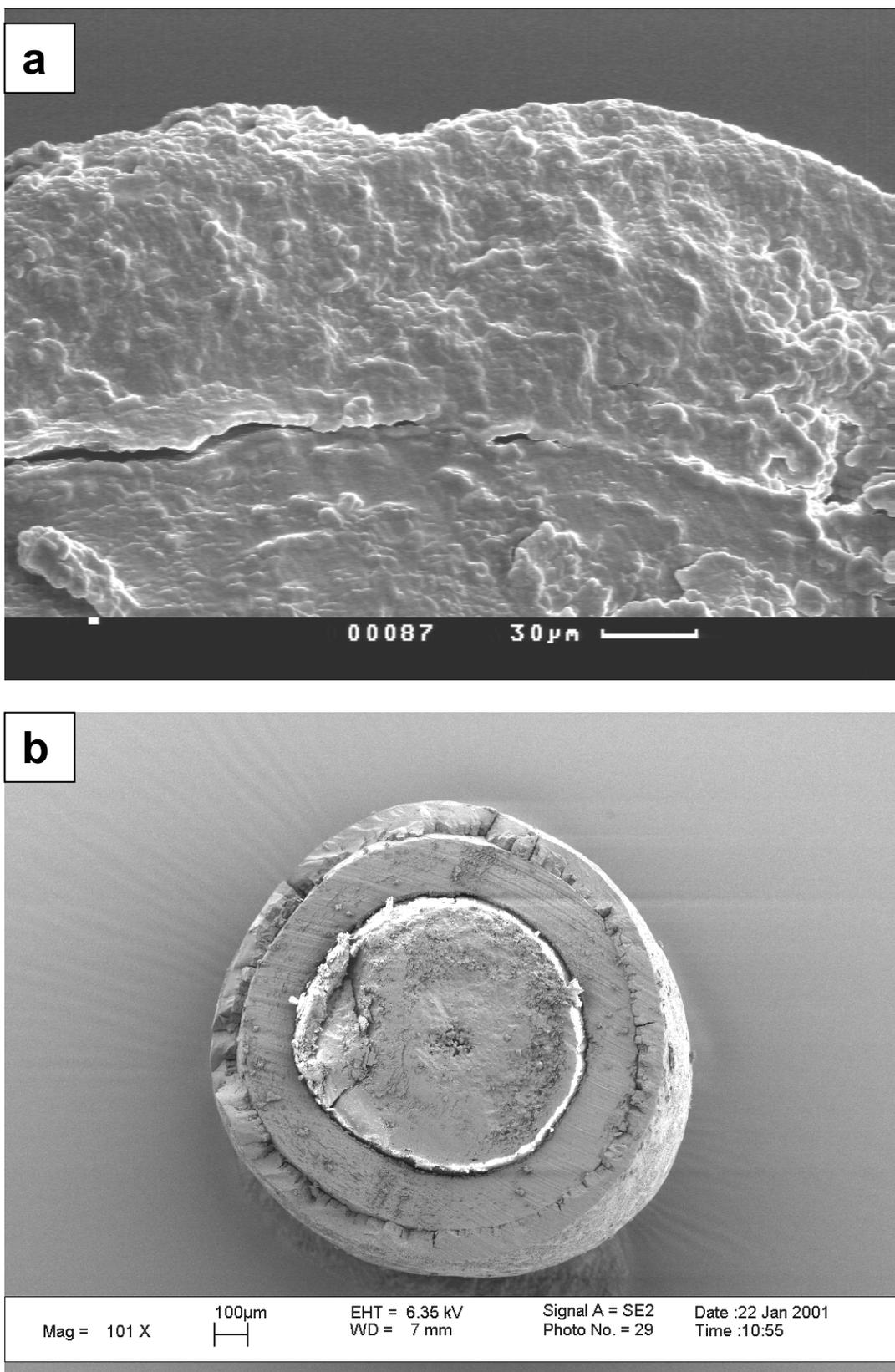


Figure 3.23: SEM pictures of enteric coated pellets;
a) the cross-section of a pellet coated with CAP and DBS (Product Hh), magnification 400x; b) the cross-section of a pellet coated with CAP and TEC (Product Jj), magnification 101x.

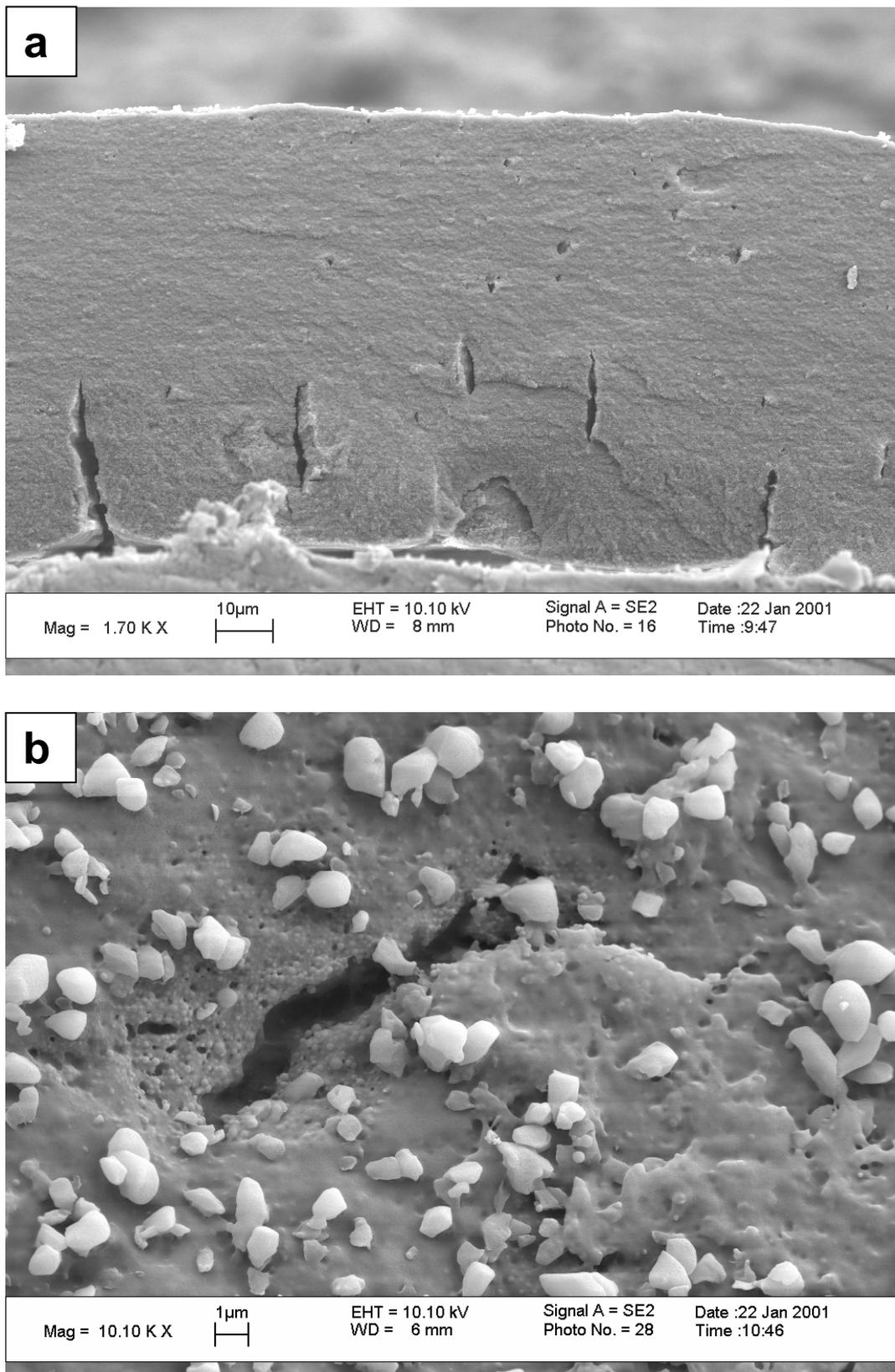


Figure 3.24: SEM pictures of enteric coated pellets with CAP and TEC;
a) the cross-section of a CAP-EC-Nico pellet (Product Jj), magnification 1,700x; b) the surface of a CAP-EC-Nico pellet (Product Jj or Kk), magnification 10,100x.

3.3.2 Swelling

The swelling in 0.1 N HCl of EC-Nico pellets was investigated with Product Cc and Product Ee. These pellets almost did not swell in the acid medium. The swelling of 0.4 % - 0.5 % as shown in the Table 3.9 was very small. The enteric coated pellets (Product Ff, Jj and Kk) also had the same small swelling as their cores (EC-Nico pellets). This small value may be due to the resistance to the acid medium of the EC layer, which is not soluble in this medium.

Product	D1 ± SD	D2 ± SD	ΔD ± SD	Swelling
		(pixel)		(%)
Cc	200 ± 1	201 ± 2	1 ± 1	0.5
Ee	231 ± 1	232 ± 2	1 ± 1	0.4
Ff	240 ± 2	241 ± 2	1 ± 1	0.4
Jj	252 ± 2	253 ± 1	1 ± 1	0.4
Kk	220 ± 2	221 ± 2	1 ± 1	0.5

Table 3.9: Swelling property of different products in 0.1 N HCl, 22 °C; D1: diameter before swelling, D2: diameter after 2 h, Cc and Ee: EC-Nico pellets, Ff: CAP-EC-Nico pellets (CAP+DEP), Jj and Kk: CAP-EC-Nico pellets (CAP+TEC).

3.3.3 Content of nicotinamide in one pellet

The content of nicotinamide inside one pellet of different products was varied. Product Aa or Nico pellet without further coatings contained 8.9 ± 0.2 % w/w of nicotinamide based on total weight of one pellet. One pellet after coating with the subcoat EC (Product Cc) contained 7.8 ± 0.4 % w/w of nicotinamide.

3.3.4 Release of nicotinamide from coated pellets

The cumulative percentage of nicotinamide release during the first five minutes from two types of EC-Nico pellets (Product Cc and Ee) was 1.6 and 1.5 % (Table 3.8). This means the EC layer can control the release of nicotinamide. The dissolution profiles of different products containing nicotinamide can be seen in Figure 3.25. The release of nicotinamide from Product Cc in buffer was not significantly different from that in HCl (data not shown). The release of nicotinamide from Product Cc was higher than that from the Product Ee over a time period of 180 min. However, even after 180 min the cumulative percentage of release of these two products was not more than 50 %.

The cumulative percentage of nicotinamide release surprisingly increased after coating with CAP. More than 50 % of nicotinamide were released within the first five minutes at which the enteric layers consisted of CAP and DEP or DBS. This may be due to the affect of an enteric layer coated above EC layers. The coating conditions may cause the change of the EC structure during or after the coating with CAP layers. Almost the same result was achieved with CAP and TEC but the release was smaller than from the other two formulations. Only 6 % of nicotinamide of Product Jj was released within five minutes and the cumulative content remained lower than 20 % over 180 min. However, the release of nicotinamide within the first five minutes from Product Jj (~ 6.1 %) was also higher than from its cores (~ 1.5 %). Product Kk also released higher nicotinamide in the first five minutes (~ 24.4 %) compared to its cores (~ 1.6 %). This result may also depend on the change of the EC structure during or after an enteric coating process.

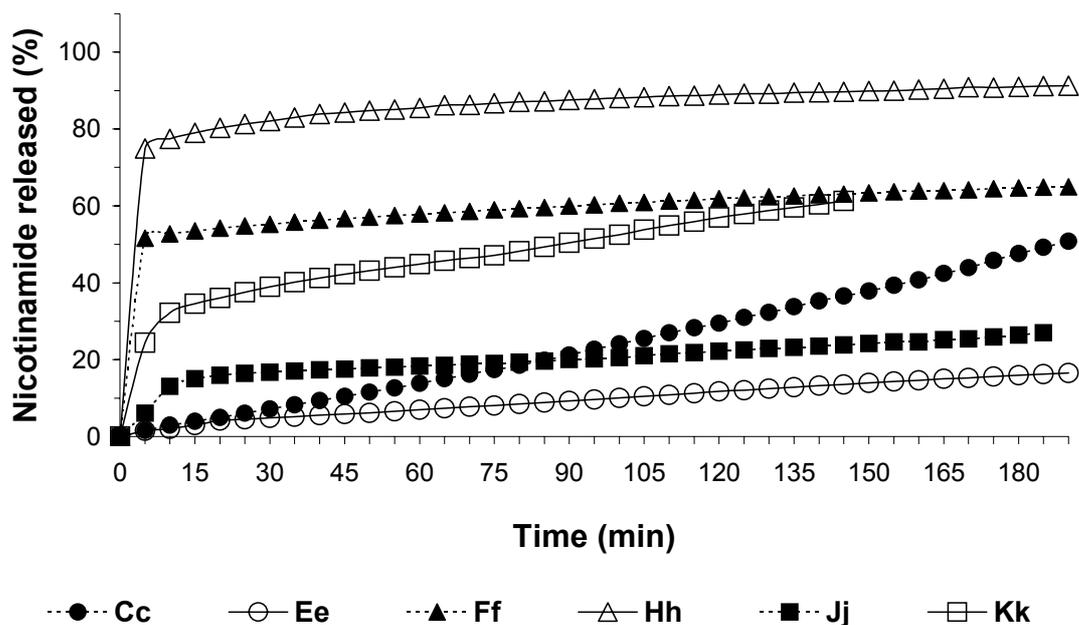


Figure 3.25: Dissolution profiles of differently coated pellets containing nicotinamide in 0.1 N HCl at 37 °C without (Products Cc and Ee) and with enteric coats containing different plasticizers (Products Ff to Jj) and Product Ee as cores;

Ff: CAP with DEP at a coating amount of 13 mg cm⁻²; Hh: CAP with DBS at a coating amount of 25 mg cm⁻²; Jj: CAP with TEC at a coating amount of 50 mg cm⁻²; Kk: CAP with TEC at a coating amount of 39 mg cm⁻² and Product Cc as cores.

3.3.5 Optical appearance after the release study

The optical appearance of EC-Nico pellets with (Product Ff, Kk) and without CAP layer (Product Cc and Ee) after contact with the acidic dissolution medium or buffer pH 6.8 was observed under a light microscope (Figure 3.26 and 3.28). It was found that Product Ee still had the intact round structure after 120 min in both media. This means only the diffusion of the drug was the cause for the release and not the erosion of the outer polymer structure. On the other hand, the outer CAP layer of Product Ff was broken and changed from the original clear film into an opaque film after exposure to 0.1 N HCl for 30 min. As expected, the CAP layer in buffer of pH 6.8 seemed to be completely dissolved and only the EC layer was still intact as seen in Figure 3.27b.

Product Cc in the buffer also showed the intact EC film layer. The substances inside the core were completely dissolved and diffused out of the core. Product Kk, with Product Cc as cores, was broken after 120 min in HCl.

3.3.6 Content of free phthalic acid in coated pellets

The high performance liquid chromatogram of the standard mixture (Figure 2.19, part 2.2.15) showed that the two peaks of nicotinamide and free phthalic acid were well separated. The retention time of nicotinamide (I) was 4.4 min and of free phthalic acid (II) was 10.8 min. This means the selected method was suitable for detecting the amount of free phthalic acid in the dosage form containing nicotinamide.

The CAP coated pellets (Product Ff) were used as a sample. The peak of free phthalic acid can be clearly separated from the peak of a high amount of nicotinamide (data not shown). Results show that the amount of free phthalic acid was 3.98 ± 0.06 % w/w, calculated from the standard curve using the peak area. This value of free phthalic acid was not higher than the limit of 6 % w/w in the U.S. Pharmacopeia XXIII <28> but higher than the limit of USP XXIV <26>, BP 1993 <27> and EP 2000 <30>, which was 3 % w/w. The value of free phthalic acid of polymer coated on the pellets was higher than that of the received polymer raw material „Aquacoat CPD“. The specification of the amount of free phthalic in different charges of polymer used showed the value between 0.4 - 0.7 % w/w. The high value of phthalic acid in coated pellets may be due to the hydrolysis of CAP during the storage or the coating process and also from the phthalyl groups in the plasticizer „DEP“, which can give free phthalic acid as well. Therefore it was not recommended to use DEP as a plasticizer when an indicator as free phthalic acid was selected to follow up the stability of CAP. Other plasticizers may be used instead of DEP, for examples DBS or TEC because they do not contain phthalyl groups.

Eshra <53> mentioned that the extraction in water alone was less efficient than in the mixture of methanol and water and that the extraction required at least 30 min to reach equilibrium. However, he found that the measurement did not only show high recoveries (~ 100 %) but also large standard deviations (~ 30 % for phthalic and ~10 % for acetic acid) at an extraction time of 30 min.

Roxin, Karlsson and Singh <155> have used the new method to extract the free acid from the CAP powder sample. They weighed an exact amount of CAP which was then suspended in CO₂-free water and shaken for various lengths of time, ranging from 10 to 120 min at room temperature. Samples were then centrifuged and filtered prior to analysis by the chromatographic method. The results showed that equilibrium was not reached at 120 min in all cases. Therefore they developed a new extraction method based on a CAP precipitation. An exact weight of CAP was dissolved in THF by stirring and water was added dropwise with vigorous stirring, allowing the polymer to precipitate out. The samples were centrifuged and the supernatant filtered before the analysis by chromatography. The results of the chromatographic analysis showed a high recovery (~100 %) and lower standard deviations (1 % for phthalic acid and 10 % for acetic acid at the quantification limit). The relative standard deviation of the process was 4.1 % for phthalic acid and 4.4 % for acetic acid. The high performance liquid chromatographic (HPLC) analysis of free acids was performed by using different HPLC-column and the best results were obtained with a C18 column using 10 % methanol in 0.025 mM phosphate buffer of pH 3 at 1 ml/min, injection volume 20 µl. The retention time for acetic acid was 1.7 min, compared to 8.4 min for phthalic acid. Roxin, Karlsson and Singh <155> also showed the amount of total acid content of about 1.5 % w/w in the fresh CAP powder sample. 0.15 – 0.66 % was free acetic acid and 0.98 – 1.08 % was free phthalic acid. When CAP powder samples were stored at various conditions the free phthalic acid concentration rised while the acetic acid concentration fell below detection levels. The absence of acetic acid in these samples may be explained by the fact that acetic acid was volatile. The increase of water partial pressure, means increasing in % r.h., at a constant temperature caused an increase in the phthalic acid concentration. The higher temperatures at constant vapor pressure of water seemed to result in lower phthalic acid content, although still much higher than in fresh material. This can be explained on the basis of the adsorption isotherm for water. At higher temperatures, the CAP powder absorbed less water (for the same water activity) and therefore there was a lower level of hydrolysis, resulting in less free acid. Thus humidity or moisture had a greater effect on the storage stability of CAP powder than temperature did. These results recommend that both these factors must be simultaneously taken into account when evaluating CAP film tablet coating or powder stability data.

Bodmeier and Chen <20> have determined the acidic degradation products such as acetic, propionic, butyric, and phthalic acid in aqueous pseudolatexes of cellulosic esters by a high performance liquid chromatography (HPLC). The pseudolatexes of cellulose acetate, cellulose acetate butyrate, and cellulose acetate propionate were prepared by a high pressure emulsification-solvent evaporation method. Cellulose acetate phthalate (Aquateric) was redispersed in water prior to analysis to result in a 10 % w/v pseudolatex. The chromatographic method was developed by using the isocratic, reversed-phase HPLC to quantify the organic acids: acetic, propionic, butyric and phthalic acid, formed as a result of ester hydrolysis in pseudolatexes of cellulosic esters. Peaks of the three aliphatic acids with a mobile phase of 0.025 M phosphate buffer:methanol (80+20 % v/v, pH 3) were well separated. The retention times for acetic acid is 2.6 min whereas the retention time for phthalic acid is about 8 - 9 min. The retention time of phthalic acid in pure phosphate buffer was larger than 60 min. The peak heights increased and the peaks became sharper by increasing methanol concentration. A methanol concentration of 20 % v/v was selected because of only minor reductions in retention times and increased column pressures at higher methanol concentrations. The samples had to be acidified with phosphoric acid to a pH < 3 so that only the unionized form will be retained on the stationary phase. In addition to the sample pH, the mobile phase was buffered to pH 3, which suppressed the ionization of the acids. The pKa values of acetic acid are 4.76 and those of o-phthalic acid are 2.95 and 5.41. More than 98 % of the aliphatic acids were in the unionized form at a pH of 3.

The method developed in this present study shows that the results were comparable to the recent data in the literature <155,20>. This HPLC-method was not complicated to be used in determination of free phthalic acid in the CAP-coated pellets although a high amount of water-soluble drug as nicotinamide was present. Therefore if the stability of the CAP-coated pellets should be monitored by using free phthalic acid as an indicator, the HPLC-method seems to be suitable.

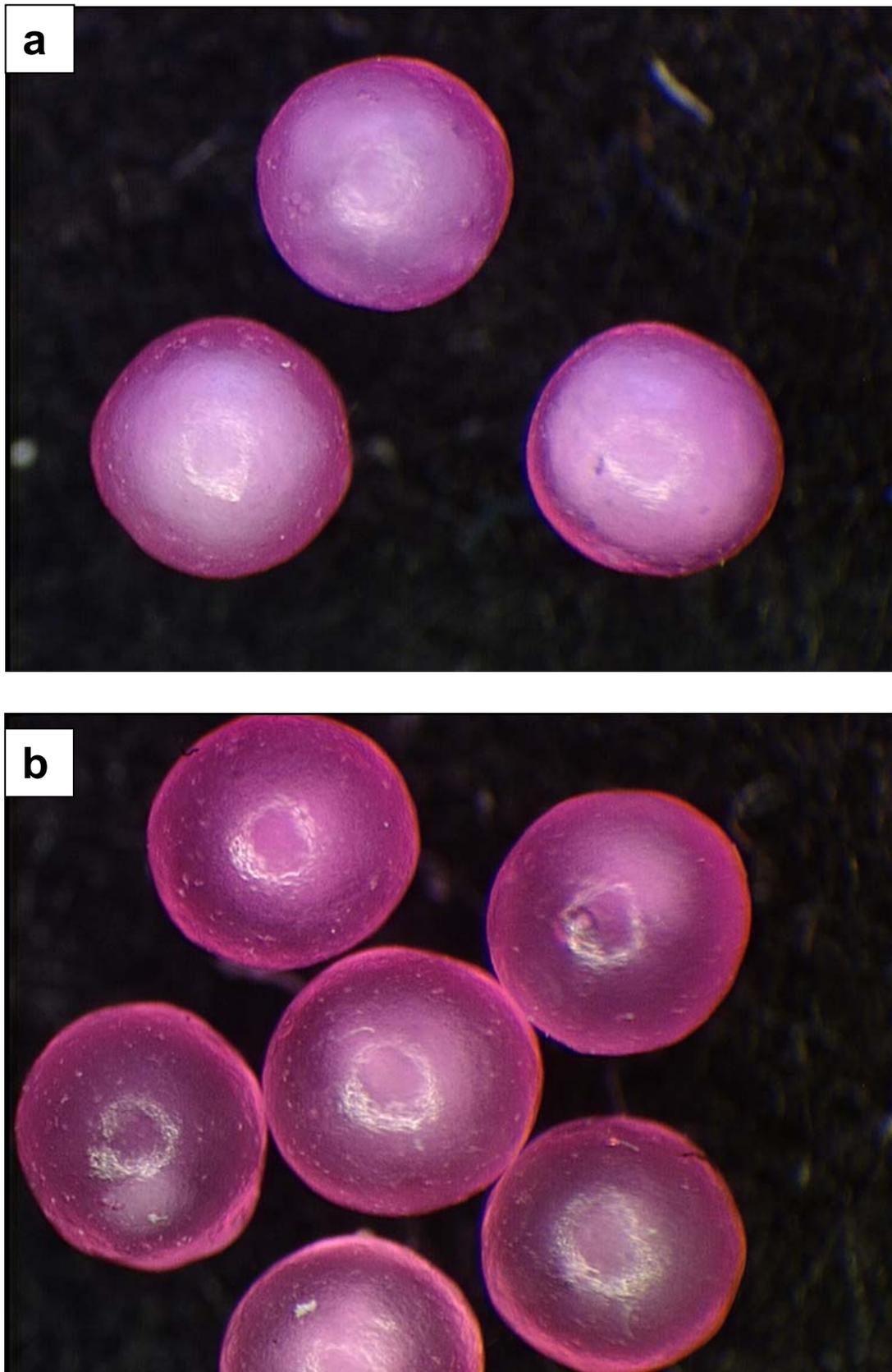


Figure 3.26: Pellets coated with a subcoat from EC (Product Ee) after exposure to different media at 37 °C, for 120 min; a) 0.1 N HCl; b) phosphate buffer pH 6.8.

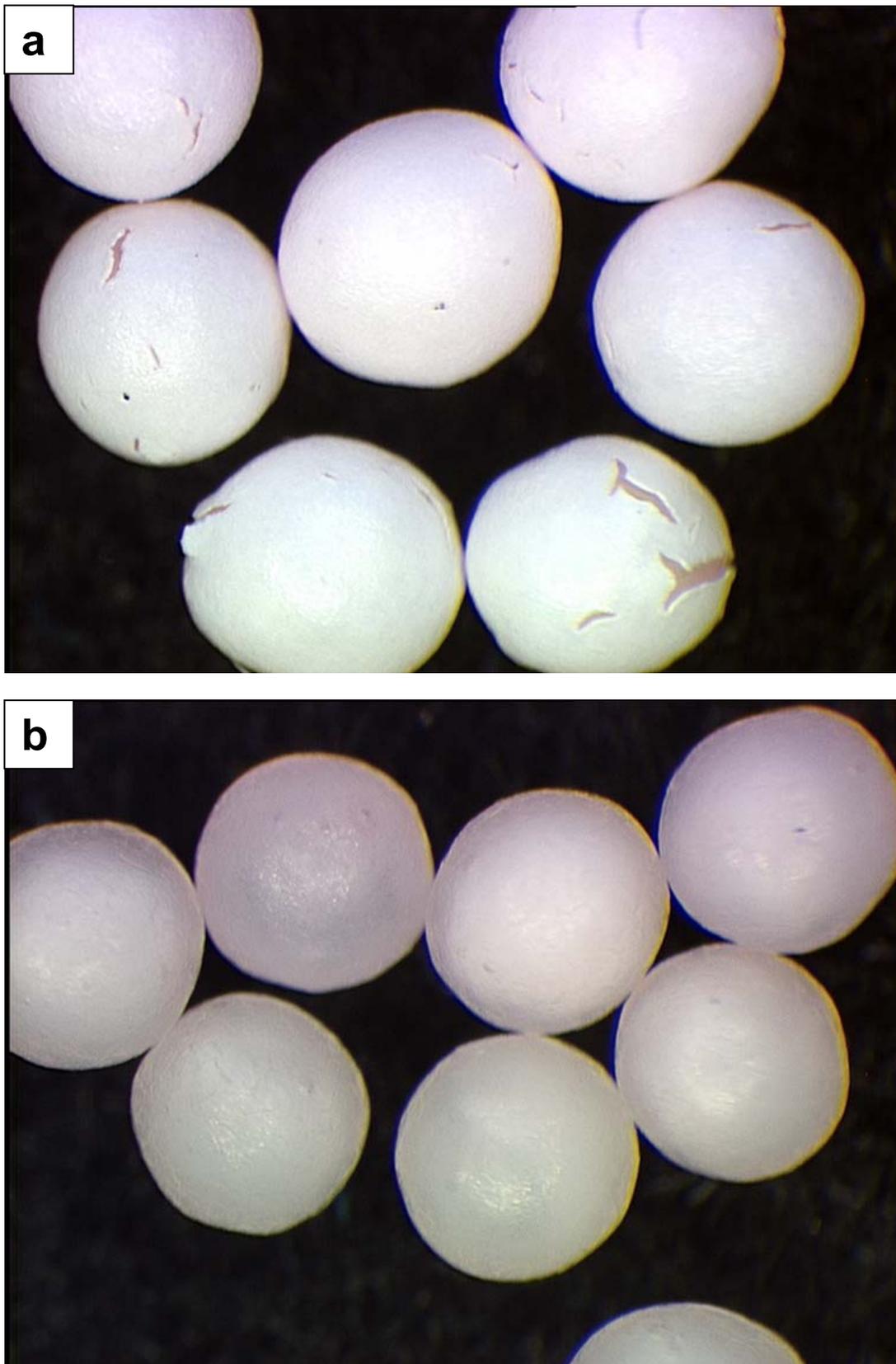


Figure 3.27: Enteric coated pellets with CAP and DEP (Product Ff) after exposure to different media at 37 °C;

a) 0.1 N HCl, for 30 min.; b) phosphate buffer pH 6.8, for 120 min.

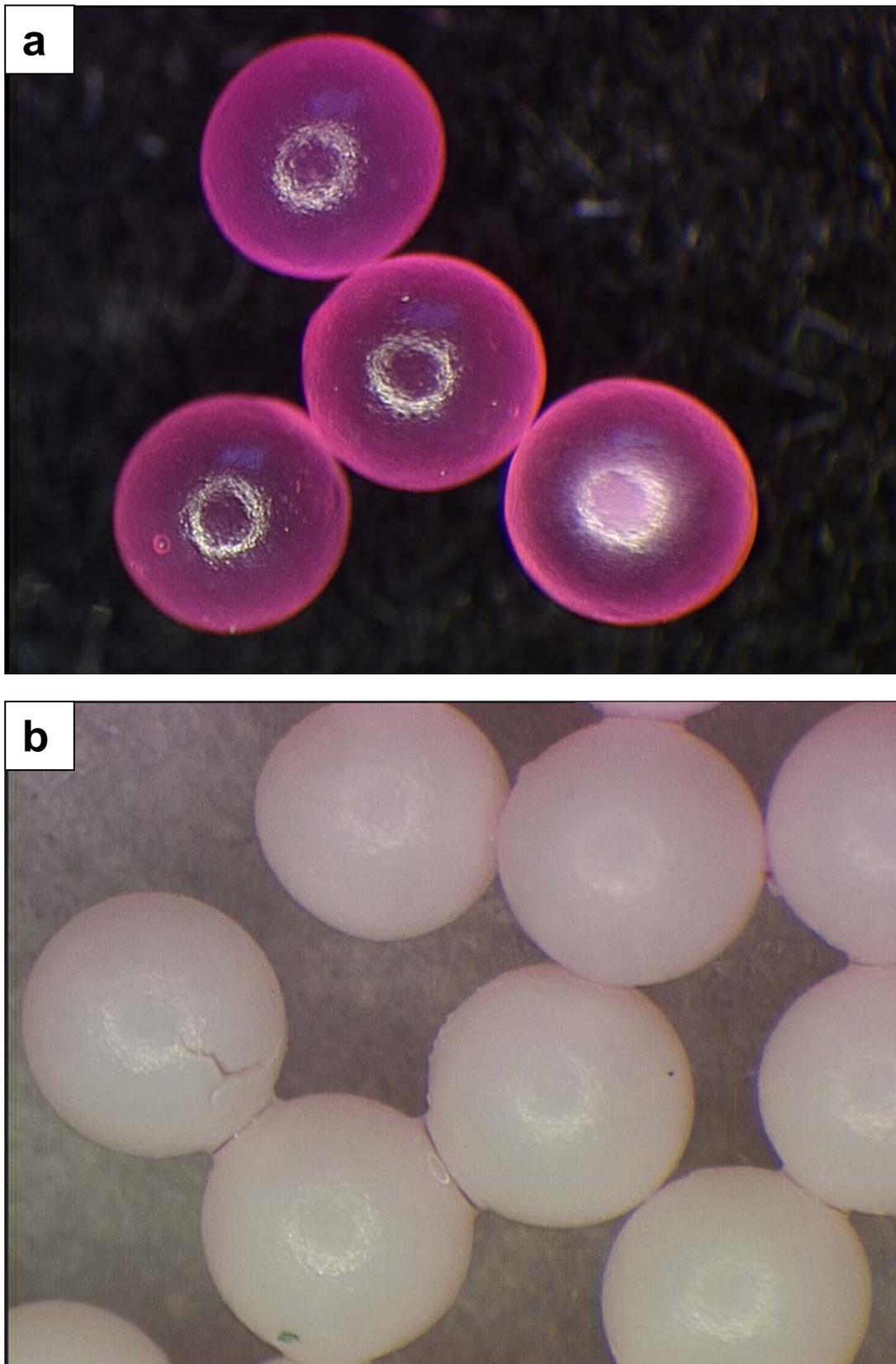


Figure 3.28: *Coated pellets after exposure to different media at 37 °C for 120 min; a) pellets coated with a subcoat from EC (Product Cc) after exposure to phosphate buffer pH 6.8; b) enteric coated pellets with CAP and TEC (Product Kk), still wet after exposure to 0.1 N HCl.*

3.3.7 Discussion

Ethyl cellulose was used in this work because of its nonionic and moisture barrier properties. The subcoat prepared from EC was then compared to that one prepared from HPMC.

Ethyl cellulose has been used as coating material for oral sustained release dosage forms since a long time. However, if the thickness of EC layer was not too thick it can be used as a moisture barrier. Aquacoat ECD-30, an aqueous ethyl cellulose dispersion, is an alternative to respective organic solution. The film forming process of aqueous polymer dispersions is different in comparison to organic solutions. Stable films are formed after concentration of the aqueous dispersion, deformation of the latex particles and interdiffusion of the polymer chains.

Obara and Mc Ginity <117> have investigated the influence of processing variables on the properties of free films prepared from aqueous polymeric dispersions by a spray technique. The mean tensile strength of free films from Aquacoat ECD, a high minimum film formation temperature (MFFT) latex, was slightly higher at higher processing temperature but this was not significant. The spraying rate did not alter the mechanical properties of films prepared from this pseudolatex. Due to the high MFFT of about 30 °C of the Aquacoat ECD and 23 % TEC dispersion, a significant influence of processing temperature on film properties was anticipated. At a surface temperature of 30 °C, and spray rate of 0.8 g/min many small cracks were evident in the films. At the surface temperature of 40 °C and 50 °C, intact films were obtained. The spray rates i.e. 1 g/min and 2.5 g/min did not influence the properties of films prepared at 50 °C. This was expected since the size of dispersed particles is similar to that of the Eudragit L dispersions (about 0.2 µm). Obara and Mc Ginity suggested that TEC would be an ideal plasticizer for Aquacoat ECD based on the data of MFFT which can form clear films at lower temperatures than with DEP or DBS. Apart from this the water soluble plasticizer can well distribute into the polymeric dispersion and therefore can rapidly reach the equilibrium. The water insoluble such as DEP or DBS were often emulsified into the dispersion and the equilibrium time can sometimes be quite longer.

In another work of Obara and McGinity <116>, they have studied the properties of free films prepared from aqueous dispersions of EC by a spray method and a cast method. The EC dispersion contained 24 % DBS. The surface appearance of EC films prepared by the cast method was influenced by the concentration of the solid. An „orange peel“ was seen at the solid concentrations of less than 15 % w/w. An increase in the solid concentration to 25 % improved the surface appearance of the film to a smoother one but cracks were observed in some part of films. However, the spray method provided uniform films without any cracks even at a solid concentration of 10 %. The MFFT of this dispersion was approximately 30 °C. Therefore the brittle films especially from the cast method may be due to the incomplete coalescence. The elongation of these films was about 2 - 5 %, the elastic modulus was about 180 – 206 MPa.

In summary, EC films were weak in both the dry and wet state with low puncture strength and elongation values. In contrast, acrylic-based polymeric films were stronger and more flexible <21,67>.

EC is a nonionic polymer. Therefore the release of drug from the EC-coated products is expected to be pH-independent. However, several studies with Aquacoat ECD-coated beads showed a faster drug release in simulated intestinal fluid when compared to simulated gastric fluid. It was mentioned that the faster drug release may be due to the ionization of sodium lauryl sulfate (SLS) <21,67>. The release study of Aquacoat ECD-coated beads containing chlorpheniramine maleate (CPM) confirmed the effect of the surfactant. At the concentration of 6 % SLS the release of the drug in the buffer pH 7.4 was faster than that in 0.1 N HCl. The faster initial drug release may be an indication of better wetting of beads in pH 7.4 buffer. SLS has a pKa of 1.9 and will be surface-active only in the ionized state. SLS is approximately 10 % ionized in 0.1 N HCl and completely ionized in pH 7.4 buffer. The wetting hypothesis was confirmed by measuring the contact angles between pseudolatex cast EC films and these two dissolution media. The contact angle of the surfactant-free EC films was the same in both media. However, the contact angle decreased with increasing concentrations of SLS in the film and was significantly lower on films wetted with pH 7.4 buffer than on the films wetted with 0.1 N HCl. Cetyl alcohol which was used as a stabilizer for the pseudolatex also had a pronounced effect on the drug release. The drug release decreased with increasing concentration of the cosurfactant. The presence of cetyl alcohol rendered the film coat more hydrophobic as indicated by an increased contact

angle. The results clearly demonstrated that the pH-dependent drug release from Aquacoat ECD-coated beads was caused by the presence of the nonionic surfactant and not the polymer. The water-insoluble plasticizer existed in the aqueous phase predominantly in the emulsified and not dissolved form. The recent report also showed that the water-insoluble plasticizers (DBS) were not completely taken up by the colloidal polymer particles within a 24 h period. After a week of mixing visible DBS droplets in Aquacoat ECD were observed. However, another report showed that the uptake of DBS was complete within 30 min irrespective of the amount used and the uptake rate was faster with increasing solid content of pseudolatex or when smaller quantities of plasticizer were incorporated. This may have important implications for the coating with polymer dispersions when compared to organic polymer solutions in which the plasticizer is completely dissolved. During coating in addition to the plasticized polymer particles the emulsified plasticizer droplets will be sprayed onto the solid dosage forms. This could result in an uneven plasticizer distribution within the film <21,67>.

A curing step is often recommended to accelerate the coalescence of the polymer particles. During the curing step the coated products are subject to a heat treatment above the T_g of the polymer or about 10 °C above the MFFT. This is achieved either by storing the coated products in an oven or through further fluidization in the heated fluidized bed coater immediately after the completion of the coating process. Higher curing temperatures could cause excessive tackiness and agglomeration of the coated products. The effect of curing was reported for example with chlorpheniramine maleate beads coated with pseudolatex of EC. The cores were coated at 40 °C and thereafter were treated with heat at 40 °C, 50 °C and 60 °C for 1 - 24 h. It was found that the drug release in pH 7.4 buffer was strongly affected by the curing conditions. The release of drug from uncured cores was more than 80 % after 2 h. The curing at 40 °C for 24 h was insufficient but the curing at either 50 °C or 60 °C resulted in a significant reduction in drug release (up to less than 25 % after 2 h). The curing effect also depends on the amount of a plasticizer e.g. TEC. If the concentrations of a plasticizer were high enough the curing step may not be necessary <21,67>.

Depending on the physicochemical properties of the drug and polymeric coatings curing could influence the performance of the pseudolatex-coated dosage forms differently. Whilst curing of the Aquacoat ECD-coated CPM beads produced a retarding effect in the drug release the curing of ibuprofen beads coated with a comparable coating system resulted in more complex drug release pattern. The release of ibuprofen in

pH 7.4 buffer was initially rapid with ibuprofen beads cured at 50 °C for 15 min then the release was decreased with increasing curing time up to 4 h. However, at the curing time excess of 4 h the drug release increased again. It was mentioned that the initial decrease in drug release (up to a curing period of 4 h) was due to the further coalescence of the polymer particles in the EC film. The increase in drug release (curing periods in excess of 4 h) could be explained with the migration of ibuprofen from bead interior to the bead surface through the EC coating during the curing step. It was mentioned that the different results of release may be due to the melting point of CPM and ibuprofen. Ibuprofen has a much lower melting point (75 - 77 °C) than CPM (130 °C - 135 °C). The drug-polymer affinity coupled with the drug's low melting point could thus serve as an explanation for the phenomenon of the drug migration. The diffusion of quiafenesisin, another low-melting point drug through the vapor phase across the Aquacoat ECD coating during storage of the coated beads has also been reported. Although the bed temperature was above the MFFT of the pseudolatex evaporation of water during the coating process could have resulted in a cooling effect and might have kept the temperature on the bead surface below the MFFT. The release of the water-insoluble drug such as ibuprofen was reported to be primarily by solution/diffusion through the hydrophobic polymer. On the other hand, CPM, the water-soluble drug, was not released by a solution/diffusion mechanism from the beads because of its negligible diffusible property. Moreover, CPM which was layered onto beads will exert the osmotic pressures within coated dosage forms upon dissolution and these osmotic pressures could cause the microrupturing of the wet state polymeric films especially the weak polymeric membrane as Aquacoat ECD.

This present study shows that the subcoat from EC can well cover the surface of pellets. Films resulting from EC and DBS as a plasticizer were homogeneous and therefore can well control the release of nicotinamide from the core. The maximum of release of nicotinamide over 120 min was less than 30 % from EC coated pellets at every thickness (20 - 160 µm). At the highest EC-thickness of 160 µm, the release could be kept lower than 20 % over 180 min because of the properties of EC, as it was not dissolved in 0.1 N HCl or phosphate buffer. Therefore EC cannot be used as a subcoat without limitations. The controlled release property of EC depended on the thickness of the film. If a fast release was required then only a thin film from EC should be used as a subcoat. The EC coated pellets still had their round form after contact with acidic or

buffer medium. This means only the diffusion of nicotinamide was responsible for the release of the drug and not the erosion. Trials by using EC coated pellets at two different EC-thicknesses were made. The results show that CAP-EC-Nico pellets with two different thicknesses of EC subcoat were not gastric resistant over 2 h. The release of nicotinamide was more than 10 %, which was the limit of the Pharmacopeia. Surprisingly the release of nicotinamide from the pellets after coating with CAP was higher than that from EC-Nico pellets without CAP layer. Enteric coated pellets with CAP and DEP were broken after exposure to 0.1 N HCl for only 30 min inspite of a low swelling of the EC coating. On the other hand the film from CAP and TEC was more stable and the coated pellets did not break fast in the acidic medium.

The unsatisfying enteric property of CAP-coated product was due to the incomplete coalescence of the CAP polymer as details mentioned in 3.1 - 3.2.

3.4 Pellets with nicotinamide and a combination of EC and PVA (100 parts + 30 parts) as a subcoat

a) Placebo: HPMC pellets

The HPMC coated pellets (Product pP) were achieved from the combination of a formulation **R1** and a process number **X7**, as demonstrated in the Table 2.28.

b) Nicotinamide loaded pellets: Nico pellets

The Nico pellets (Product aA) were achieved from the combination of a formulation **R3** and a process number **X8**, as demonstrated in the Table 2.28.

c) A combination of EC and PVA as a subcoat: E&P-Nico pellets

The E&P-Nico pellets have a green colour as a marker was used. These pellets (Product bB to cC) were achieved from the combination of a **R6** and a process number **X11**, as demonstrated in the Table 2.28.

d) Enteric coated pellets: CAP-E&P-Nico pellets

The CAP-E&P-Nico pellets still have a green colour caused by the marker. These pellets (Product dD to oO) were achieved from different combinations of a formulation and a process number, as demonstrated in the Table 2.28.

3.4.1 Film quality, diameter and weight of pellets

The physical properties of raw materials used for this process and of the finished products are shown in Table 3.10. The thickness of the HPMC layer (HPMC pellets) as measured from SEM was about 10 ± 3 μm . The mean diameter of these pellets measured by an image analyser was 980 ± 36 μm . The mean weight of one HPMC pellet 'Product pP' was 0.67 ± 0.01 mg, which was lower than that of sugar spheres. The reason for this was mentioned before. One Nico pellet had a mean weight of 0.78 ± 0.02 mg and a mean diameter of 1010 ± 35 μm . The thickness of the nicotinamide layer

of 'Product aA' was about $23 \pm 3 \mu\text{m}$ and the weight gain from nicotinamide and HPMC was 11.0 % w/w. The subcoat from a combination of EC and PVA (E&P) has been achieved in two different thicknesses; i.e. 66 ± 4 and $130 \pm 8 \mu\text{m}$ with amounts of E&P of 36 and 67 % w/w respectively. The SEM photograph in Figure 3.29a shows the thickness of the E&P layer of 'Product cC' and that the layer was not homogeneous. The polymer layers were separated from each other like multiple fiber layers. The mean weight and the mean diameter of one pellet compared between cores (Product aA) and E&P-Nico pellets (Product bB and cC) allowed to calculate the amounts of E&P-polymer coated per pellet, namely from 37 to 76 mg cm^{-2} . The physical properties of CAP-coated pellets are also stated in Table 3.10 Product dD showed the layer of CAP and DEP with cracks distributed around the surfaces (the same as in the other parts 3.2 - 3.3). There was no difference between the CAP film layer from Aquateric (Product eE) or Aquacoat CPD (Product dD) as mentioned before in the part 3.2. The CAP and DBS film layer from Product fF showed the same result as mentioned before in the part 3.2. The best enteric layer from CAP can be achieved from TEC as a plasticizer. A cross section of the CAP and TEC layer (Product nN) showed an almost homogeneous film structure (Figure 3.29b). However, the surface of these pellets showed also small cracks (Figure 3.30a). In order to try to improve the elasticity of the film from CAP and TEC, the polymer HPMC-AS was added to the combination of CAP and TEC, R14 (Table 2.22). The SEM photograph (Figure 3.30b) shows small cracks around the surface of these coated pellets (Product oO). The whole surface of cores (Product cC) was well covered by the film from CAP, TEC and HPMC-AS, to be seen in the Figure 3.31. Therefore there is no significant difference between these two formulations.

The mean weight of one CAP-E&P-Nico pellet (Product nN) from Product bB as cores was $1.47 \pm 0.02 \text{ mg}$ while the mean diameter of these pellets was $1310 \pm 40 \mu\text{m}$ at the coating amount of 36 mg cm^{-2} . The mean weight of one CAP-E&P-Nico pellet (Product mM) and Product cC as cores was increased up to $2.25 \pm 0.05 \text{ mg}$ while the mean diameter of one pellet was $1495 \pm 45 \mu\text{m}$ at the coating amount of 63 mg cm^{-2} . Although the weight gain of the total batch for Product mM and Product nN was the same, i.e. 45 % w/w, the coating amount calculated from the amount of polymer over one square centimetre was different. This may be due to the fact that the Product nN has smaller cores and consequently more surface area which needs more polymers to achieve the same coating amount.

Product	Weight gain of total batch (% w/w)	Thickness of the layer ($\mu\text{m} \pm \text{SD}$)	Weight of pellet (mg \pm SD)	Diameter of pellet ($\mu\text{m} \pm \text{SD}$)	Coating amount (mg cm^{-2})	Release within the first five minutes (% \pm Range)
SS	0.0 ^a	800-1000 ^g	0.68 \pm 0.01	970 \pm 37	n	n
pP	3.5 ^b	10 \pm 3 ^h	0.67 \pm 0.01	980 \pm 36	n	n
aA	11.0 ^c	23 \pm 3 ⁱ	0.78 \pm 0.02	1010 \pm 35	n	n
bB	36.0 ^d	66 \pm 4 ^j	1.08 \pm 0.02	1175 \pm 45	37.0 ^l	3.7 \pm 0.2
cC	67.0 ^d	130 \pm 8 ^j	1.39 \pm 0.02	1320 \pm 43	76.0 ^l	3.0 \pm 0.2
dD	12.0 ^e	22 \pm 6 ^k	1.60 \pm 0.02	1360 \pm 47	15.0 ^m	37.4 \pm 0.5
eE	14.0 ^e	26 \pm 4 ^k	1.64 \pm 0.02	1370 \pm 44	18.0 ^m	n
fF	24.0 ^e	33 \pm 8 ^k	1.98 \pm 0.01	1470 \pm 42	43.0 ^m	68.1 \pm 1.0
gG	6.0 ^e	11 \pm 4 ^k	1.48 \pm 0.02	1340 \pm 40	7.0 ^m	62.2 \pm 1.0
hH	17.5 ^e	34 \pm 3 ^k	1.71 \pm 0.03	1385 \pm 43	23.0 ^m	60.6 \pm 1.0
il	20.0 ^e	40 \pm 2 ^k	1.76 \pm 0.03	1395 \pm 43	27.0 ^m	10.6 \pm 0.5
jj	31.0 ^e	62 \pm 4 ^k	1.98 \pm 0.02	1440 \pm 45	43.0 ^m	n
kk	45.0 ^e	90 \pm 5 ^k	2.26 \pm 0.03	1495 \pm 50	64.0 ^m	5.0 \pm 0.3
lL	45.0 ^e	90 \pm 4 ^k	2.26 \pm 0.02	1495 \pm 45	64.0 ^m	n
mM	45.0 ^e	90 \pm 5 ^k	2.25 \pm 0.05	1495 \pm 45	63.0 ^m	2.3 \pm 0.2
nN	45.0 ^f	89 \pm 6 ^k	1.47 \pm 0.02	1310 \pm 40	36.0 ⁿ	5.5 \pm 0.2
oO	20.0 ^e	40 \pm 3 ^k	1.64 \pm 0.01	1395 \pm 42	18.0 ^m	10.7 \pm 0.5

Table 3.10: Properties of different products showing weight gain of total batch, thickness of the layer, weight of pellet, diameter of pellet, coating amount, release within the first five minutes; ^a = weight gain of total batch of sugar spheres (% w/w), ^b = weight gain of total batch of HPMC pellets to sugar spheres, Product SS, (% w/w), ^c = weight gain of total batch of Nico pellets to HPMC pellets, Product pP, (% w/w), ^d = weight gain of total batch of E&P-Nico pellets to Nico pellets, Product aA, (% w/w), ^e = weight gain of total batch of CAP-E&P-Nico pellets to E&P-Nico pellets, Product cC, (% w/w), ^f = weight gain of total batch of CAP-E&P-Nico pellets to E&P-Nico pellets, Product bB, (% w/w), ^g = size of sugar spheres, Product SS (μm), ^h = thickness of the HPMC layer (μm), ⁱ = thickness of the nicotinamide and HPMC layer (μm), ^j = thickness of the E&P-subcoat layer (μm), ^k = thickness of the enteric coating layer (μm), ^l = coating amount of the E&P-subcoat on Product aA (mg cm^{-2}), ^m = coating amount of the enteric coat on Product cC (mg cm^{-2}), ⁿ = coating amount of the enteric coat on Product bB (mg cm^{-2}), n = not measured.

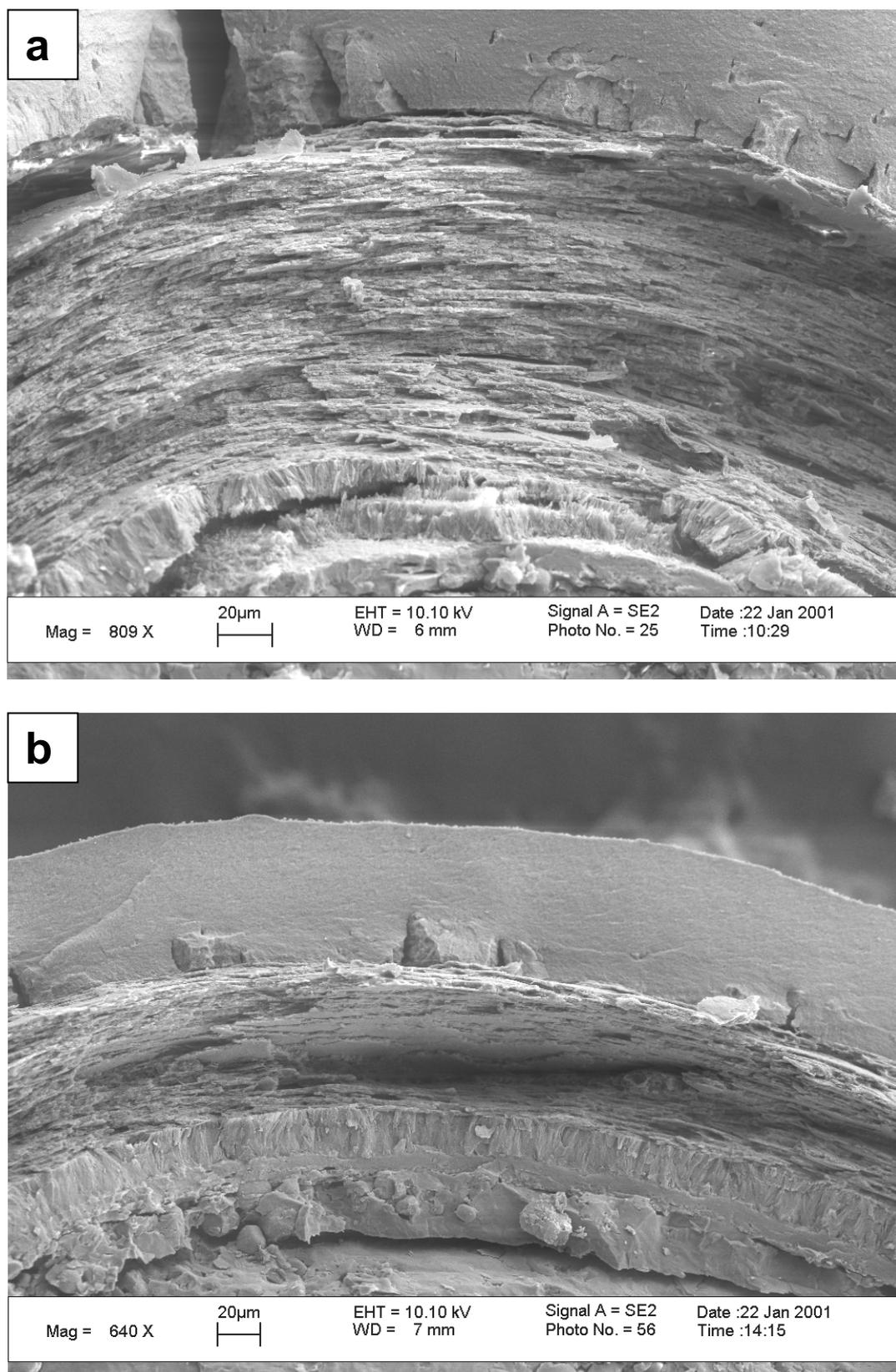


Figure 3.29: SEM pictures of coated pellets; a) the cross-section of E&P-Nico pellet (Product cC), magnification 809x; b) the cross-section of a coated pellet with CAP and TEC (Product nN), magnification 640x.

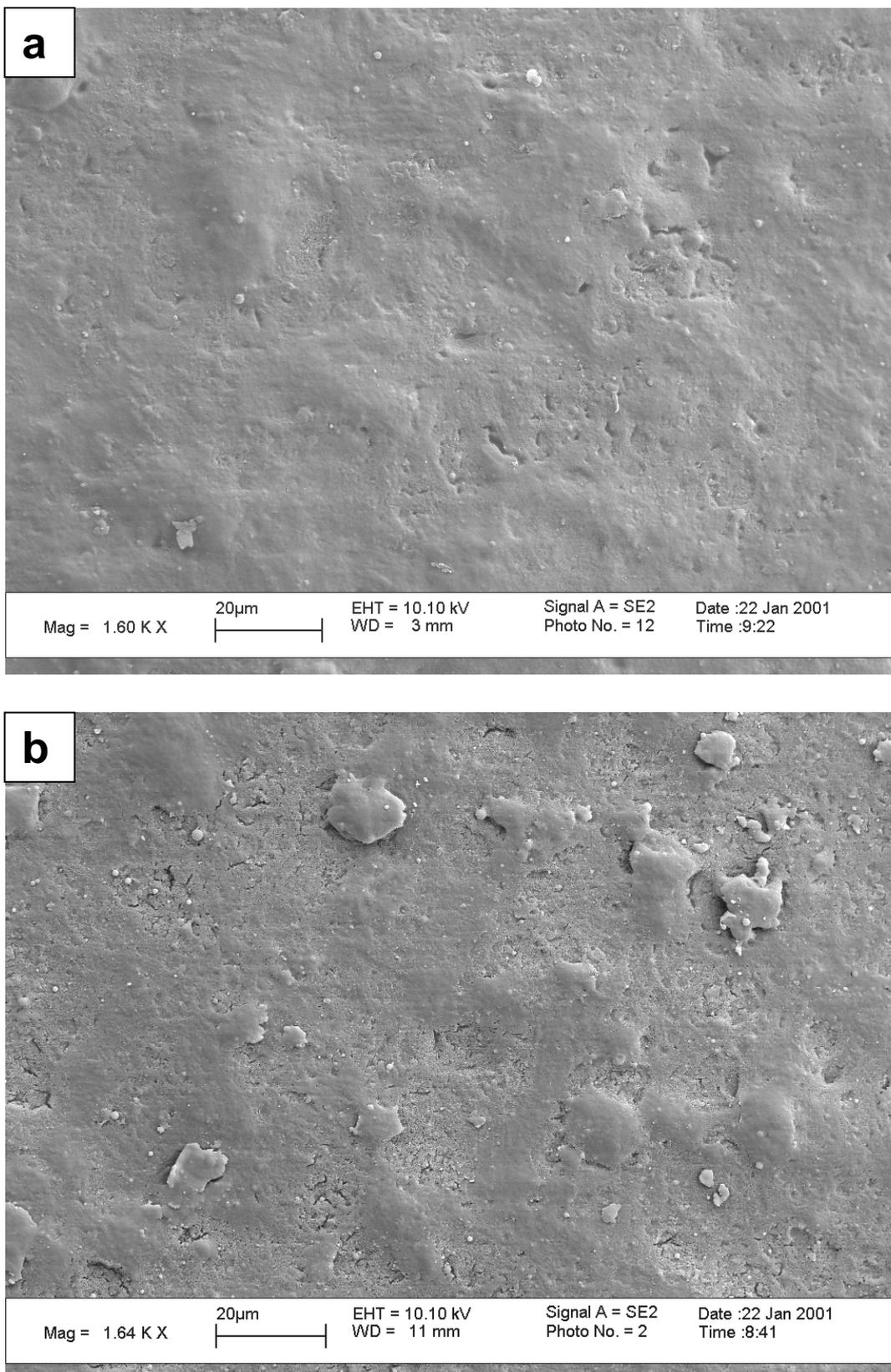


Figure 3.30: SEM pictures of enteric coated pellets; a) the surface of a coated pellet with CAP and TEC (Product gG to nN), magnification 1600x; b) the surface of a coated pellet with CAP, HPMC-AS and TEC (Product oO), magnification 1640x.

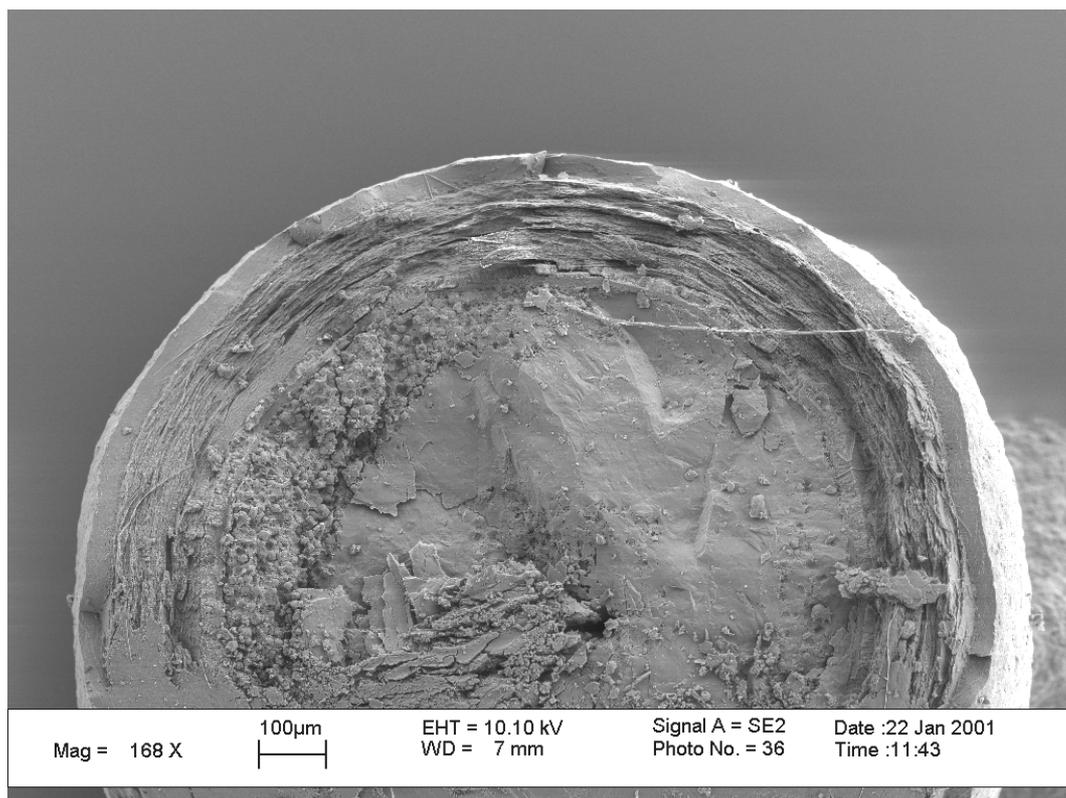


Figure 3.31: SEM picture of the cross-section of an enteric coated pellet with CAP, HPMC-AS and TEC (Product oO), magnification 168x.

3.4.2 Swelling

The swelling in 0.1 N HCl of E&P-Nico pellets was investigated with Product bB and Product cC. These pellets have two different thicknesses. The swelling of pellets with a higher thickness (Product cC) was 8 % as shown in Table 3.11. The enteric coated pellets (Product dD, mM and nN) in the acid medium were broken after 30 min and therefore the swelling cannot be measured.

Product	D1 ± SD	D2 ± SD (pixel)	ΔD ± SD	Swelling (%)
bB	211 ± 1	220 ± 3	9 ± 2	4
cC	230 ± 3	248 ± 5	19 ± 3	8
dD	237 ± 2	-	-	crack
mM	246 ± 2	-	-	crack
nN	228 ± 3	-	-	crack

Table 3.11: Swelling property of different products in 0.1 N HCl, 22 °C; D1: diameter before swelling, D2: diameter after swelling, bB and cC: E&P-Nico pellets, dD: CAP-E&P-Nico pellets (CAP+DEP), mM and nN: CAP-E&P-Nico pellets (CAP+TEC).

The high swelling property of some enteric polymer was reported by Thomas and Bechtold <185>. The swelling of coated tablets was determined by exactly weighing each tablet before and immediately after the 2 h testing for gastric resistance in 0.1 N HCl. The weight gain equal to the water uptake was expressed as a percentage of the initial weight. HPMCAS seems to be a very stable gastro-resistant aqueous coating that underwent little swelling during the test for gastro-resistance and showed virtually no changes in disintegration time during the storage. The coatings made from the CAP-pseudolatex Aquateric or the ammonia-based CAP formulation showed marked swelling in the resistance test and an increase in the disintegration time when stored at 40 °C. Probably this can be attributed to the late film formation since film-coated tablets tended to stick together during storage. However, the swelling of tablets coated with HPMCAS was not significantly different after storage at 25 °C and 35 °C.

3.4.3 Content of nicotinamide in one pellet

The content of nicotinamide inside one pellet of different products was varied. Product aA or Nico pellet without further coatings contained 8.9 ± 0.1 % w/w of nicotinamide based on total weight of one pellet. One pellet after coating with a subcoat

from the combination of EC and PVA (Product bB and cC) contained 8.5 ± 0.4 % w/w of nicotinamide.

3.4.4 Release of nicotinamide from coated pellets

The cumulative percentage of nicotinamide released during the first five minutes from two types of pellets coated with a subcoat from the combination of EC and PVA (Product bB and cC) was 3.7 and 3.0 % (Table 3.10). After 60 min the release of nicotinamide was more than 50 %. This means that the subcoat layer from a combination of EC, PVA and DBS as a plasticizer can control the extent of release of nicotinamide. The dissolution profiles of different products containing nicotinamide can be seen in Figure 3.32.

The cumulative percentage of nicotinamide release unexpectedly increased after coating with CAP. Within the first five minutes nicotinamide was released to more than 60 %, at which the enteric layer was prepared from CAP and DBS (Product fF) or CAP and TEC at the lower coating amount (Products gG and hH). This may be due to an affect of the enteric layer coated above the E&P layer. The coating conditions may cause a change of the E&P structure during or after CAP coating, as mentioned before in the part 3.3.4. At the higher amount of CAP and TEC the release of nicotinamide became smaller (Products iI to nN). However, the release of nicotinamide was more than 20 % after 120 min in 0.1 N HCl at the highest film thickness of 90 ± 5 μm (Products kK and mM). CAP coated pellets with a thinner subcoat (Product nN) had also high release of nicotinamide, more than 70 % after 120 min, therefore the smaller % swelling from this subcoat was not really improving the gastric resistance property.

The combination of CAP, HPMC-AS and TEC (Product oO) gives no significant difference in controlling the release of nicotinamide compared to the mixture of CAP and TEC alone (Product iI), as shown in Table 3.10 or Figure 3.32. These results were in accordance with the results from SEM.

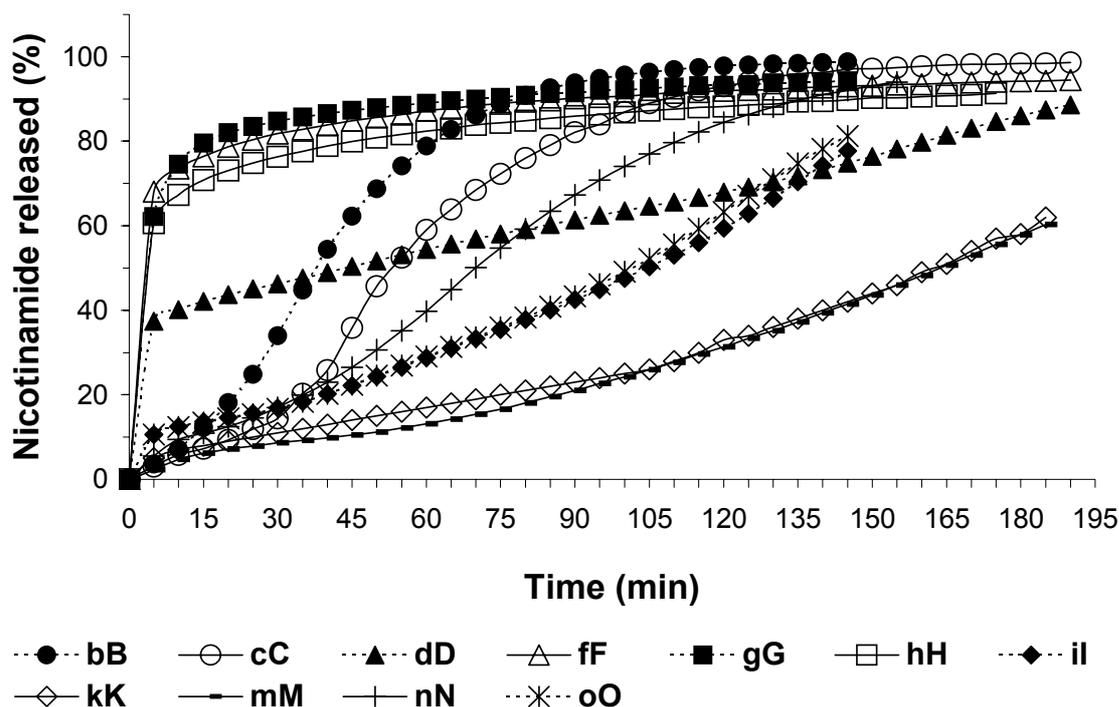


Figure 3.32: Dissolution profiles of differently coated pellets containing nicotinamide in 0.1 N HCl at 37 °C without (bB and cC) and with enteric coats containing different plasticizers (dD to mM) and Product cC as cores; dD: CAP with DEP at a coating amount of 15 mg cm⁻²; fF: CAP with DBS at a coating amount of 43 mg cm⁻²; gG to mM: CAP with TEC with increasing thicknesses of enteric coat in mg cm⁻²; gG:7, hH:23, il:27, kK:64, mM:63; kK: production with intermediate drying phase; mM: similar to kK but with cyclone instead of filters set; nN: similar to mM at a coating amount of 36 mg cm⁻² and Product bB as cores; oO: CAP and HPMCAS (10o + 30 parts) with TEC at a coating amount of 18 mg cm⁻² and Product cC as cores.

3.4.5 Optical appearance after the release study

The optical appearance of E&P-Nico pellets without CAP layer (Product cC) after contact with the acidic dissolution medium or buffer pH 6.8 after 120 min was observed under a light microscope (Figure 3.33). It was found that Product cC still had an intact outer layer with only small cracks in acidic medium, whereas the pellets were broken in a buffer. This means that the release of nicotinamide from the coated pellets was accelerated by the cracks or broken parts.

Pellets coated by using CAP and DEP (Product dD) or CAP and TEC (Product nN) were broken after contact with 0.1 N HCl for 30 min (Figure 3.34). Only the outer CAP layer was broken and changed from the original clear film into an opaque film.

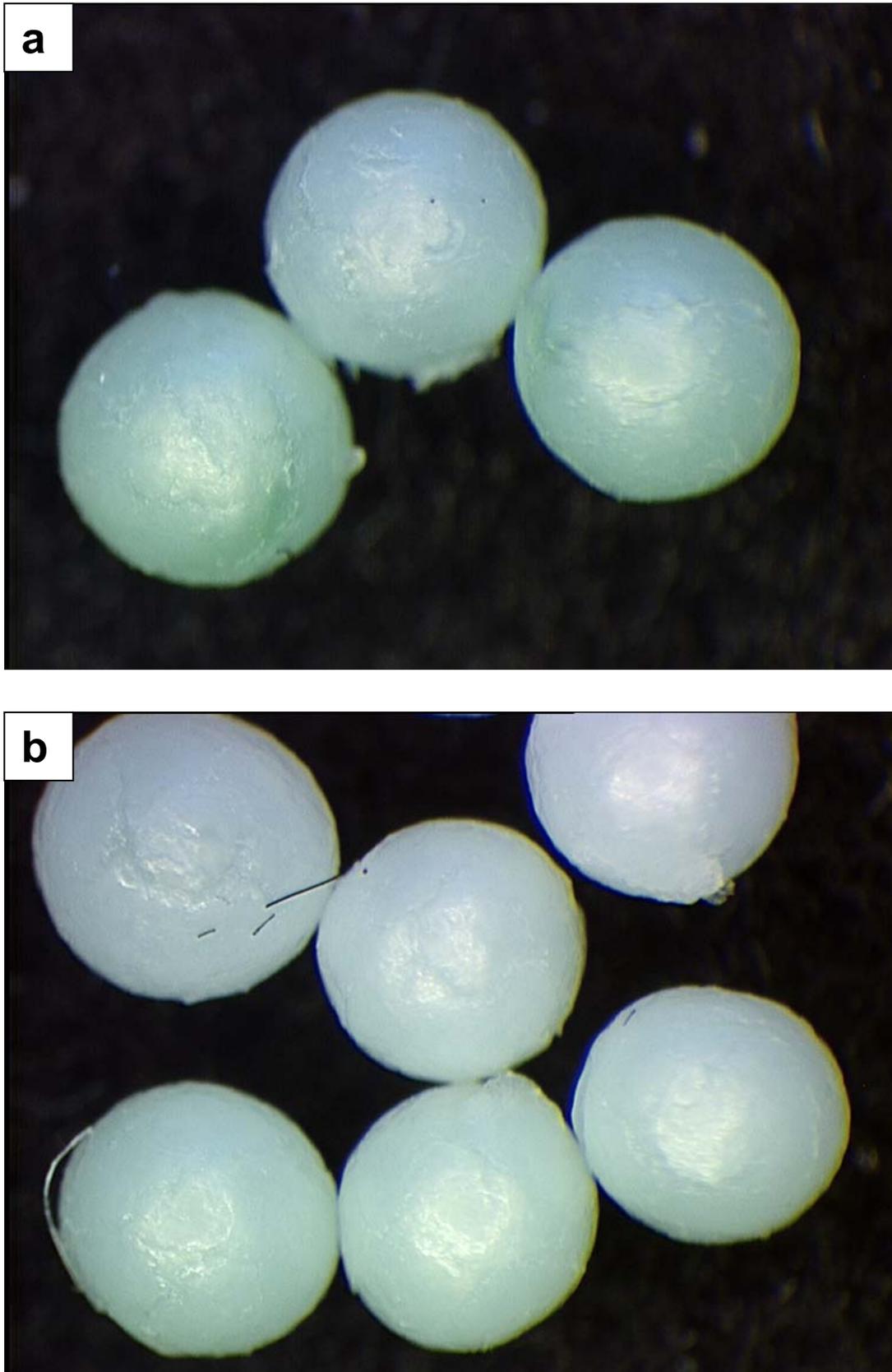


Figure 3.33: Pellets coated with a subcoat from EC and PVA (100 + 30 parts) (Product cC) after exposure to different media at 37 °C for 120 min; a) 0.1 N HCl; b) phosphate buffer pH 6.8.

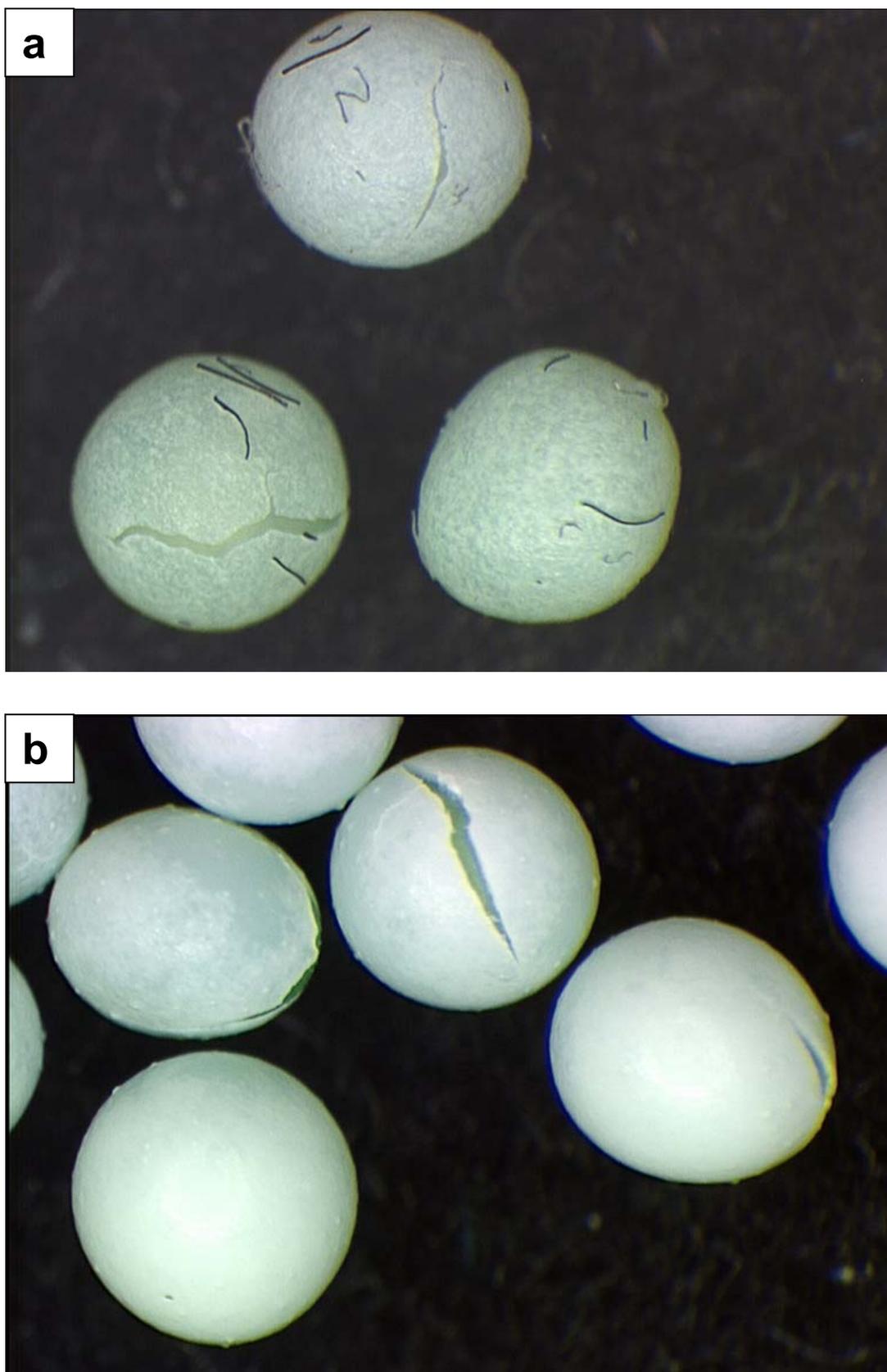


Figure 3.34: Enteric coated pellets after exposure to 0.1 N HCl, 37 °C for 30 min; a) Pellets coated with CAP and DEP (Product dD); b) Pellets coated with CAP and TEC (Product nN).

3.4.6 Discussion of results with similar systems and comparison with present findings

Some publications reported about the coating by using a combination of EC and other polymers.

Gilligan and Po <63> studied many factors that affected the drug release from EC coated pellets. Dextromethorphan hydrobromide (DH) loaded beads were coated with EC aqueous dispersion containing 0 - 12 % w/w HPMC and 24 % w/w of total polymer solids of triethyl citrate. The theoretical level of coating is 6.48 % w/w. These DH impregnated seeds were coated using the Uniglatt Laboratory Unit. Coating conditions were: an inlet temperature of 27 - 31 °C, coating mixtures were pumped to the atomiser at a rate of 3 ml/min operating at a spray pressure of 20 psi. No post-drying was carried out. The dissolution study of coated seeds was performed in buffer pH 6.9 with 1.0 M constant ionic strength. The variation in the percentage increase is attributed to the different nature of the plasticizers employed and the viscosity grade of EC. The increase in the drug release rate was obtained by the amount of increased HPMC. The release data in the present study were fitted to first-order kinetics. A comparison of electron micrographs of pellets coated with an EC pseudolatex film with or without HPMC before and after dissolution showed that after dissolution numerous pores and cracks were present in the polymer film. By this observation they comment that the cracks were not related to the presence of HPMC in the films or caused by the leaching of HPMC from the film but rather to an incompletely formed polymer film coating. Approximately 80 % of DH was released within 2 h from EC without HPMC. It seemed that incomplete film formation could be responsible for the rapid drug release from the pellets. Therefore the effect of storage and certain conditioning procedures on the in vitro release of DH from EC-coated pellets were investigated. After the EC-coated pellets were stored for 4 months at room temperature, it was found that the rate of drug release from the coated pellets before and after 4 months storage was a significant difference. The decrease in release rate can be related to further gradual coalescence. The effect of conditioning of coated pellets can be determined by conditioning pellets at 60 °C for 1 - 16 h after initial film formation. The release rate constants of pellets coated with EC (with or without HPMC) were markedly different to the rate constant before conditioning. That means the conditioning of coated pellets at 60 °C produced a decrease in the

release rate of DH from pellets. This decrease is not due to drug loss but rather to the effect of temperature on the film coating. The effect of pH on the rate of drug release from EC coated pellets was also investigated. The pKa of DH was 9.12. Therefore at pH of 6.9, 0.6 % of DH is in the unionised form and at pH 2.1 a negligible amount of DH is in the unionised form. This difference in the percentage of the unionised form of DH could explain the higher release rate constant at the higher pH value if the main transport process is partitioning of the drug into the polymer structure as in case of the pellets containing 0 % w/w HPMC. Another possible explanation for higher release rate constant at higher pH value is due to the presence of sodium lauryl sulphate in the aqueous dispersion formulation. Sodium lauryl sulphate has a pKa of 1.9 and it could effect the partitioning of drug into the simulated gastrointestinal fluids by virtue of its state of ionization under acidic or basic conditions, whereas pellets coated with EC containing high HPMC (12 %) show no significant difference in the rate constant at two pH. This may be due to HPMC that leached from the polymer film after contact with medium and caused the formation of pores. The presence of pores and cracks in the film ensures that diffusion of drug from the core to the surrounding sink medium occurs.

Frohoff-Hülsmann, et al. <59> have investigated the release mechanisms of theophylline pellets coated with an aqueous ethyl cellulose dispersion containing plasticisers and HPMC as a water soluble pore former. The dispersion was prepared by combining appropriate quantities of aqueous ethyl cellulose dispersion, plasticizer and HPMC solution and then mixing with glass blade stirrer for 30 min before and after the standing time of 23 h. The pore former HPMC was added as a solution of a maximum concentration of 10 % to the aqueous dispersion. The percentage of plasticizers refers to the film without HPMC. The maximum concentration was not higher than 20 % in order to prevent sticking. The percentage of pore former refers to the entire film. The coating of pellets was performed in a fluidized bed apparatus, equipped with a bottom-spray nozzle. The bed temperature was adjusted to 10 °C above the MFFT, but to a minimum of at least 40 °C. The coating dispersions were pumped with a flow rate of 1 - 2 g/min. The coated pellets were then dried in the same apparatus for 5 min at the above mentioned temperature. The film coating consisting of ethyl cellulose and plasticizer amounts to about 12 % of the weight of the diffusion pellets.

The MFFT values decrease with increasing level of added plasticizers, with increasing standing time of the aqueous plasticized polymer dispersion and in some cases with increasing amount of pore former. The standing time is defined as the minimum time period which is necessary for the plasticized aqueous polymer dispersion to reach a constant MFFT value. The distribution of plasticizers between the aqueous and the polymer phase is time dependent. Influence of the water solubility of plasticizers on the standing time of plasticized EC dispersion was demonstrated. The water insoluble plasticizers DBS and DBP need 7 and 3 h, respectively, to reach the maximum concentration in the ethyl cellulose. DEP and TEC, the more water soluble plasticizers, distribute between polymer aqueous phase during the stirring time of 30 min. The water solubility of the plasticizers effects the concentration gradient between the aqueous and the polymer phase and thus the standing time of the polymer dispersion. The MFFT values of the ethyl cellulose dispersion containing DBS and DBP decrease with increasing amounts of HPMC. In contrast, the effect of HPMC on the aqueous polymer dispersion containing DEP and TEC seems to disappear. The MFFT varies between 46 °C and 43 °C. They found that the bed temperature of 40 °C or 10 °C above the MFFT, respectively, during the coating of the pellets in the fluidized bed apparatus is not sufficient to reach a release rate of coated pellets which is independent of curing conditions. Curing of coated pellets in an oven can cause a decrease of the drug release rates to an endpoint. That means the interdiffusion of the pseudolatex particles is not complete without the curing process. The curing temperature which is necessary to reach a constant release rate is for example 1 h and 70 °C for coated pellets containing 20 % DBS. The amount of plasticizer as well as the type of plasticizer influence the film formation and therefore the adequate curing temperature and time period. Pellets coated with 11 % DEP and TEC need curing conditions from 1 h at 100 °C and 90 °C, respectively, to reach stable coatings. Another possibility to lower the relatively high curing temperatures to reach a constant and low release rate is the curing at higher relative humidities <59>.

Pellets coated with an aqueous ethyl cellulose dispersion, containing DBS and HPMC, show a two-phase release profile. The comparison of release rates from pellets coated with plasticizers of different water solubility should clarify the reason for the two-phase release profile. The release rates of diffusion pellets plasticized with TEC and DEP increase with increasing amount of pore former from 10 to 30 % in the coatings. After a short lag-time an approximate zero-order release rate can be observed. The pore

former migrates after exposure to the aqueous medium and the drug diffused through water-filled pores. The reason for the different release profiles of TEC and DEP containing pellets may be the different content of plasticizer after coating and curing process of the pellets due to the evaporation of the plasticizer. Pellets coated with EC and 12.5 % DBP or DBS and HPMC also show increasing release rates with increasing amount of HPMC from 10 to 30 %. However, the release curves do not take a linear course, but show a two-phase profile. During the first phase the release is fast and characterized by drug diffusion through water-filled pores after the migration of the water soluble pore former comparable to the release mechanism of pellets coated with TEC and DEP. During the second phase the free volume between the polymer chains is dramatically reduced and therefore the permeability of the coating obviously decreased. The remaining film containing ethyl cellulose and plasticizer is able to shrink. The drug is supposed to diffuse mainly through the plasticized ethyl cellulose coatings. The requirement for the reduction of the free volume between the polymer chains is the exceeding of the glass transition temperature (T_g) of the swollen ethyl cellulose in the medium. The extent of shrinking differed between coated pellets plasticized with DBP and DBS. DBS probably retained almost completely in the coating whereas DBP distributed partially out of the coating into the aqueous medium according to their different water solubility and partition coefficient <59>.

Volatility and migration of plasticizers is the reason for the loss of plasticizer content. Loss of plasticizer can occur after coating, curing and/or after storage at stress conditions of coated pellets. DBP does not tend to volatilize. The residual amount of DBP varies between 82 % and 93 % after curing at 80°C for 1 h. In contrast to DBP, DEP has a high tendency to volatilize during the coating and curing process of the pellets. The content of DEP decreases after coating at 53 % and curing 1 h at 100 °C to 28 – 21 %. The direct volatility measurements show low values for DBP and DBS, an intermediate value for TEC and a high value for DEP. Plasticizers leach out of the polymer according to their physical and chemical properties. The relatively water soluble plasticizer DEP migrated almost completely from the pellets coatings within 0.5 - 5 h in 0.1 N HCl solution at 37 °C. In the same period of time DBP is recovered between 30.5 % and 38 % in the release medium. The fast loss of plasticizer during the drug release from coated pellets plasticized with the fairly water soluble DEP caused a zero-order release rate.

The release of theophylline from pellets coated with aqueous EC dispersion, HPMC and TEC or DEP, is independent of the storage at ambient conditions over 31 months. Only the 4 months' storage at stress conditions caused a partial decrease of the theophylline release rate. It can be assumed that the coalescence of the latex particles is completely achieved according to the constant release rate of these coated pellets during the storage at ambient conditions. The influence of the higher temperature and relative humidity was possibly based on structural modifications of the film which only arise under these conditions. In contrast, the release rates of coated pellets containing 12.5 % DBP and 20 % or 30 % HPMC increased with increasing storage time at ambient conditions as well as at stress conditions. Coated pellets with 20 % DBP or DBS did not show any influence of storage on the release rate. In conclusion, the drug release is dependent on the physical state of the swollen ethyl cellulose and on the migration of the water soluble pore former. The first mechanism is, if the pore former mostly migrated from the coating, the type and amount of plasticizer in the swollen coating and the temperature of release medium influence the release rate to a large extent. If the film forming polymer is present in the glassy state as it is after the migration of the water soluble plasticizer and pore former at temperatures above T_g , the drug diffuses through water filled pores. The second mechanism is, if the pore former mostly migrated from the coating and the ethyl cellulose, in the rubbery state as it is the case with the water insoluble plasticizer at temperature below T_g . The drug release rate is characterized by a two-phase release profile as a result of pore shrinking. The third mechanism occurred if the migration of the pore former is incomplete. A high ionic strength of the release medium caused a reduced hydration of the pore former. The drug diffused through a swollen heterogeneous membrane containing EC, HPMC and insoluble plasticizer <59>.

Rekhi, Mendes, Porter and Jambhekar <149> have studied aqueous ethylcellulose formulations by using Aquacoat ECD for coating of propranolol HCl. The effects of varying the concentration of the fixing agent HPMC was investigated. The fluid-bed process conditions and formulation characteristics of the drug adhesion layer were examined to assess the tendency of beads to agglomerate while the fixing solution was applied. The results showed that the layering process at the low inlet air temperatures up to 55 °C at atomizing pressure of 2 bar caused aggregation. The inlet air temperature of 55 °C and the atomizing air pressure of 1 bar neither caused a problem

with aggregation nor spray drying but if the temperature was too high (65 °C) the spray drying occurred. The higher levels of HPMC in the formulation tended to increase the risk of agglomeration. The higher atomizing air pressure (2 bar) also increased the tendency for the beads to accumulate in the filter bags. They stated that the percentage of drug released from Aquacoat-coated beads increased if the amount of HPMC used was increased. This result demonstrated that the drug release rate may be affected by the core substrate; perhaps because of imperfections in the cores caused by higher amounts of HPMC. However, they did not mention any details about the swelling property of HPMC. They used a high amount of HPMC (up to 50 % w/w to drug content) in their study. This high amount of HPMC may cause a higher swelling than the amount of 25 % fixing agent. The release of propranolol HCl from beads coated with Aquacoat was higher at pH 7.5 compared to the release at pH 1.2. The release achieved 100 % after 8 h in simulated intestinal fluid pH 7.5. Normally the release of drug from beads coated with EC should not depend on the pH. The pH dependence in their study may be attributed to the pH-dependent solubility of the drug or to the composition of the coating dispersion which included a surfactant-sodium lauryl sulfate.

Steuernagel <205> studied the prevention of the formation of an alkali-CAP salt by using a seal-coat employing HPMC or a combination of HPMC and Aquacoat ECD.

HPMCAS was used as an enteric polymer for some products.

This present work shows that the HPMCAS dispersion still contained big particles which may come from HPMCAS particles because the dispersion of Aquacoat CPD did not contain such big particles. For this reason if HPMCAS should be used furthermore the grinding of HPMCAS particles before adding into the aqueous dispersion is suggested. The reduction of polymer particles after preparing the dispersion may be also recommended e.g. by homogenizing technique. The effect of grinding enteric polymer for improving the property of film resulted from an aqueous formulation was demonstrated by Thoma and Bechtold <185>. They found that the film formation from aqueous dispersion of micronized HP-55 was affected by the degree of micronization and was improved by reducing the particle size of this polymer.

HPMCAS was of interest to be used as enteric coating polymer because it was reported that HPMCAS was more stable than CAP. The stability of HPMCAS was determined in

the way that the coating material Aqoat-AS-MF was stored under the condition of at 60 °C and 100 % r.h. for many days. After 14 days, the free acid content in form of succinic acid was about 1.8 % w/w. CAP, on the other hand, produced free phthalic acid more than 5 % w/w only after 6 days at the same condition. This means HPMCAS is more chemically stable than CAP <80>. However, the cellulosic derivatives such as HPMCAS and CAP were more permeable than acrylic polymers due to their hydrophilicity and less dense molecular arrangements <65>.

Thoma and Bechtold <185> studied the influence of aqueous coatings on the stability of enteric coated pellets and tablets. The tablets cores were manufactured by wet granulation technique. The coating was performed in a lab scale fluidized bed coater and the aqueous coating dispersion of HPMCAS was kept cool during manufacture at a temperature not exceeding 12 °C. For comparison pancreatin pellets and tablets containing riboflavine were coated with various aqueous and organic enteric polymers such as HPMCAS, HP, Eudragit L, CAP, etc. The gastric resistance of enteric coated pancreatin pellets was observed by determination of the lipase activity after the pellets were exposed to 0.1 M HCl for 2 h. They found that a higher amount of coating materials was required to achieve gastro-resistance when using aqueous coating compared to organic formulations. The moisture-sensitive pancreatin enzymes were damaged both by humidity and heat during aqueous coating. The extent of damage depended on the coating equipment used. During the storage coatings obtained from aqueous dispersions showed changes in enteric performance or release characteristics as a consequence of three chemical/physical mechanism i.e. hydrolysis of ester linkages in the polymer or plasticizer, evaporation of the plasticizer, delayed film formation. The active ingredient pancreatin induced hydrolysis of the ester based film-former HPMCAS. The plasticizer glyceryl triacetate in HPMCAS-coated pancreatin pellets was almost completely hydrolyzed by the enzymes, whilst TEC was lost by evaporation through permeable packaging material at elevated temperatures. The open storage at elevated temperatures and humidities caused changes in the surface structure of HPMCAS coatings, consisting of a smoothing of the originally porous film and sticking. The riboflavin tablets coated with Aqoat were stable when stored under stress conditions. On the other hand tablets coated with ammonia-neutralized aqueous solution or water-based dispersion of CAP were unstable.

Thoma and Bechtold <185> also found that the undercoating was suitable to decrease the amount of coating material required. They used both HPMC and povidone (PVP) as a film former for the undercoating. They found that the undercoat of 4 % PVP of HPMCP-coated pancreatin pellets can increase the gastro-resistance property which can be seen by the increasing of the lipase activity after exposure to 0.1 N HCl for 2 h. The results showed that the minimum film thickness required for the film-coated riboflavin tablets to achieve gastro-resistance was different. The CAP polymer as an organic solution or an ammonia-neutralized solution needed the thickness of about 40 μm , whereas an aqueous dispersion of CAP needed a higher thickness of about 80 μm to achieve this resistance. The formulation from HPMCAS, however, needed smaller thicknesses than that from CAP. The thicknesses of about 30 μm and 50 μm were enough to achieve the resistance for the organic solution and the aqueous dispersion, respectively. If the swelling of the tablets was considered then the required minimum thicknesses differed. The thicknesses of 40 μm , 110 μm , 55 μm , and 80 μm were necessary for the coating formulations of CAP organic solution, CAP aqueous dispersion, HPMCAS organic solution and HPMCAS aqueous dispersion, respectively to achieve the swelling less than 10 %.

The effect of the curing conditions to the HPMCAS-coated pancreatin pellets was also studied. The content of TEC used as a plasticizer in the coating formulation was determined. The content of TEC in HPMCAS-coated pellets without curing was about 80 %. The curing temperatures of 40 °C to 60 °C can reduce the TEC content from 60 % to 35 %, respectively. The coating conditions such as inlet air temperature can also affect the TEC content. The results showed that the TEC content in coated pellets without curing was reduced from 80 % to 65 % if the inlet air temperature was increased from 35 to 65 °C.

After storage of HPMCAS coated pancreatin pellets for 3 months at the elevated temperature of 40 °C the originally porous film had already fused together to a considerable degree. The moist storage at 40 °C and 75 % r.h. for 3 months led to a closure of all pores, associated with a sticking of pellets.

If TEC was used as a plasticizer in films applied to pancreatin pellets no degradation products such as citric acid were found. Therefore the loss of TEC may be due to the evaporation. Glyceryl triacetate as a plasticizer, however, produced practically quantitative degradation products such as acetic acid, mono- and diacetate.

During the production of coatings from dispersions of micronized film-formers, e.g. HPMCAS, there was a risk of coagulation at elevated temperatures, for example in the drying zone of the coating apparatus, especially if the formulation contained sufficient plasticizer. If the polymer particles did not fuse together during the coating process then coagulate inclusions can become apparent as unevenness in the coating appearing as spikes on the surface of coated products.

Thoma and Kräutle <187> studied the stability of pancreatin tablets coated with aqueous dispersion of HPMCAS-LF. The disintegration time of pancreatin tablets coated with aqueous dispersion of HPMCAS-LF was slightly reduced after storage at 25 °C but kept constant from 3 – 12 months. The disintegration time of these coated tablets after storage at 35 °C slightly increased and then kept constant from 3 – 12 months. However, the product which was stored at the higher relative humidity (25 °C & 70 % r.h.) for only 6 months could not be tested because they fused together. The disintegration time of tablets coated with an aqueous dispersion of HPMCAS with triacetin as a plasticizer kept constant (less than 30 min) after storage at temperatures of 25 °C, 30 °C and 40 °C for 6 months. This means that the storage temperatures in the range of 25 – 40 °C did not cause a different affect to the disintegration time of the HPMCAS-coated tablets.

Obara and Mc Ginity <117> have investigated the influence of processing variables on the properties of free films prepared from aqueous polymeric dispersions by a spray technique. They found that the mechanical values of free films from Aqoat were significantly decreased at a slower spray rate e.g. from 16.2 to 4.8 MPa at the surface temperature of 40 °C. The processing temperature, however, did not affect film properties due to the lower MFFT of plasticized polymer. The temperature between 30 °C and 40 °C was not a significant factor provided the sprayed film had a sufficient moisture. At 30 °C, the surface was kept under a sufficient moisture at a spray rate of 0.8 g/min. At 40 °C, the lower spray rate resulted in brittle films of significantly lower tensile strength and elongation. It was possible that spray-dried particles were trapped in the films prepared from low spray rates, resulting in an incomplete coalescence of the polymer. The result suggested that specific moisture content was required for complete film formation from the Aqoat aqueous dispersion. The differences in moisture requirements between the Aqoat and Eudragit L polymers could be due to the size of

the polymeric particles. The mean particles size of Aqoat dispersion was reported to be approximately 5 μm which was larger than that of Eudragit L latex (0.2 μm). Therefore the free film from Aqoat dispersion had a higher MFFT and a higher moisture content would be required for the complete coalescence of the harder and larger particles.

The free films for the mechanical tests were prepared by the spraying technique. The final film thickness was approximately 150 μm . Aqoat and 28 % TEC can form clear films at room temperature. Therefore the MFFT, which was determined as the minimum temperature where the film was clear and free of cracks, was less than 23 °C <117>.

In this present work the drying process was also performed during the spraying step because the spraying rate was kept low at 0.8 g/min. Therefore the rapid drying will be the reason for small cracks in the surface. The increase of the spray rate was not possible because the formation of agglomerations would occur. To avoid agglomerations the high air flow was used but this will also cause a rapid drying rate. Moreover, in the preparation of free films it was possible to increase spray rates almost without a limit because it was not necessary to consider the movement of the product. The free films were prepared on the stationary place and polymer particles in the dispersion had enough time to fuse together by help of capillary force and then coalesce by having certain heat. In the coating apparatus the high spray rates cannot be increased without a limit because if the product was overwetting (high spray rate and slow drying) the formation of agglomerations would occur. The agglomerations can sometimes be hindered by increasing the processing air flow which means an increase of the drying rate. The high drying, however, will cause a spray drying and loss of coating polymer particles. The reduction of overwetting can be done by using slower spray rates. However, in such a case the overdrying should be considered. The overdrying will again cause a formation of dried polymer particles before they can fuse together and coalesce as a continuous film layer .

An important factor for film formation is the driving force that causes the coalescence of polymeric particles which results from water evaporation or capillary force. Since coalescence occurs only above the MFFT, temperature and water evaporation are considered to be major factors which affect the film properties of coating materials. The cast methods have been widely used for the preparation of polymeric films from organic or aqueous dispersions. However, polymeric particles will tend to settle during the

drying process in the cast method which will lead to uneven film formation. Therefore the transfer of conditions from the casting method to the spraying method must be carefully done.

Obara and McGinity <116> have studied the properties of free films prepared from aqueous dispersions of HPMCAS by a spray method and a cast method. It was found that the 10 % HPMCAS dispersion cannot be atomized through the spray nozzle. Therefore a 5 % dispersion was used. The formulation of HPMCAS (Aqoat-MF) aqueous dispersion contained 28 % TEC as a plasticizer. The free films prepared from a cast method of aqueous HPMCAS dispersion had uneven film formation because of the high standard deviation of the mechanical properties such as tensile strength, elongation and elastic modulus. This may be due to the settling of the polymer particles during drying stage. Moreover, during the drying process film formation began at one position in the spread dispersion and gradually progressed throughout the plate, simultaneously water was expelled from the drying areas to the remaining wet regions of the spread dispersion. This movement of water can cause an uneven distribution of a plasticizer in the film and cause heterogeneous film. The elongation of HPMCAS films measured from the spray method (3 %) was lower than that from the cast method (6 % – 8 %). This may be due to the fact that the spray-dried particles can be entrapped in the film in the spraying technique which can lead to hard and brittle films. The elastic modulus of HPMCAS films was high for films both prepared from a spray (750 MPa - 780 MPa) and cast method (270 - 300 MPa). The transparent films occurred at 40 °C but did not occur at 30 °C. Therefore the MFFT of this dispersion was between 30 °C and 40 °C.

Scheiffele, Kolter and Schepky <164> studied different products (free films and coated tablets) prepared from Aqoat-MF suspension. The aqueous dispersion of unpigmented Aqoat-MF composed of Aqoat powder, SLS, TEC (28 % to Aqoat-MF) and water. The aqueous dispersion of pigmented Aqoat-MF composed of 7 % Aqoat powder, 0.21 % SLS, 0.24 % colour, 2.1 % talc, 0.24 % titanium dioxide, 1.96 % TEC and 88.25 % water. The coating apparatus Accela Cota 24 inch was used to coat the caffeine tablets. The coating of tablets with Aqoat-MF dispersion was performed by using air inlet temperature of 70 °C, product temperature of 33 - 35 °C, spraying rate was 40 g/min and postdrying at 30 °C for 60 min. The resistance to gastric juice was reached at a

coating amount of 11 mg/cm² for Aqoat-MF. It was found that films prepared from Aqoat were uniformly smooth. The MFFT of Aqoat-MF dispersion without pigment but containing TEC (28 %w/w to Aqoat-MF) was 35 °C and the value of MFFT of this dispersion with pigment (Sicovit 3.4 %w/w, talc 30 % and titanium dioxide 3.4 %w/w) was 7 °C. It can be concluded that the MFFT of the liquid preparation was decidedly reduced by the addition of pigments. The T_g of unpigmented Aqoat-MF was 117 °C and after adding pigments the T_g was reduced to 55 °C. On the other hand, the T_g of unpigmented Aquateric was 48 °C and after adding pigments the T_g was reduced to 56 °C. In the test for coagulation under shear and heat it can be seen that the pigmented dispersion of Aqoat-MF displayed coagulation of about 15 %. The particle size distribution of the unpigmented dispersion of Aqoat-MF was 7 µm. The water vapor permeability and proton permeability of free films from Aqoat-MF was reported to be high. Perhaps due to the high mean particle size of the polymer. The weight of enteric-coated tablets especially tablets which are coated with Aqoat-MF was increased up to 34 % during the resistance tests in artificial gastric fluid after 2 h at the coating level of 8 mg/cm². Probably due to the swelling of the film. The resistance against artificial gastric fluid of tablets coated with the aqueous dispersion of Aqoat-MF was higher than that of Aquateric.

The problematic of enteric coating of pellets with HPMCAS was reported. Schmidt and Niemann <169> studied the coating of pellets by using both organic and aqueous-based systems of Aqoat AS-MF. The neutral pellets were loaded with bisacodyl and were used as cores. The coating process was performed in a miniature laboratory-scale fluid-bed pan coater which was developed by Schmidt and Niemann <168>. This apparatus was originally a pan coater but it was developed so that the core bed was slightly fluidized by the inlet air flow due to the small dimensions of the coating pan. It was commented that this technique will allow a rapid drying and a loss of coating materials will be negligible. Small batches of 50 to 100 g of pellets can be coated in this apparatus. The bed temperature was 35 °C for both systems with the mean spraying rate of about 0.5 ml/min. They found that there was a high loss of coating material at about 17 % and 9 % for the coating process by an aqueous and organic system, respectively. However, the organic-solvent based film of HPMCAS at a coating level of 25 % provided gastroresistance for more than 6 h. An aqueous suspension of HPMCAS produced films

with a short gastro-resistance of below 0.6 h. After doubling the coating level of water-based HPMCAS films (58 %) the protection was prolonged to 3.4 h <168,169>.

Nagai, Sekigawa and Hoshi <106> studied the coating of pellets with HPMCAS. The suitable plasticizer for HPMCAS was reported to be TEC because of the high percentage of recovery of TEC and the good acid resistance property. Fukui, et al <61> has reported that the water-soluble plasticizers such as TEC and triacetin showed greater compatibility to HPMCAS. The results were consistent with the suppression of the drug release in 0.1 N HCl. The particle sizes of HPMCAS should be less than 5 μm for aqueous coating for determining smooth films. If the particle sizes were higher than 15 μm it was reported that the surface of the film obtained was rough. In granules coating talc is sometimes added as a filler and it often enhances the acid resistance of the film. Therefore they used the aqueous coating formulation contained 10 parts HPMCAS, 3 parts TEC, 5 parts talc and 82 parts water. The aqueous coating of granules containing riboflavin with HPMCAS yielded homogeneous films and they were resistant to artificial acid fluid. However, the surface views of the HPMCAS-coated cores contained discontinuous coalescence region. The acid resistance property of these granules may be due to the high amount of talc (50 % w/w with respect to HPMCAS) in the coating formulation. The stability of HPMCAS-coated products was examined. Almost no difference was observed after storage for 90 days at 40 °C and 75 % r.h. The pancreatin granules coated with HPMCAS retained their acid resistance (more than 90 % amylase activity) after high-temperature storage. The tensile strength of HPMCAS film was reported to be the same as that of other polymers such as HPMCP or CAP. However, the elongation of HPMCAS was higher which means that HPMCAS has a better plasticity <106>.

This part of study shows that a combination of EC and PVA can be used as a subcoat. The release of nicotinamide from the E&P-Nico pellets was fast enough so that there was no effect of delay release. The unsatisfying result of gastric resistant was due to the incomplete coalescence of the CAP particles, details of which were mentioned in 3.1 - 3.2.

3.5 Pellets with nicotinamide and a combination of PVA and EC (100 parts + 30 parts) as a subcoat

a) Placebo: HPMC pellets

The HPMC coated pellets (Product pp) were achieved from the combination of a formulation **R1** and a process number **X7**, as demonstrated in the Table 2.29.

b) Nicotinamide loaded pellets: Nico pellets

The Nico pellets (Product aa) were achieved from the combination of a formulation **R3** and a process number **X8**, as demonstrated in the Table 2.29.

c) A combination of PVA and EC as a subcoat: P&E-Nico pellets

The P&E-Nico pellets have a blue colour as a marker was used. These pellets (Product bb) were achieved from the combination of a **R7** and a process number **X12**, as demonstrated in the Table 2.29.

d) Enteric coated pellets: CAP-P&E-Nico pellets

The CAP-P&E-Nico pellets still have a blue colour caused by the marker. These pellets (Product cc to jj) were achieved from different combinations of a formulation and a process number, as demonstrated in the Table 2.29.

3.5.1 Film quality, diameter and weight of pellets

The physical properties of the raw material used for this process and of the finished products are shown in Table 3.12. The thickness of the HPMC layer (HPMC pellets) as measured from SEM was about $10 \pm 4 \mu\text{m}$. The mean diameter of these pellets measured by an image analyser was $970 \pm 34 \mu\text{m}$. The mean weight of one HPMC pellet (Product pp) was $0.66 \pm 0.01 \text{ mg}$. One Nico pellet (Product aa) had a mean weight of $0.75 \pm 0.02 \text{ mg}$ and a mean diameter of $980 \pm 33 \mu\text{m}$. The thickness of the

nicotinamide layer was about $20 \pm 5 \mu\text{m}$ and the weight gain from nicotinamide and HPMC was 11.4 % w/w.

The subcoat from a combination of PVA and EC has been achieved in a thickness of $38 \pm 4 \mu\text{m}$ by a weight gain from Nico pellets of 97 % w/w. The SEM photograph in Figure 3.30a shows the thickness of the P&E layer of Product bb and that the layer was almost homogeneous. The mean weight and the mean diameter of one pellet compared between cores (Product aa) and P&E-Nico pellets (Product bb) allowed to calculate the amounts of the PVA and EC polymer mixture coated per pellet, namely 20 mg cm^{-2} .

Physical properties of CAP coated pellets are also stated in Table 3.12. The SEM photograph of the cross-section of the Product ee shows the inhomogeneous layer of CAP and DBS and that many particles did not form a continuous film, i.e. will not have reached the MFFT (Figure 3.35b). Product cc shows inhomogeneous regions within the layer of CAP and DEP (Figure 3.36a). All the coated pellets of this product showed also pores dispersed at the surface (Figure 3.36b). There was also no difference between the CAP film layer from Aquateric (Product Gg) or Aquacoat CPD (Product Ff) as judged from physical properties as mentioned before. The best enteric layer from CAP can be achieved from TEC as a plasticizer. A cross section of the CAP layer (Product jj) showed an almost homogeneous film structure (Figure 3.37a). The whole surface of the cores (Product bb) was well covered by the CAP layer but uneven regions can be well demonstrated (Figure 3.37b).

The mean weight of one CAP-P&E-Nico pellet (Product jj) from Product bb as cores was $1.42 \pm 0.01 \text{ mg}$ while the mean diameter of these pellets was $1295 \pm 40 \mu\text{m}$ at the coating amount of 66 mg cm^{-2} .

In general, the standard deviations of the diameter of all products in Table 3.12 are not more than $40 \mu\text{m}$. This shows the well-controlled course of the coating processes.

Product	Weight gain of total batch (% w/w)	Thickness of the layer ($\mu\text{m} \pm \text{SD}$)	Weight of pellet (mg \pm SD)	Diameter of pellet ($\mu\text{m} \pm \text{SD}$)	Coating amount (mg cm^{-2})	Release within the first five minutes (% \pm Range)
SS	0.0 ^a	800-1000 ^f	0.68 \pm 0.01	970 \pm 37	n	n
pp	3.5 ^b	10 \pm 4 ^g	0.66 \pm 0.01	970 \pm 34	n	n
aa	11.4 ^c	20 \pm 5 ^h	0.75 \pm 0.02	980 \pm 33	n	n
bb	20.0 ^d	38 \pm 4 ⁱ	0.90 \pm 0.01	1000 \pm 40	20.0 ^k	76.9 \pm 1.0
cc	12.0 ^e	20 \pm 2 ^j	1.02 \pm 0.02	1140 \pm 40	15.0 ^l	n
dd	24.0 ^e	35 \pm 14 ^j	1.05 \pm 0.01	1155 \pm 35	19.0 ^l	n
ee	14.0 ^e	25 \pm 3 ^j	1.12 \pm 0.01	1190 \pm 32	28.0 ^l	n
ff	17.5 ^e	34 \pm 3 ^j	1.08 \pm 0.01	1170 \pm 33	23.0 ^l	6.5 \pm 0.5
gg	31.0 ^e	62 \pm 4 ^j	1.24 \pm 0.02	1240 \pm 33	43.0 ^l	3.3 \pm 0.2
hh	45.0 ^e	90 \pm 5 ^j	1.45 \pm 0.02	1300 \pm 35	70.0 ^l	2.4 \pm 0.2
jj	45.0 ^e	89 \pm 6 ^j	1.42 \pm 0.01	1295 \pm 40	66.0 ^l	1.6 \pm 0.2

Table 3.12: Properties of different products showing weight gain of total batch, thickness of the layer, weight of pellet, diameter of pellet, coating amount, release within the first five minutes;

^a = weight gain of total batch of sugar spheres (% w/w), ^b = weight gain of total batch of HPMC pellets to sugar spheres, Product SS, (% w/w), ^c = weight gain of total batch of Nico pellets to HPMC pellets, Product pp, (% w/w), ^d = weight gain of total batch of P&E-Nico pellets to Nico pellets, Product aa, (% w/w), ^e = weight gain of total batch of CAP-P&E-Nico pellets to P&E-Nico pellets, Product bb, (% w/w), ^f = size of sugar spheres, Product SS (μm), ^g = thickness of the HPMC layer (μm), ^h = thickness of the nicotinamide and HPMC layer (μm), ⁱ = thickness of the P&E-subcoat layer (μm), ^j = thickness of the enteric coating layer (μm), ^k = coating amount of the P&E-subcoat on Product aa (mg cm^{-2}), ^l = coating amount of the enteric coat on Product bb (mg cm^{-2}), n = not measured.

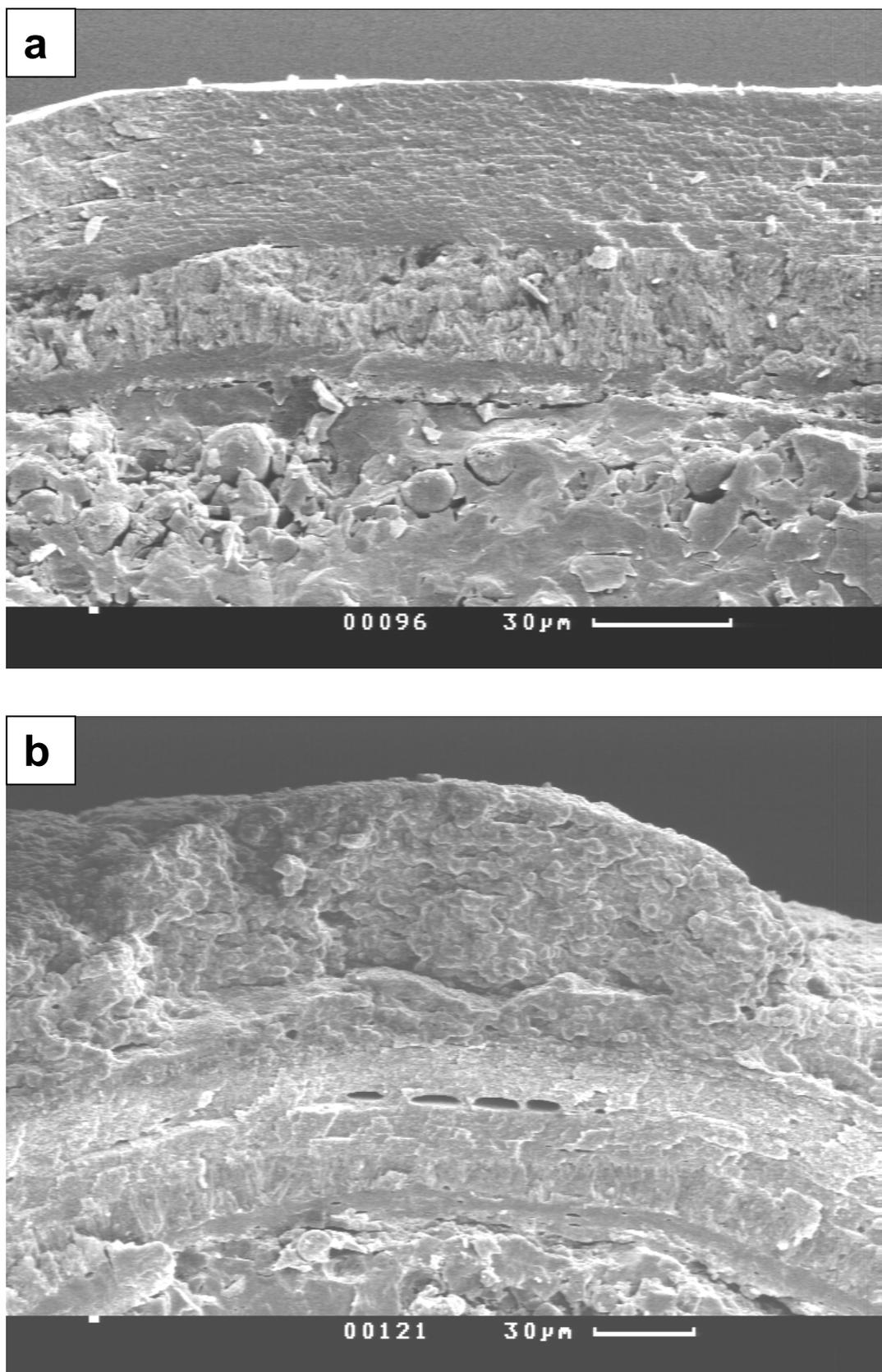


Figure 3.35: SEM pictures of coated pellets; a) the cross-section of a pellet coated with a subcoat from PVA and EC (100 + 30 parts) (Product bb), magnification 600x; b) the cross-section of an enteric coated pellet with CAP and DBS (Product ee), magnification 430x.

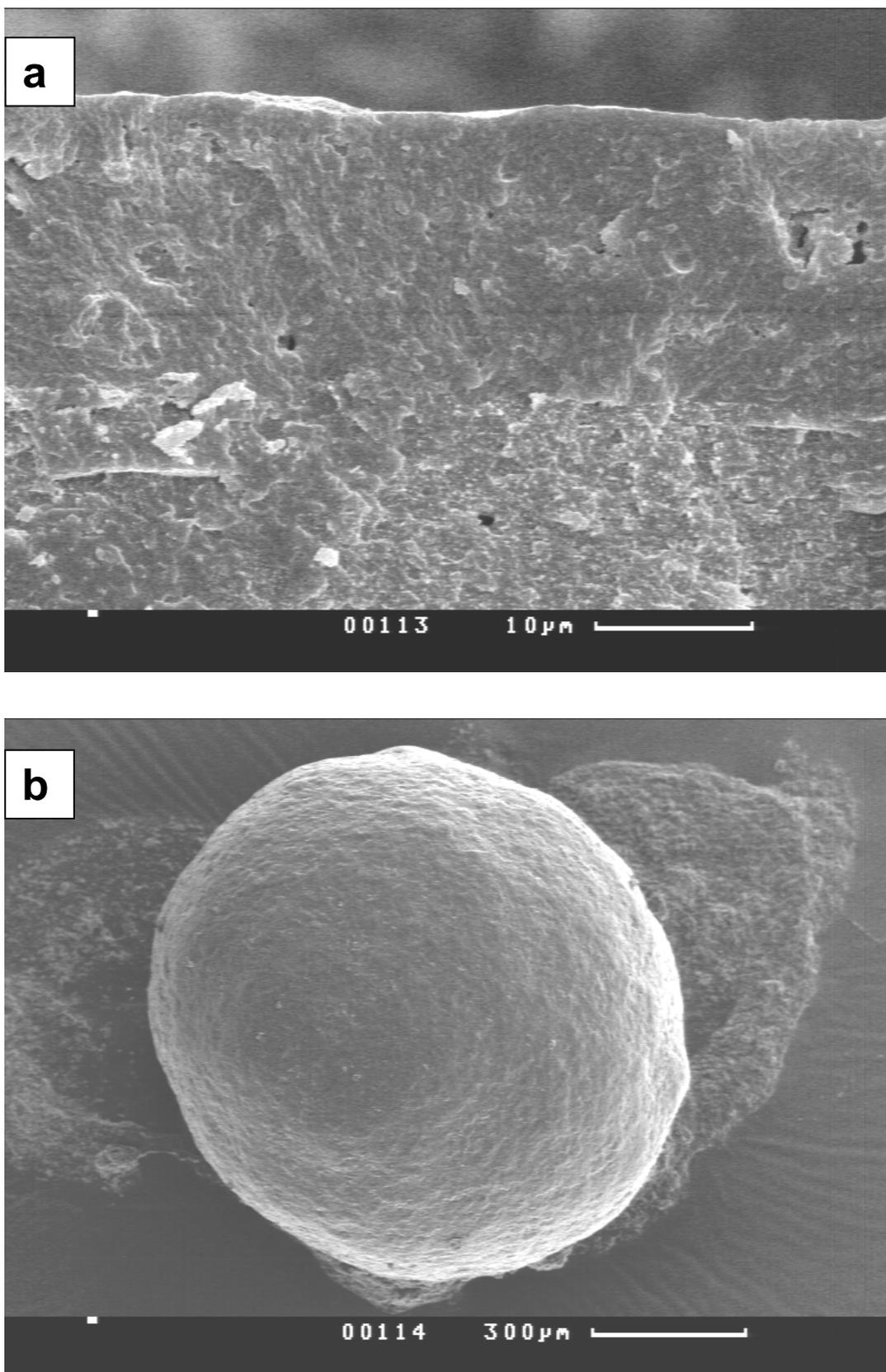


Figure 3.36: SEM pictures of enteric coated pellets with CAP and DEP (Product cc); a) the cross-section of a coated pellet, magnification 2010x; b) top view of a coated pellet, magnification 67x.

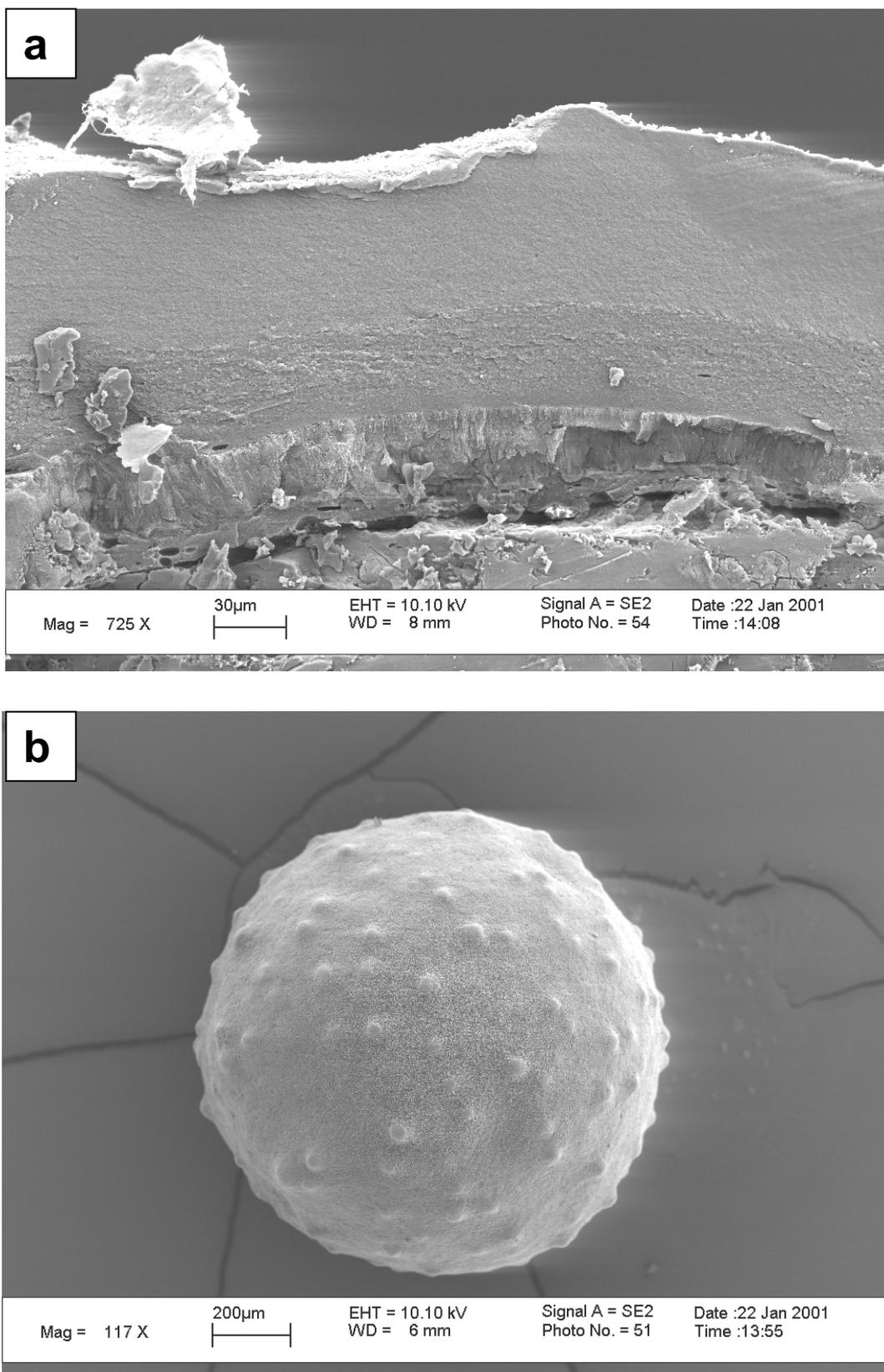


Figure 3.37: SEM pictures of enteric coated pellets with CAP and TEC (Product jj); a) the cross-section of a coated pellet, magnification 725x; b) top view of a coated pellet, magnification 117x.

3.5.2 Swelling

The swelling in 0.1 N HCl of P&E-Nico pellets (Product bb) was very high, i.e. 43 %, as shown in the Table 3.13. The enteric coated pellets with two different plasticizers (Product cc and jj) were tested in the acidic medium. They cracked after 30 min, therefore the swelling cannot be measured.

Product	D1 ± SD	D2 ± SD (pixel)	ΔD ± SD	Swelling (%)
bb	185 ± 1	264 ± 2	79 ± 1	43
cc	193 ± 3	-	-	crack
jj	212 ± 2	-	-	crack

Table 3.13: Swelling property of different products in 0.1 N HCl, 22 °C; D1: diameter before swelling, D2: diameter after swelling, bb: P&E-Nico pellets, cc: CAP-P&E-Nico pellets (CAP+DEP), jj: CAP-P&E-Nico pellets (CAP+TEC).

3.5.3 Content of nicotinamide in one pellet

The content of nicotinamide inside one pellet of different products was varied. Product aa or Nico pellet without further coatings contained 9.1 ± 0.2 % w/w of nicotinamide based on total weight of one pellet. One pellet after coating with a subcoat from the combination of PVA and EC (Product bb) contained 8.6 ± 0.3 % w/w of nicotinamide.

3.5.4 Release of nicotinamide from coated pellets

The cumulative percentage of nicotinamide released during the first five minutes from differently coated pellets is demonstrated in Table 3.12. The dissolution profiles of different products containing nicotinamide can be seen in Figure 3.38. The release from coated pellets with the subcoat from a combination of PVA and EC, but without enteric coating, reached 100 % after 10 min. The cumulative percentage of nicotinamide release decreased after coating with CAP. At higher amounts of CAP and TEC the release of nicotinamide became smaller (Product ff to hh). However, the release of nicotinamide was more than 80 % after 120 min in 0.1 N HCl at every thickness.

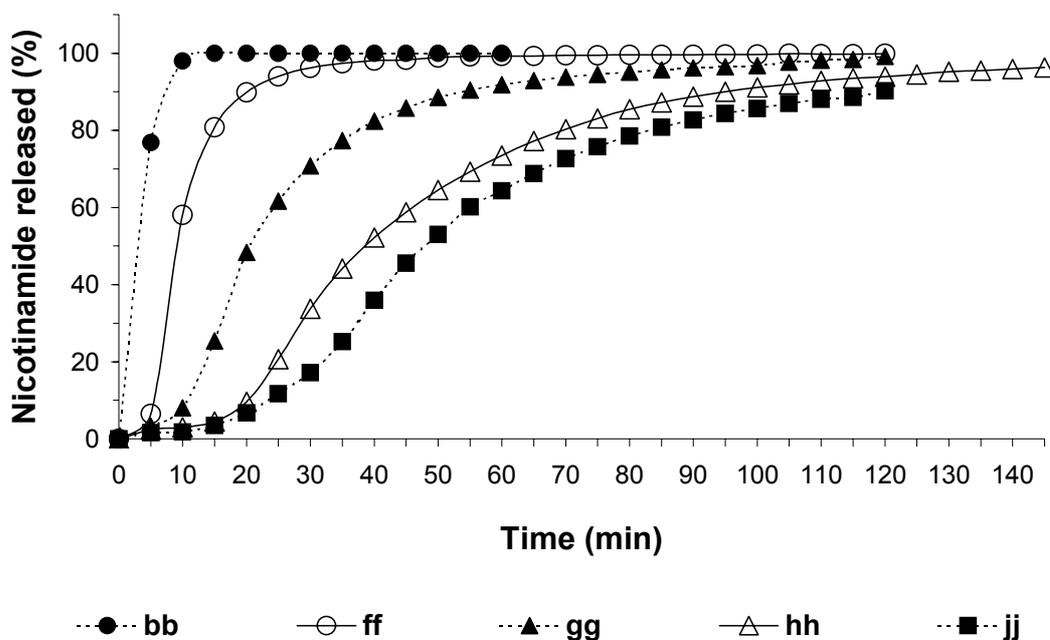


Figure 3.38: Dissolution profiles of differently coated pellets containing nicotinamide in 0.1 N HCl at 37 °C without (Product bb) and with increasing thicknesses of enteric coats in mg cm^{-2} (Product ff to jj) on Product bb as cores;
 ff:23, gg:43, hh:70, jj:66; hh: production with intermediate drying phase;
 jj: similar to Product hh but with cyclone instead of filters set.

3.5.5 Optical appearance after the release study

The optical appearance of the enteric coated pellets with different plasticizers after the release study is demonstrated in Figure 3.39 and Figure 3.40. Enteric coated pellets both with DEP and TEC as a plasticizer were broken after 30 min in 0.1 N HCl. These pellets after exposure to the phosphate buffer for 30 min still had their shell. This means the outer layer was not completely dissolved, the diffusion of the drug is responsible for the release.

3.5.6 Optical characterization of pellets after storage

The following storage conditions demonstrated the highest humidity at each temperature that allowed the enteric coated pellets to flow freely and did not stick together.

Temperature (°C)	Relative humidity (% r.h.)
25	57.5
30	56.0
35	54.0

Table 3.14: The highest humidity at each temperature that still allowed the enteric coated pellets and a combination of PVA and EC (100 + 30 parts) as subcoat (Product cc) to flow after 30 days of storage.

In summary it was found that Product cc will have an acceptable physical property after 30 days of storage when the relative humidity was not higher than 60 % r.h. However, if the temperature was above 35 °C the pellets began to stick together even at the relative humidity of only about 30 % r.h. If the result is compared to Product EE, part 3.2.8, it is obvious that CAP-coated pellets with a subcoat from a combination of PVA and EC (Product cc, part 3.5.6) were more sensible to temperature than CAP-coated pellets with a subcoat from HPMC (Product EE). The Product cc can freely flow only when the temperature did not exceed 35 °C, whereas Product EE can tolerate a temperature up

to 50 °C. At the highest stress condition of 50 °C and 80 % r.h., the CAP-coated pellets liquefied. This means, if an accelerated chemical degradation test should be performed with CAP-coated pellets the temperature and the relative humidities should not exceed 40 °C and 60 % r.h., respectively. In this range of temperatures and humidities, the physical property of the CAP-film is still acceptable and the chemical degradation of the coated pellets may then be observed and not the physical damage.

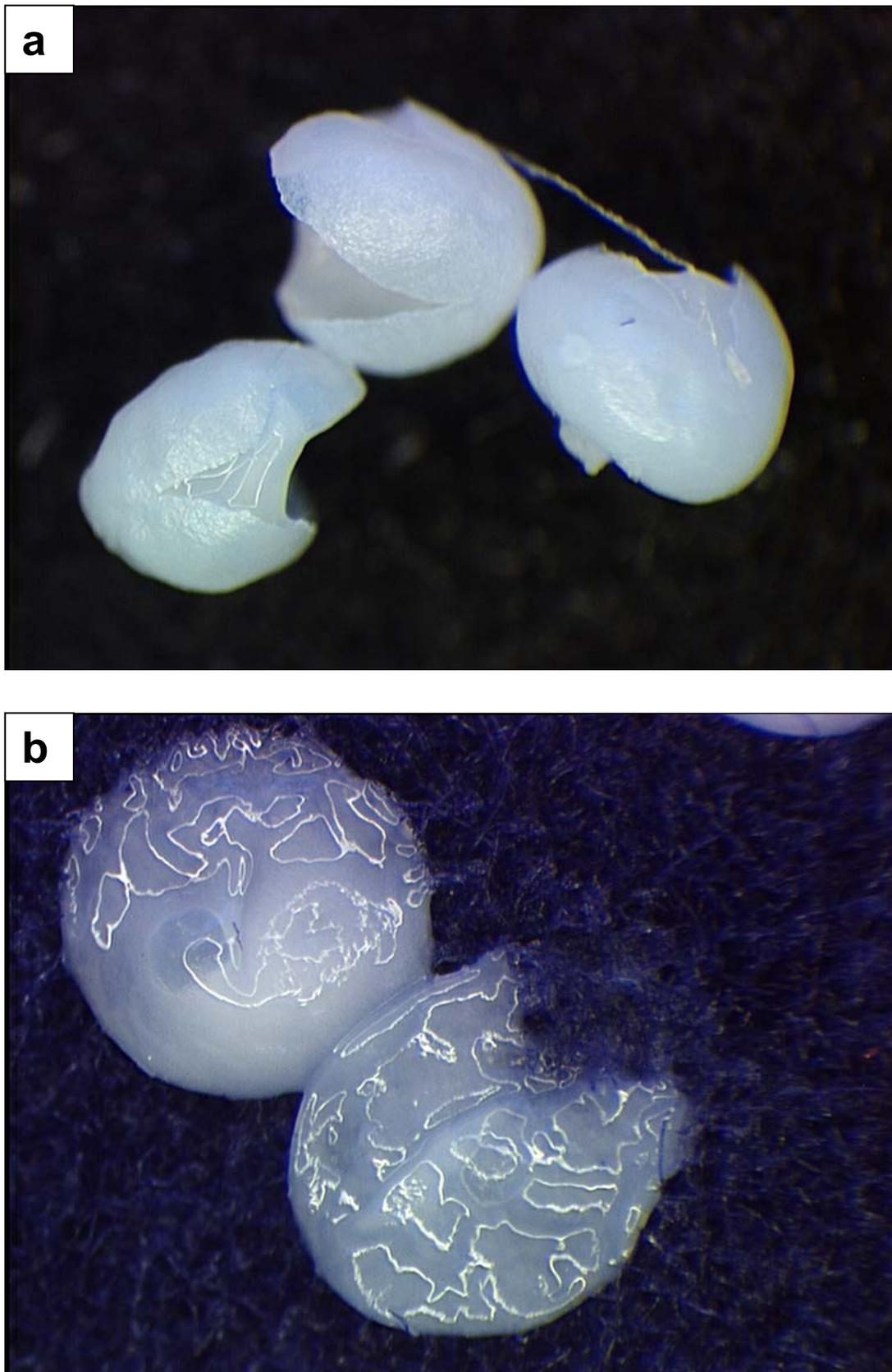


Figure 3.39: Enteric coated pellets with CAP and DEP (Product cc) after exposure to different media at 37 °C, for 30 min; a) 0.1 N HCl; b) phosphate buffer pH 6.8.

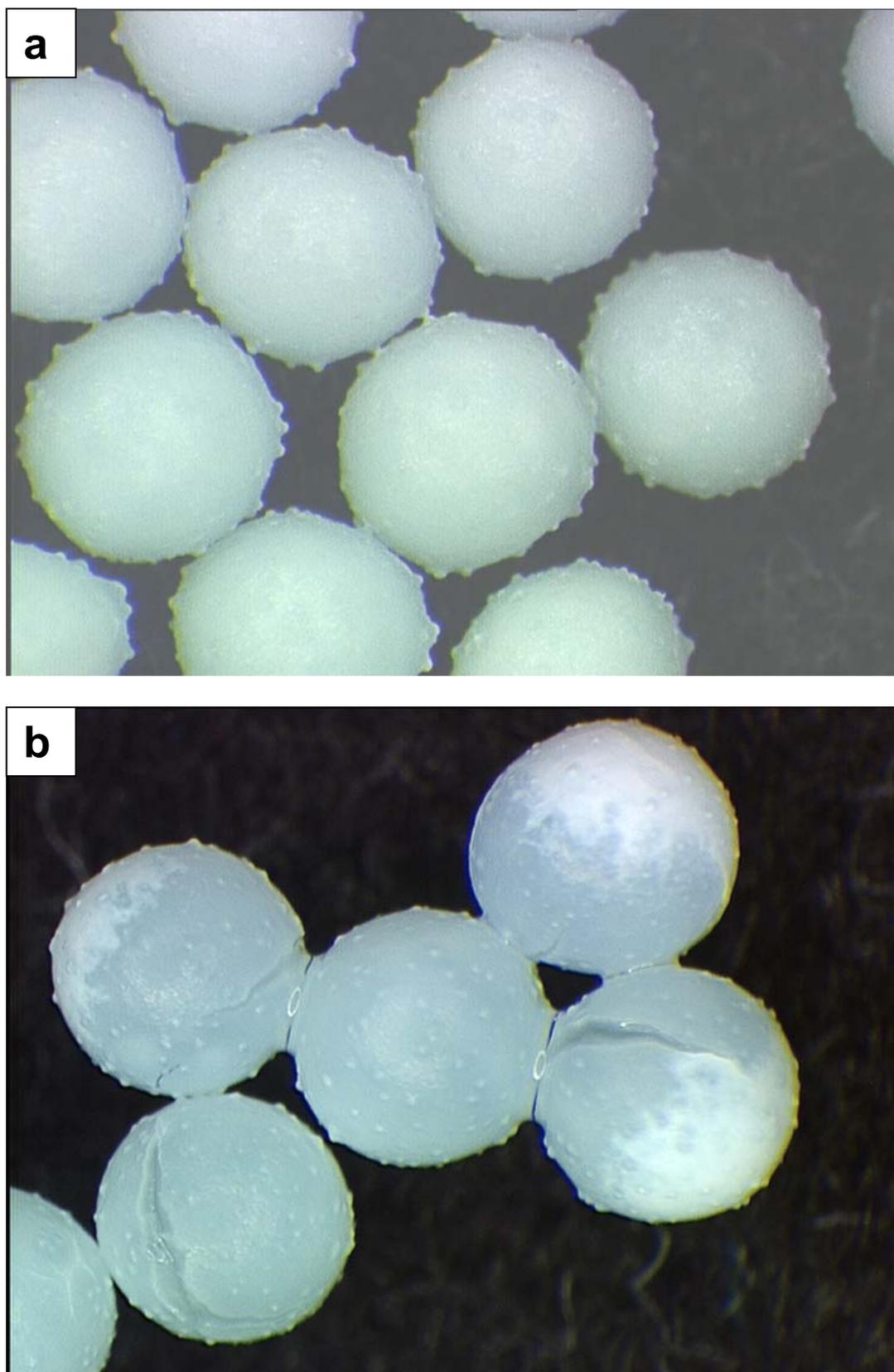


Figure 3.40: Enteric coated pellets with CAP and TEC (Product jj);
a) before and; b) after exposure to 0.1 N HCl, 37 °C, for 30 min.

3.5.7 Discussion

PVA is available in different viscosity grades. It was used as an excipient in many fields e.g. production of paper, polymerisation, textile, foils and ceramics <142>. In the pharmaceutical field, it can be used as a stabilizer in emulsion, filler in tableting, pelletisation, microencapsulation or sponges etc., but the use of PVA as a film forming agent is not published. Therefore it is of interest to study the possibility to use PVA for coating of pellets because it was mentioned <142> that PVA can be used as a moisture barrier. In order to compare the properties of the PVA film other neutral polymers were used i.e. hydroxypropyl methylcellulose, ethylcellulose.

However, from the preliminary studies PVA cannot be used alone because of a problem in processing. Therefore the combinations with EC were studied. Only few reports were related to PVA. Moldenhauer, et al <105> have demonstrated the possibility to use PVA in coating formulations. However, only the sugar coating was successfully performed by using PVA as a suspension stabilizer. One of the coating formulations contained PVA, talc, calcium carbonate, titanium dioxide, Aerosil 200, hydroxy ethylcellulose, saccharose and water. Tablets that were coated with this suspension in a pan coater had a smooth and glossy surface. However, PVA cannot be added to more than 3 % w/w into the suspension because it will cause the uneven surface of the tablets. The other formulation without sugar that was used successfully contained PVA, hydroxy ethylcellulose, Aerosil 200, titanium dioxide, calcium carbonate, talc, glycerol, Tween 20 and water. This shows that these aqueous suspensions contained high amount of insoluble substances which can be stabilized by adding PVA. The authors have also studied an organic-based formulation containing PVA to coat tablets but the result of this film coating was not satisfying. This may be due to the low solubility of PVA in this organic solvent which was mentioned that it will cause the polymer not to form the continuous film.

The swelling of PVA was reported by some researchers. Quintanar-Guerrero, et al. <146> have studied the swelling of PVA which was used as an excipient in the production of tablets. Matrix tablets were produced by mixing a drug and PVA at the ratio of 20:80 then compressed into a tablet with a diameter of 11 mm. The swelling studies were performed in pH 7.0 buffer. The diameters during a time interval were determined by an image analyser. The swelling index was calculated as a percentage from the surface area of the tablets. The highest swelling index was about 10 %. The

change of tablet area, which showed the process of swelling, occurred in three different stages which were intimately related to the polymer dissolution. The first stage was a rapid initial swelling resulting in an increased area. The second stage was a period with an approximately constant area. The third stage was a decrease of the tablet area. They have found that the thickness of the gel layer gradually increased during the dissolution test. Thus the delivery of drug was governed by the drug concentration gradient along the diffusion path length.

Sakellariou, Hassan and Rowe <160> have reported that HPMC and PVA are thermodynamically incompatible. The PVA used in this recent study was a random copolymer of poly(vinyl alcohol-co-vinyl acetate) with 88 % vinyl alcohol content. The incompatibility was demonstrated as the mixture of these two polymers segregated into two phases. Moreover, they have studied the effect of PEG 6000 on a 50:50 w/w mixture of HPMC and PVA. They found that PEG 6000 is a poor plasticizer for the two pure polymers and it had no effect on the behaviour of either HPMC-rich or PVA-rich phases of the mixtures. PEG 6000 segregated into a separate phase due to its thermodynamic incompatibility with both phases of the mixture in agreement with theoretical predictions based on the solubility parameters of the individual components and the interaction energy density of the mixture. The phase separation may be due to the inability of these molecules to contribute to hydrogen bonding and dipole-dipole interactions with each other.

Shlieout <175> has studied the mechanical properties (elastic behaviour and internal stress) and the swelling behaviour of two types of polyvinyl alcohol which were separately compressed as tablets.

The coating process by using PVA or a combination of PVA and EC was not reported. This present study shows that a combination of PVA and EC can be used as a subcoat because of the fast dissolution of a drug (nicotinamide) from the coated pellets. However, the stability of CAP-coated pellets with a subcoat from a combination of PVA and EC was not yet tested because of the non-resistance against gastric fluid of the film. It is, however, of interest to test this aspect in a further study e.g. another doctoral work. The unsatisfying result of gastric resistance was due to the incomplete coalescence of the CAP particles, details of which were mentioned in 3.1 - 3.2.

3.6 Pellets with nicotinamide but without any subcoat

a) Placebo: HPMC pellets

The HPMC coated pellets (Product pP) were achieved from the combination of a formulation **R1** and a process number **X7**, as demonstrated in the Table 2.30.

b) Nicotinamide loaded pellets: Nico pellets

The Nico pellets (Product aA) were achieved from the combination of a formulation **R3** and a process number **X8**, as demonstrated in the Table 2.30.

c) Enteric coated pellets: CAP-Nico pellets

The CAP-Nico pellets have a white colour. These pellets (Product kk to oo) were achieved from different combinations of a formulation and a process number, as demonstrated in the Table 2.30.

3.6.1 Film quality, diameter and weight of pellets

The thickness, diameter and the weight of the HPMC coated pellets (Product pP) or Nico pellets (Product aA) were the same as mentioned in the part of 3.4.1.

These pellets containing nicotinamide were afterwards directly coated with enteric coating. The physical properties of the enteric coated pellets are demonstrated in the Table 3.15. The SEM photograph of the cross-section of Product kk in Figure 3.41a shows the layer of CAP and DEP, whereas the layer of pellets coated with CAP and DBS of Product mm is demonstrated in Figure 3.41b. The SEM-results of the enteric layers of these pellets were the same as of pellets with different subcoats. CAP and DBS resulted in pellets with many uneven regions (Figure 3.42a). The best enteric layer also resulted from CAP and TEC (Figure 3.42b). However, small cracks dispersed on the surfaces of pellets coated with CAP and TEC were observed (Figure 3.43).

The mean weight of one CAP-Nico pellet (Product oo) from Product aA as cores was 1.15 ± 0.01 mg, while the mean diameter of these pellets was 1155 ± 37 μm at the coating amount of 46 mg cm^{-2} . These pellets weighed less than the others in part 3.2 to 3.5 because they did not have any subcoats.

Product	Weight gain of total batch (% w/w)	Thickness of the layer ($\mu\text{m} \pm \text{SD}$)	Weight of pellet ($\text{mg} \pm \text{SD}$)	Diameter of pellet ($\mu\text{m} \pm \text{SD}$)	Coating amount (mg cm^{-2})	Release within the first five minutes (% \pm Range)
SS	0.0 ^a	800-1000 ^e	0.68 \pm 0.01	970 \pm 37	n	n
pP	3.5 ^b	10 \pm 3 ^f	0.67 \pm 0.01	1000 \pm 36	n	n
aA	11.0 ^c	23 \pm 3 ^g	0.78 \pm 0.02	1010 \pm 35	n	n
kk	19.0 ^d	35 \pm 5 ^h	0.88 \pm 0.01	1080 \pm 40	13.0 ⁱ	90.0 \pm 1.0
mm	32.0 ^d	88 \pm 43 ^h	0.99 \pm 0.01	1140 \pm 50	26.0 ^j	92.0 \pm 1.0
nn	25.0 ^d	45 \pm 3 ^h	0.98 \pm 0.02	1100 \pm 42	25.0 ^j	81.0 \pm 2.0
oo	45.0 ^d	79 \pm 5 ^h	1.15 \pm 0.01	1155 \pm 37	46.0 ^j	48.0 \pm 1.0

Table 3.15: Properties of different products showing weight gain of total batch, thickness of the layer, weight of pellet, diameter of pellet, coating amount, release within the first five minutes;

^a = weight gain of total batch of sugar spheres (% w/w), ^b = weight gain of total batch of HPMC pellets to sugar spheres, Product SS, (% w/w), ^c = weight gain of total batch of Nico pellets to HPMC pellets, Product pP, (% w/w), ^d = weight gain of total batch of CAP-Nico pellets to Nico pellets, Product aA, (% w/w), ^e = size of sugar spheres, Product SS (μm), ^f = thickness of the HPMC layer (μm), ^g = thickness of the nicotinamide and HPMC layer (μm), ^h = thickness of the enteric coating layer (μm), ⁱ = coating amount of the enteric coat on Product aA (mg cm^{-2}), ^j = not measured.

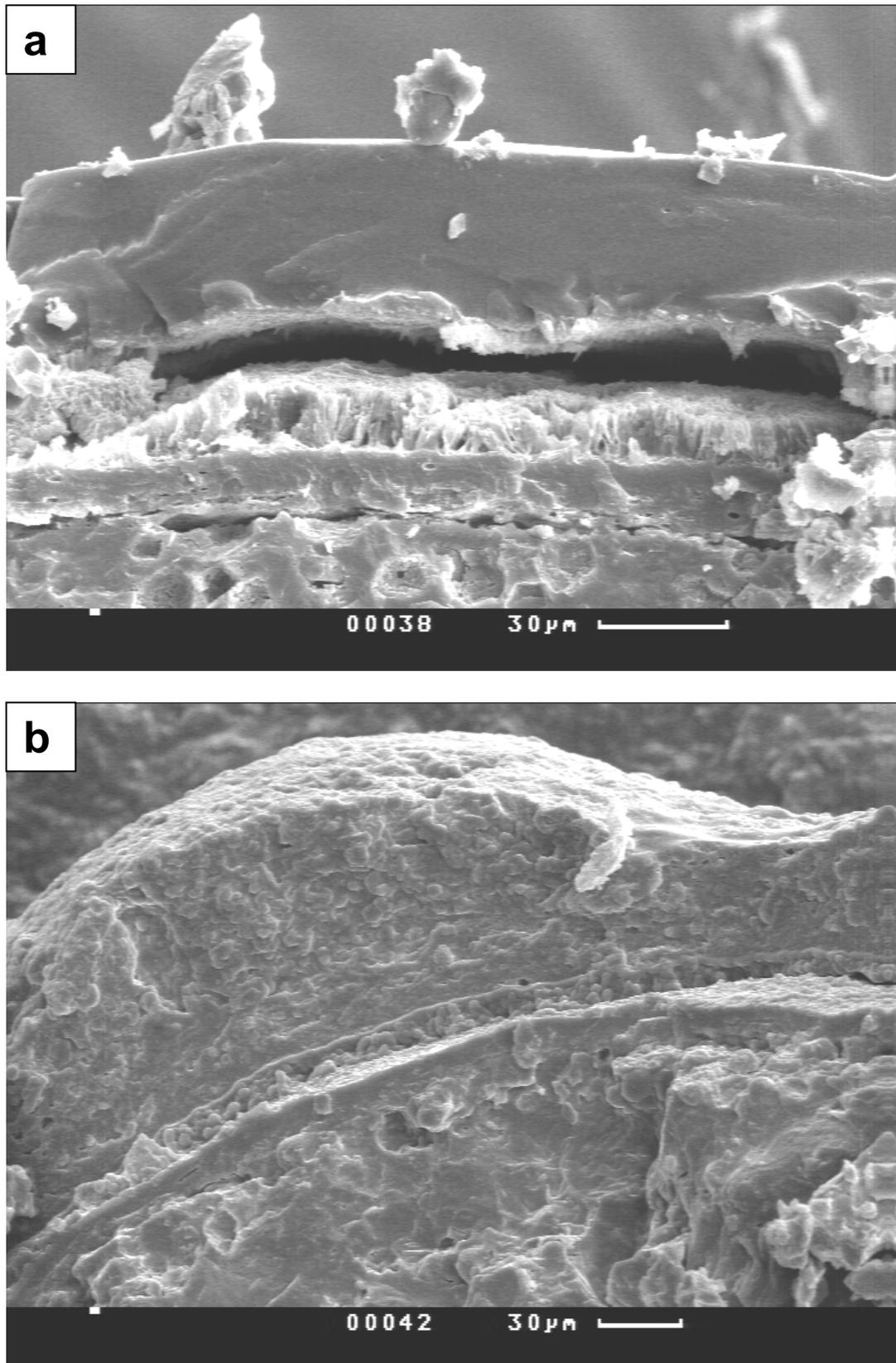


Figure 3.41: SEM pictures of enteric coated pellets; a) the cross-section of a pellet coated with CAP and DEP (Product kk), magnification 560x; b) the cross-section of a pellet coated with CAP and DBS (Product mm), magnification 350x.

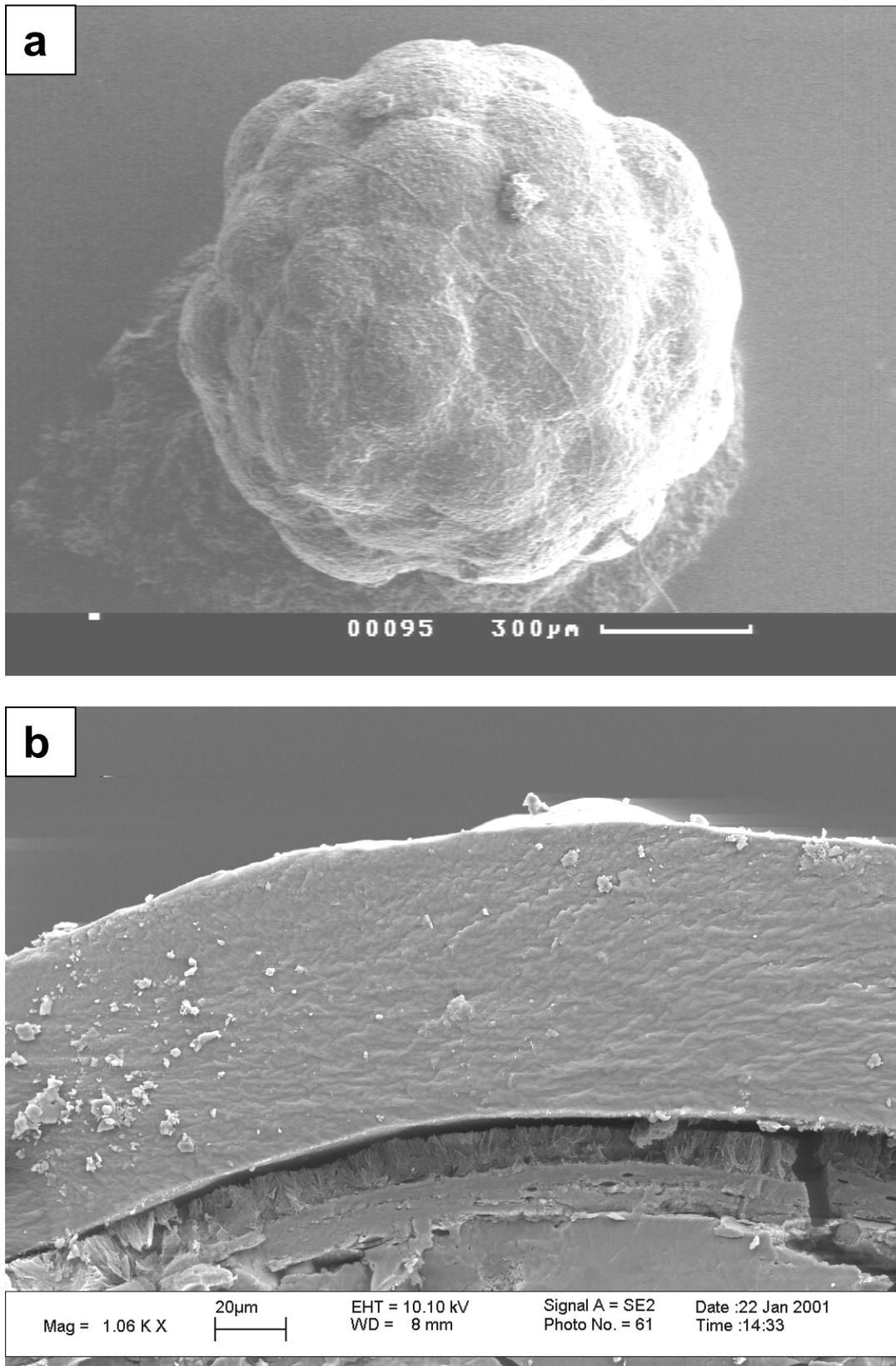


Figure 3.42: SEM pictures of enteric coated pellets; a) the top view of a pellet coated with CAP and DBS (Product mm), magnification 64x; b) the cross-section of a pellet coated with CAP and TEC (Product oo), magnification 1060x.

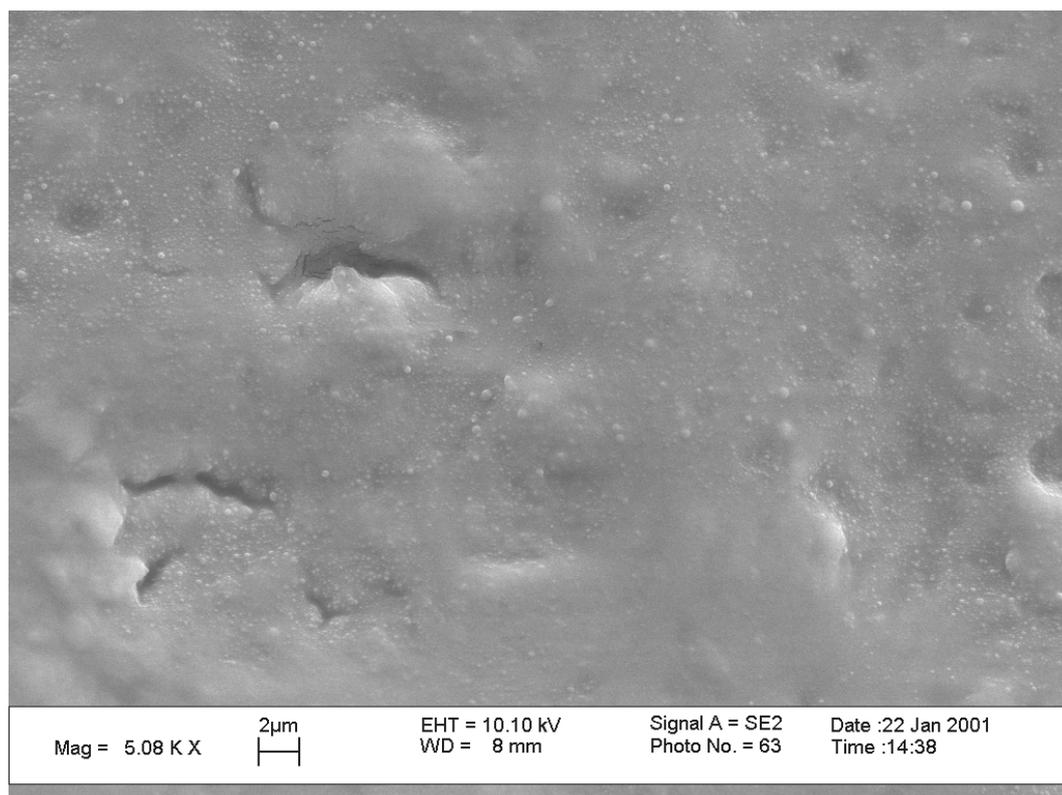


Figure 3.43: A SEM picture of the surface of a pellet coated with CAP and TEC (Product oo), magnification 5000x.

3.6.2 Swelling

The swelling in 0.1 N HCl of pellets coated with CAP and TEC (Product oo) was an example to demonstrate again that these pellets dissolved in the acid medium. Table 3.16 shows the comparison between enteric coated pellets with the same formulation containing CAP and TEC with (Product mM and nN) and without subcoats (Product oo). If the pellets carried a subcoat of a combination from EC and PVA, the pellets were broken but if the pellets did not have any subcoat they were dissolved and their diameter decreased after exposure to an acid medium for 30 min.

Product	D1 ± SD	D2 ± SD (pixel)	ΔD ± SD	Swelling (%)
bB	211 ± 1	220 ± 3	9 ± 2	4
cC	230 ± 3	248 ± 5	19 ± 3	8
mM	246 ± 2	-	-	crack
nN	228 ± 3	-	-	crack
oo	203 ± 2	-	-	dissolving

Table 3.16: Swelling property of different products in 0.1 N HCl, 22 °C; D1: diameter before swelling, D2: diameter after swelling, bB and cC: E&P-Nico pellets, mM and nN: CAP-E&P-Nico pellets (CAP+TEC), oo: CAP-Nico pellets (CAP+TEC).

3.6.3 Content of nicotinamide in one pellet

The content of nicotinamide inside one pellet of different products was varied. Product aA or Nico pellet without further coatings contained 8.9 ± 0.1 % w/w of nicotinamide based on total weight of one pellet. One pellet without any subcoat after coating with different enteric coats (Product kk to oo) contained 8.3 ± 0.3 % w/w of nicotinamide.

3.6.4 Release of nicotinamide from coated pellets

The cumulative percentage of nicotinamide released during the first five minutes from enteric coated pellets with different formulations is demonstrated in Table 3.15. The dissolution profiles of different enteric coats are shown in Figure 3.44. The release from all products reached 100 % after 60 min. Only a small resistance against 0.1 N HCl can be achieved from CAP and TEC at the thickness of about 80 μm.

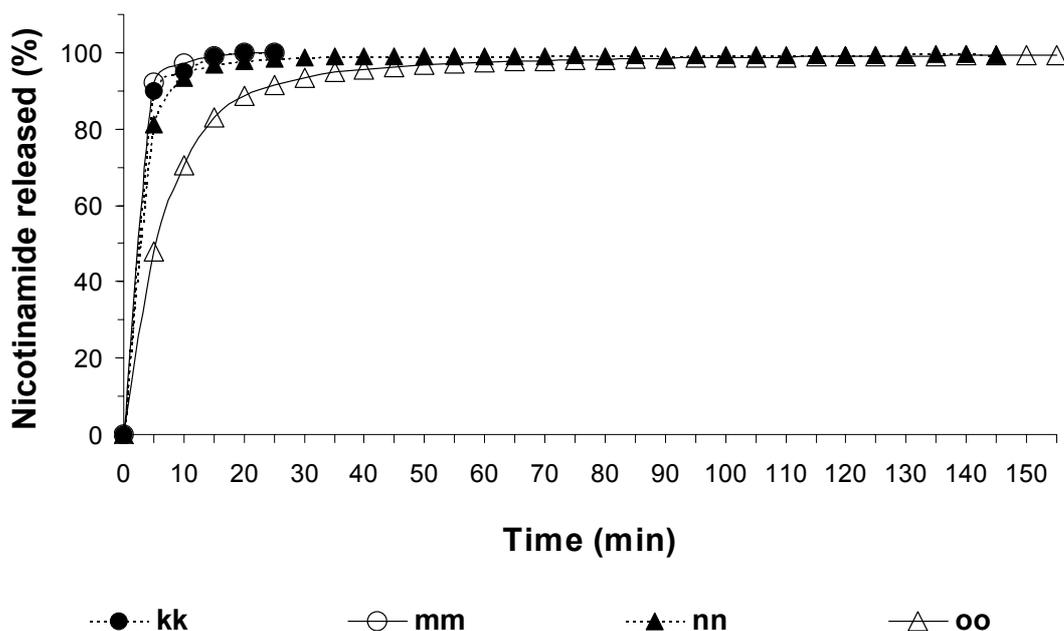


Figure 3.44: Dissolution profiles of differently coated pellets containing nicotinamide in 0.1 N HCl at 37 °C without subcoat but with enteric coats containing different plasticizers (Product kk to oo) and Product aA as cores; kk: CAP with DEP at a coating amount of 13 mg cm⁻²; mm: CAP with DBS at a coating amount of 26 mg cm⁻²; nn: CAP with TEC at a coating amount of 25 mg cm⁻²; and oo: CAP with TEC at a coating amount of 46 mg cm⁻².

3.6.5 Optical appearance after the release study

The optical appearance of enteric coated pellets with CAP and TEC (Product oo) after the release study is demonstrated in Figure 3.45. These pellets were broken after exposure to 0.1 N HCl for 30 min. Other pellets with another plasticizer (DEP) show the same result of breakage after 30 min.

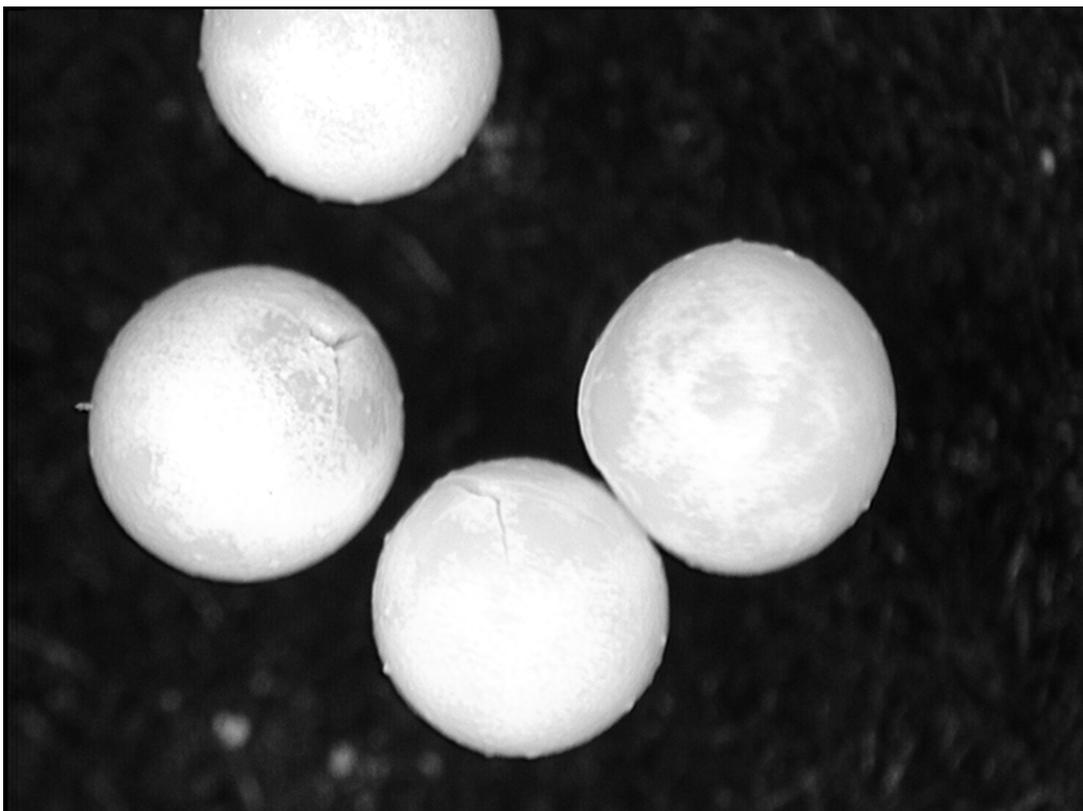


Figure 3.45: Optical appearance of pellets coated with CAP and TEC (Product oo) after exposure to 0.1 N HCl, 37 °C for 30 min.

3.6.6 Discussion

The nicotinamide loaded pellets without any subcoat subsequently coated with CAP shows no gastric resistance property. The release of nicotinamide from the pellets was higher than that one with a subcoat. Therefore the non-resistance property of CAP layer was not only caused by the swelling of the subcoat but also from the incomplete coalescence of the film. Details of which were mentioned in 3.1 - 3.2.

4. Comparative discussion

The investigations were carried out by spraying first the sugar spheres in the size range of 800 - 1000 μm with a HPMC solution in order to obtain a mechanically protecting layer. The thickness of this HPMC layer was about 7 - 10 μm . The diameter and the weight of the resulting spheres was about 970 - 980 μm and 0.65 - 0.67 mg, respectively. Hereafter these HPMC-coated pellets were covered with a layer of nicotinamide on the basis of HPMC as a binder. Nicotinamide was recrystallized as rod-like crystals during drying at the surface of the HPMC-coated spheres. The structure of this layer was porous but bound together because of HPMC. The thickness of this nicotinamide layer was about 20 - 23 μm with a weight gain of about 9 - 11 % w/w. The diameters and weights of these pellets were between 980 - 1010 μm and 0.75 mg - 0.80 mg, respectively. The content of nicotinamide in one pellet was about 8 % w/w - 8.5 % w/w.

Different neutral polymers, i.e. HPMC, EC and PVA, have been tested for their suitability for use as a subcoat. With PVA, various types were used to choose the suitable one for further investigations. The effectiveness of the PVA-films to provide a moisture barrier has been studied in comparison with films prepared from HPMC or Sepifilm on the basis of Karl-Fisher titration. The pellets coated with PVA were stored under different temperatures and humidities and taken out after a certain time period to determine the content of water in the pellets. The results showed that stored PVA-coated pellets had not taken much water after 3 weeks. The water content in the pellets after 3 weeks of storage was not higher than 3 % w/w at the highest stress condition of 50 °C and 80 % r.h.. Pellets stored under room condition showed a water content of about 1 - 2 % w/w. When PVA-coated pellets were compared to HPMC-coated pellets after storage no difference of the water content was obvious. However, the preliminary test with different PVA solutions showed that PVA alone could hardly be used as a subcoat. The PVA solution alone leads to higher sticking of the pellets when sprayed in the fluidized bed apparatus. For this reason PVA was only used in mixtures with EC in the main part of studies. EC can hinder the stickiness caused by PVA, and the dispersion of PVA and EC can better be sprayed at higher spraying rates. Mowiol 4-98 was used as source for PVA because it has a low molecular mass and a low viscosity.

In the main part of studies the nicotinamide loaded pellets were covered with one of four subcoats of HPMC, EC, two combinations of EC and PVA in different relations (100 + 30 parts, and 30 + 100 parts). Each one was marked with a different colour. The thickness of the subcoat prepared from HPMC was varied from 12 to 38 μm ; from EC it was varied from 19 to 160 μm ; for the combination of EC and PVA (100 + 30 parts) it was varied from 66 to 130 μm ; and for the combination of PVA and EC (100 + 30 parts) it was about 38 μm . The ranges of resulting diameters and weights of nicotinamide loaded pellets after coating with these subcoats varied for HPMC from 1040 to 1100 μm and 0.81 - 0.92 mg, for EC between 1030 and 1305 μm and 0.88 - 1.48 mg for the combination of EC and PVA (100 + 30 parts) from 1175 to 1320 μm and 1.08 mg to 1.39 mg, for the combination of PVA and EC (100 + 30 parts) the diameter increased to about 1000 μm and the weight to about 0.90 mg. The values of diameter and weight and their standard deviations showed that the coating process was well carried out and homogeneously coated pellets resulted.

The results of sieve analyses showed that the diameter of pellets measured by the sieving technique was comparable to that measured by an image analyser. Whilst the sieving method was faster, it created a mechanical stress by the vibration. Therefore the non-destructive method by image analysis was preferred for the determination of the diameter of the pellets.

The swelling of nicotinamide loaded pellets in 0.1 N HCl after coating with a subcoat from HPMC was 25 %, with a subcoat from EC it was only 0.5 %, with a subcoat from a combination of EC and PVA (100 + 30 parts) it was 4 - 8 %, while with a subcoat from a combination of PVA and EC (100 + 30 parts) it was 43 %. A combination of PVA and EC gave the highest value of swelling followed by the value from HPMC. Both these polymers or polymer mixtures are hydrophilic. All four subcoats prepared from polymers or polymer mixtures showed an acceptable coating with fast release of the drug. Only the combination of EC and PVA (100 + 30 parts) resulted in films with separated polymer layers. The films of the three other formulations, i.e. HPMC, EC and the combination of PVA and EC (100 + 30 parts), were homogeneous.

The different thicknesses of the subcoat prepared from EC (48 and 160 μm) and a combination of EC and PVA (66 and 130 μm) was tested to observe the effect of the thickness on the release or the swelling of pellets after coating with CAP.

Films prepared from CAP with DEP as a plasticizer showed cracks, whereas films prepared from CAP and DBS showed great unevenness. The pellets coated with the above mentioned CAP formulations were not resistant to 0.1 N HCl for 2 h. For this reason another plasticizer was selected. TEC is more hydrophilic than DEP and DBS and TEC does not contain phthalyl groups therefore TEC was used. Films prepared from CAP with TEC showed a better internal structure but also contained cracks. High dust occurred when the pellets were coated with CAP and TEC under the high process air flow because of the spray drying, and the filters were quickly blocked. The process had to be interrupted, the filters had to be cleaned, new filters had to be inserted into the coating apparatus before further coating steps could be performed.

The test with a cyclone as a dust collector showed that it was preferable to make use of a cyclone instead of filters. Besides it allowed a continuously running process and the time of coating was shortened as well. Consequently, all processes to coat pellets with CAP and TEC were performed with a cyclone.

A great batch of pellets containing methyl orange was prepared for preliminary tests. Methyl orange has a yellow colour in a basic medium and a red colour in a moderately acidic medium. Therefore the diffusion of the artificial gastric fluid (0.1 N HCl) through the polymer layers towards the core can be monitored by observing the colour change of methyl orange in 0.1 N HCl over a certain period of time. A release test by monitoring the release of methyl orange from the CAP-coated pellets was also possible.

As already mentioned films prepared from a combination of CAP and TEC had a rather good film structure. However, after the diffusion test it was found that the gold-orange coloured pellets had changed their colour into pink after 10 min in 0.1 N HCl at the latest. Contrary to this there was a delay of release in 0.1 N HCl of the CAP-coated pellets containing methyl orange, especially at the high thickness of about 90 μm . Further investigations by using FTIR and NMR showed that it was possible that a salt

formation between the nitrogen atom of methyl orange and a hydrogen atom of phthalyl groups of CAP was responsible for this delay.

Pellets with a subcoat from HPMC or a combination of PVA and EC (100+30) and then coated with CAP and TEC showed the uneven surface, while pellets coated under the same conditions with a subcoat from EC or a combination of EC and PVA (100+30) showed even surfaces. The unevenness may be due to the hydrophilicity of the subcoats. According to the result of the release tests none of the pellets coated with CAP and TEC and other additives was resistant against 0.1 N HCl up to 2 h.

The swelling of the CAP-coated pellets and HPMC used as a subcoat could not be measured because of the dissolving of the pellets in 0.1 N HCl. When the pellets had a subcoat prepared from EC and a coat of CAP, then the swelling remained low at 0.5 %. Surprisingly, when pellets had a subcoat prepared from a combination of EC and PVA (100 + 30 parts) or PVA and EC (100 + 30 parts), these CAP-coated pellets were broken after a short time (less than 30 min) exposure to 0.1 N HCl. This may be due to the fact that the CAP film layer cannot tolerate the high swelling of these subcoats (up to 43 %).

Further enteric coating tests were made with a combination of CAP and HPMCAS, which should increase the elasticity of the film. However, the resistance to the acidic medium was not improved by this combination.

In summary, none of the pellets coated with CAP (with different plasticizers such as TEC, DEP or DBS) was gastric resistant up to 2 h. The pellets with nicotinamide but without any subcoats had not at all a gastric resistance property. All these results may most probably be due to the incomplete coalescence of the colloidal CAP polymer particles.

The effect of curing, i.e. treatment of CAP-coated pellets after having finished the coating process, for different times under different temperatures (40 – 80 °C) and humidities (up to 75 % r.h.), was also investigated. This additional procedure is recommended generally in the literature as well as by polymer manufacturers, to improve the formation of a homogenous film coat. However, the results showed that the

film structures were not improved as compared to those obtained without curing. The coats still contained cracks or unevenness as before curing.

The optical appearance of the pellets stored under different conditions (25 - 50 °C and 30 - 80 % r.h.) showed that pellets coated with CAP cannot be stored above 40 °C and 60 % r.h. as a sticking occurred. The physical properties of the films would hereby be lost.

The content of free phthalic acid was determined by HPLC. Pellets coated with a formulation containing CAP and DEP showed about 4 % of free phthalic acid. This value was not higher than the limit of 6 % w/w in the USP XXIII but higher than the limit of the USP XXIV which reduced this value to 3 % w/w. The high value of phthalic acid in the coated pellets may have resulted from hydrolysis of CAP (and/or DEP, in case this was used as plasticizer) during the coating process and during the storage period. This was, however, not further investigated.

5. Conclusion

The quality of enteric coats from aqueous dispersions of cellulose acetate phthalate, prepared from either Aquateric or Aquacoat CPD and applied in a fluidized-bed apparatus equipped with a Wurster column onto pellets of about 1 mm diameter, seemed to be sensitive to the formulation, coating process and loading substrates. Apparently, only a small region of a combination of a suitable formulation and suitable coating conditions can result in CAP-coated pellets which are resistant to the artificial gastric fluid (0.1 N HCl) in the pharmacopoeial test.

When a subcoat was used to hinder the possible chemical interaction between a basic drug and the enteric, acidic polymer CAP one should also consider the property of the subcoat-forming polymer itself. A subcoat from the hydrophilic polymer HPMC or a PVA-rich polymer mixture of PVA and EC exhibited high swelling. In case of an enteric coat of high permeability to water, this high swelling ability can accelerate the breakage of the outer layer prepared from CAP. Moreover the nature of the subcoat can also have an additional, negative effect on the outer layer. In the present study subcoats prepared from the hydrophilic polymers HPMC or the hydrophilic mixture of PVA and EC (100 + 30 parts) resulted in an irregular and uneven outer CAP layer.

The different plasticizers used affected the film formation from aqueous dispersions of CAP. The best film structure was received from a combination of CAP and the hydrophilic triethyl citrate (TEC), and the worst film structure was obtained from a combination of CAP and the hydrophobic dibutyl sebacate (DBS). These were compared between the concentration of the substances and the coating conditions used in this study.

When during the coating process a high air stream was used in order to avoid sticking of the relatively light pellets, then dust was formed because of a spray drying of the coating dispersion. In this present study the exhaust air filters were blocked after a short time of operation. The application of a cyclone with a difference pressure as filter system solved this technical problem.

None of the CAP-coated pellets prepared was sufficiently resistant to an artificial gastric fluid (0.1 N HCl). CAP-coated pellets containing a subcoat or without any subcoat began to release nicotinamide already during the first five minutes of the release test.

The fast release of nicotinamide from the CAP-coated pellets may also have been supported by the high solubility of nicotinamide in water.

In summary several parameters including process air temperature, process air stream,, pressure and volume stream of atomizing air, and spray rates must be monitored during the Wurster-coating of pellets with aqueous dispersions of CAP. These parameters will influence the product performance and need to be optimized for each polymeric system. One simple yet expensive solution to obtain sufficient gastric resistance might be a drastic increase in the film thickness.

Prospective idea for other further studies

PVA is a hydrophilic polymer and is available in different grades of acetate ester content. The different grades of PVA will have different swelling properties. Since films prepared from HPMC are reported to have a high swelling it would be of interest to compare the resulting films to films prepared from HPMC.

In order to improve the film formation of CAP from aqueous dispersions, the combination of plasticizers such as TEC and DEP or TEC and DBS together with CAP should be investigated in the future.

Once the optimum combination of a suitable subcoat-forming polymer and a reliable gastric-resistant coat from CAP has been established, the effect of the coating conditions e.g. coating temperatures and humidities on the stability of the CAP-coated pellets containing a basic drug should be studied.

It would also be of interest to investigate the chemical stability of the pellets with different subcoats and coated with CAP. Possibly a suitable subcoat can be found which will sufficiently retard the chemical interaction between a basic drug and an acidic, enteric polymer in order to fulfil acceptable stability criteria.

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Lagerstabilität magensaftresisten-überzogener Pankreatin-Fertigarzneimittel, Pharm. Ind., 61, 3,
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7. List of instruments and software

- {1} Analytical balance, Delta Range, Type AE 166/9, Mettler AE 166, Range 162 g with E 0.1 mg, Mettler Waagen GmbH, Gießen
- {2} Analytical balance, Sartorius Elektronische Analysenwaagen, Model 1712 MP8, Range 30 g / 160 g with E 0.01 mg / 0.1 mg, Sartorius GmbH, Göttingen
- {3} Analytical balance, Sartorius Elektronische Analysenwaagen, Model 1615 MP, Range 80 g / 300 g with E 0.1 mg / 1 mg, Sartorius GmbH, Göttingen
- {4} Analytical sieve from stainless steel, size 200 mm x 50 mm, mesh width of 800, 1000, 1120, 1250, 1400, 1600 μm , F. Kurt Retsch GmbH & Co.KG, Haan
- {5} Barometer, Parath Funk Wetterstation
- {6} Barometer, Baratron, Unit PS/DVM, Type PAR-2
(PDR-C1A, Inv Nr. 550) Serial 29214, MKS Instrument Inc.,
Burlington MA, USA, with a pressure gauge, Unit DIF Gauge, Range 1000 Torr,
Input +15 VDC, Typ 223AH-A-1K, Serial 41416, Output 0-1 VDC, MKS
Instrument Inc, Burlington MA, USA
- {7} Barometer, Magnehelic, Dwyer Instruments Inc., Mich City, Ind, USA
- {8} Calliper rule, E 0.05 mm, Type Horex, Preisser, Blet, Paris, France
- {9} Camera with a 55 mm f 3.5, AF Macro Lens by Nikon, Japan with an adapter,
C-Mount, No. 31602, Hama
- {10} Cabinet for controlling temperature at 25 °C, Type 2105 Köttermann,
Hänningsen, Hannover
- {11} Cuvettes, normal opening, Quartz QS, 1.0 cm, Hellma GmbH & Co., Müllheim
- {12} Cuvettes, flow through, Quartz QS, 1.0 cm, Hellma GmbH & Co., Müllheim
- {13} Cyclone from the spray dryer, Mobile Minor Spray Dryer, Centrifugal Atomizer
Type M-02/a, A/S Niro Atomizer, Kopenhagen, Denmark
- {14} Data recording device, Linseis LSB36-III, Linsesis GmbH, Selb
- {15} Dehumidifying unit, Luftbehandlungseinheit No. 94131175, Aeromatic Fielder
AG, Bubendorf, Switzerland
- {16} Digital balance, Type Portable PT2100, Range 2500 g with E 0.01 g, Sartorius,
Otto Steiner GmbH, Hamburg
- {17} Digital balance, MP8 Type 1907004, Range 500 g / 5550 g with E 0.01 g / 0.1 g,
Sartorius, Göttingen coupled with a digital/analog converter, Type YDA 01Z,
Sartorius, Göttingen

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- {18} Dissolution test apparatus, Prolabo, No. 63761, Paris, France
 - {19} Fluidized bed apparatus Uniglatt Modell, Glatt GmbH Process Technology, Binzen
 - {20} Fluidized bed apparatus, Niro-Aeromatic Multiprozessor, Type MP-1, Powder coater, Aeromatic Fielder AG, Bubendorf, Switzerland
 - {21} Flow-meter for atomizing air, HI-TEC / EL-Flow Mass Flowmeter, Model F-112AC-HD-44-V, measurement range 2-100 l/min at 20 °C, output 4-20 mA, Mättig Mess- und Regeltechnik Vertriebs-GmbH, Unna
 - {22} Flow-meter for process air, Flowtec DMV 6336, Swingwire II, measurement range 54.2-630 m³/h at 20 °C, output 4-20 mA, with a transformer Omnigrad VU 2650, Endress+Hauser Meßtechnik GmbH & Co., Weil am Rhein
 - {23} Flow-meter for process air, integrated at Aeromatic MP-1, Dwyer Instruments Inc., Mich City, Ind, USA
 - {24} FTIR-spectroscopy, Genesis Series FTIR, Resolution 4.0, ATI Mattson Analytical Technology, Inc., Cambridge, Great Britain
 - {25} Hot air oven, Type B 5050 E, at the temperature of 30, 35, 40, 45, 50, or 60 °C, Heraeus, Hanau
 - {26} Hot air oven, built-in type, at the temperature of 70 and 80 °C, Heraeus, Hanau
 - {27} HPLC-Autosampler, Type HPMC 360, Kontron Instrument, Neufahrn
 - {28} HPLC-Columne, Type Nucleosil, 250x4.6, C18, BA 268, particle size 5 µm, Dr.Herbert Knauer KG, Bad Homburg v.d.H.
 - {29} HPLC-Degassing Unit Form, Type X-ACT, 4 Channel, Jour Reseach, Onsala, Sweden
 - {30} HPLC-Detector, Type BT 8200, Range 0.005, Wavelength: 210 nm, HPLC UV/VIS Detector, Biotronik, Maintal
 - {31} HPLC-Pump, Type Thermo Separation Products, Spectra Series P100, Darmstadt
 - {32} Hydraulic tablet press for IR-technique, Beckman, München
 - {33} Hygrometer, Hygrolog WMT 170 and Betasensor DT13, Inline-Meßlinie, dew point and temperature measurement apparatus for gas, Endress+Hauser Meßtechnik GmbH & Co., Weil am Rhein
 - {34} Hygrometer, Humidat IC II, couples with a sensor enBS-4/IC, Novasina, Zürich, Switzerland

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- {35} Image analyser: hardware, Matrox Image Processing Products, Carl Zeiss Vision GmbH 1997, Eching bei München
- {36} Image analyser: monitor, Sony Trinitron Color Graphic Display, Multiscan 17 SE II, GDM-17 SE2T5, Serial No. 6316606, Sony Deutschland, Köln-Ossendorf
- {37} Image analyser: digital camera, Hitachi 3-CCD Color Camera, Model HV-C20E/K-S4, No. 7072620, Hitachi Denshi GmbH, Rodgau
- {38} Jet-mill, Luftstrahlmühle Type Forschung 1047, Bauermann & Co., Sohlingen-Ohlip
- {39} Karl-Fischer Titration machine composed of a pH Meter (PHM 62 Standard), Autoburette (ABU 80), and a Titrator (TTT 60), Radiometer, Copenhagen, Denmark
- {40} Light microscope, Type Orthoplan, Serial No. 759225, Ernst Leitz GmbH, Bensheim with an adapter, C-Mount 0.63x, Leica Mikroskopie und Systeme GmbH, Wetzlar
- {41} Light microscope, Wild M3, Type 352873, Heerbrugg, Switzerland with an adapter, C-Mount 0.63x, Leica Mikroskopie und Systeme GmbH, Wetzlar and coupled with a ring light source, Schott, Mainz
- {42} Light source, two tubes, Type KL 150 B, Schott, Mainz
- {43} Magnetic stirrer IKA-KMO, Janke & Kunkel GmbH & Co. KG, Staufen
- {44} Magnetic stirrer with heater, Cenco Instrument M.U.N.V. Breda, The Netherlands
- {45} Mixer for powder, Type KU1, No. 3142161, Erweka-Apparatebau GmbH, Offenbach
- {46} Mixer for fluid, Ultra turrax, IKA-Ultra-Turrax, Type 45, No. 6893, Dargatz
- {47} NMR-spectroscopy, AMX400, Bruker Analytik GmbH, Rheinstetten
- {48} Nozzle for fluid, diameter 1.2 mm, 1.0 mm, and 0.8 mm, Schlick GmbH, Untersiemau
- {49} Objectmicrometer for calibration, No. 10310345, 50 mm, one section = 0.1 mm, Leica Mikroskopie und Systeme GmbH, Wetzlar
- {50} Objectmicrometer for calibration, 1 mm, one section = 0.01 mm, Leica Mikroskopie und Systeme GmbH, Wetzlar
- {51} Peristaltic pump, No. 71844, Desaga, Heidelberg
- {52} Perforated bottoms with free holes of 6.0, 8.0, 11.0, 13.0, 20.0 % compared to all possible flow region, Universität Hamburg
- {53} pH-Meter Type E 512, Metrohm AG, Herisau, Switzerland

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- {54} Printer, Type Pinwriter P60, NEC Deutschland, München
- {55} Scanning electron microscope, Cam Scan DV4, Cambridge Scanning Comp. Ltd., Cambridge, England
- {56} Scanning electron microscope, Leo 1525 Gemini, Zeiss, Oberkochen, Germany
- {57} Scalpel, disposable and sterile, Cutfix, Charge No. 96L2498, B.Braun Melsungen AG, Melsungen
- {58} Sieve machine, Type 2D, Laboratory sieving machine plan with rotary plan movement, F. Kurt Retsch GmbH & Co.KG, Haan
- {59} Spherical balls, diameter of 1 mm, Type RB-1/G20w; diameter of 1.5 mm, Type RB-1.5/III; diameter of 2 mm, Type RB-2/G20w; diameter of 2.5 mm, Type RB-2.5/G20w; diameter of 3 mm, Type RB-3/G20w; SKF Ing.- und Verkaufsbüro, Hamburg
- {60} Tableting machine, Korsch PH106, Pharmapress 100, No. 9205-71/86, Maschinen Fabrik, Berlin
- {61} Tablet hardness tester TBH 28, Erweka Apparatebau GmbH, Heusenstamm
- {62} Tablet thickness tester, Digimatic Indicator Type 543, Mitutoyo Corp, Japan
- {63} Thermocouples, Thermocoax, Miniature-Thermocouples, Type 98001591, Serial No. 3819, TKA 10/50/NN, Philips IE Deutschland GmbH, Bereich Thermocoax, Hamburg
- {64} Thermometer as reference, 0-50 °C, Goldbrand 1, division 0.1, Brand, Wertheim
- {65} Thermometer as reference, 50-100 °C, Precision 2, division 0.1, Brand, Wertheim
- {66} Thermosensor, Type GTF 101, PT100, 4-Leiter, FL=100 mm, 1/10 DIN, Greisinger electronic GmbH, Regenstauf
- {67} Ultrasound bath Sonorex, Type RK 106, No. 20083, Bandelin electronic, Berlin
- {68} UV-Spectroscopy Uvikon 930, Bio-TEK Kontron Instruments GmbH, Neufahrn
- {69} Water bath with temperature control 30-100 °C, Type NB-D8/17, No. 32567, Lauda-Thermostat, MGW Messgerät Werk Lauda, Lauda

Software programm:

{S1} Excel 97, Microsoft Corp., USA

{S2} Konvert 4.0 Linseis Software, Linseis GmbH, Selb

{S3} KS 400 Imaging System 3.0, Carl Zeiss Vision GmbH, Eching bei München

{S4} Toccata Version 910226, Frontini, R., 1993, Dissertation Universität Hamburg

{S5} HPLC Software ChromStar 4.06, SCPA, Suhr

{S5} Win-First, Fourier Infrared Software Tools, Version 2.10, ATI Mattson, 1994

{S6} Win-NMR, USA

8. Summary

The stability of cellulose acetate phthalate (CAP) coated dosage forms, especially when the dosage forms contained a basic drug, was of interest. The interaction between a basic drug and the acid polymer was reported. The possibility to increase the stability of this dosage form and to avoid the hydrolysis of the cellulose acetate phthalate polymer was studied. A suitable model for this intention was therefore a model which provided a direct contact between a basic drug and the enteric acid polymer (CAP). Sugar spheres in the size range of 800 - 1000 μm or 1000 - 1180 μm were used as cores in order to produce such a model. These cores were first coated with a thin layer of HPMC in order to achieve a barrier layer against a mechanical stress during a coating process using aqueous formulations. This HPMC layer could avoid the dissolving of the sugar from the surface of the sugar sphere cores. Hereafter a thin layer of a solid basic drug was produced by a fluidized bed process applying HPMC as a binder and finally this product was coated with CAP. The chemical or physical interaction between a model basic drug and the outer enteric acid layer (CAP) was well observed with this arrangement.

In this present work the spherical model had a thin layer of a water soluble, weak basic drug (nicotinamide). This thin layer represented the effect of an interaction which occurred because of a direct contact with the enteric acid polymer (CAP). When the drug diffuses to the outer layer it will change the properties of CAP. This diffusion can be avoided by using a seal coat (subcoat). Moreover, the subcoat may hinder the interaction between the basic drug and the enteric polymer (CAP). Different non-ionic polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC) and polyvinyl alcohol (PVA) were therefore tested to find out the possibility to use one of them as a subcoat. HPMC was used to compare the result with EC and PVA.

A development to find out a suitable aqueous formulation containing CAP and a suitable coating condition was carried out. The coating processes were performed by using a Wurster-based fluidized bed apparatus (Aeromatic-MP1). The two commercial CAP products in the form of the spray dried powder (Aquateric) and a ready-to-use aqueous dispersion (Aquacoat CPD) are investigated. Different types of plasticizers were added to the aqueous dispersions of CAP. One plasticizer is water soluble i.e. triethyl citrate

(TEC). The other two plasticizers are water insoluble i.e. diethyl phthalate (DEP) and dibutyl sebacate (DBS).

The ready coated pellets were tested under the SEM to determine the thickness, the morphology and the roughness of the film layer. The image analyser was used to determine the diameter, the swelling of the pellets, and the colour change of the indicator (methyl orange).

The weight and the diameter of the pellets were measured after building up the layers so that the amount of the CAP per square centimeters could be calculated. The swelling of the coated pellets was investigated in 0.1 N HCl to observe the property of the films which is the condition for the gastric resistance. The resistance against artificial gastric fluid was performed in a dissolution apparatus with inserted paddles. The release test was made in an artificial gastric fluid (0.1 N HCl) in order to find out whether the CAP-coated pellets were gastric resistant or not. The physical changes at different formulations and process conditions could therefore be observed. Pellets after the release test at different time periods were tested regarding defect structure under a light microscope.

For the coating processes using Aquacoat CPD and TEC as a plasticizer the coating formulations and parameters were developed based on the combination of the publications by Williams and Liu <200>, Carlin <25> and the product information of Aquacoat CPD <7>. Moreover, the effect of some additives such as magnesium stearate, talc, and EC on the film formation of CAP was studied.

For this purpose a greater batch of pellets with methyl orange (MO) as marker and HPMC as a film former was produced in order not to make use of the ready coated pellets with different subcoats. These gold colour pellets with a thin layer of HPMC and dissolved methyl orange served as a loading material for the preliminary test. Methyl orange has a yellow colour in a basic medium and a red colour in a moderately acidic medium. Therefore the diffusion of the artificial gastric fluid (0.1 N HCl) can be monitored by observing the colour change of methyl orange in 0.1 N HCl over a certain time period. The result showed that pellets containing methyl orange after coating with an aqueous dispersion of CAP changed their colour from yellow to gold-orange. This means that the coating process had already affected the methyl orange. This may be

due to the reduction of the pH around methyl orange because of free phthalic acid from CAP, as it is well known that the coating conditions can cause some hydrolysis of CAP which resulted in free phthalic acid.

A rather good film structure formed from the aqueous dispersion containing CAP and TEC. The diffusion test showed that the gold-orange coloured pellets had changed their colour into pink at the latest after 10 min in 0.1 N HCl. Contrary to this there was a delay of release in 0.1 N HCl of the CAP-coated pellets containing methyl orange, especially at the high thickness of about 90 μm . The further investigations by using FTIR and NMR showed that the salt formation between the nitrogen atom of the methyl orange and the hydrogen atom of the phthalyl groups of CAP was possibly responsible for this delay.

The use of a high process air velocity in order to hinder the agglomeration of pellets caused a high amount of fine dust because of the spray drying of the coating dispersion. This was confirmed by the real coating level which was much lower than the theoretical coating level. The coating process therefore had to be interrupted to change the filters. In order to avoid this interruption the insertion of a cyclone instead of filters was tested. The coating apparatus connected with a cyclone could continuously work without any stop. However, the resistance of the cyclone was high and comparable to the maximum resistance of the filters at which the coating process could be run. The resistance of the cyclone was constantly monitored over the whole process.

The pellets containing nicotinamide were coated with the formulation containing Aquacoat CPD and TEC as well. The coating formulations and parameters using Aquateric or Aquacoat CPD and DEP or DBS as a plasticizer were developed on the basis of the reports from Chang <31> and the product informations of Aquateric <9> and Aquacoat CPD <7>. Pellets coated with different subcoats (orange, pink, green and blue) and placebo-pellets without nicotinamide (white), but coated with HPMC, were mixed together and then further coated with CAP in different formulations and process conditions so that the pellets with different subcoats could be coated under the same conditions. The number of investigations was reduced by this way, when the parameters were altered. Pellets without any subcoats but with nicotinamide, were also mixed with placebo-pellets (without nicotinamide) and then covered with the same CAP formulations under the same process conditions as the pellets with subcoats. Hereby

the effect of the subcoat and different compositions could be compared. The different colours (orange, pink, green and blue) were used as a marker for each product for the identification and selection after finishing the process. The results showed that films prepared from CAP and DEP contained cracks, whereas films prepared from CAP and DBS had a porous and uneven structure. The swelling of the pellets coated with CAP and DEP was about 12 % whereas the swelling of pellets coated with CAP and TEC could not be measured because some parts of the pellets were dissolved after a certain time in 0.1 N HCl. Pellets containing nicotinamide and carrying a subcoat from HPMC had a high swelling of about 25 % which may have an effect on the breakage of the outer CAP layer. EC-coated pellets, however, had a very low swelling. The value was around 0.5 %. The combination of EC and PVA at two ratios gave higher values (8 % – 43 %) depending on the amount of PVA. When films were prepared from a PVA-rich mixture then the swelling was higher.

The release of nicotinamide from the CAP-coated pellets with a subcoat from HPMC or a combination of EC and PVA was very fast. Especially pellets coated with a formulation containing CAP and DEP or DBS had a high percentage of release. For example: more than 80 % of nicotinamide was released within the first 5 min when pellets had HPMC as a subcoat. The protection against the gastric fluid increased when the thickness of the CAP layer was increased. The release of nicotinamide from the pellets coated with CAP and without any subcoat was very fast so that 90 % of nicotinamide was released within the first 5 min, especially when the formulation contained DEP or DBS as a plasticizer.

A combination of CAP and HPMCAS was also tested to observe whether the elasticity of the film was improved or not. The result showed that the film prepared from this combination also contained a porous structure, and it was not resistant to 0.1 N HCl.

The effect of post-drying (curing) at different temperatures and humidities outside the coating apparatus was studied with some CAP-coated pellets. However, it was found that there was no improvement of the film formation under the studied conditions (40 °C - 80 °C and up to 75 % r.h.) and that films prepared from CAP and DEP or CAP and DBS still contained cracks or unevenness as before curing.

As the water content in the dosage form is the important factor that can affect the hydrolytic process of the polymer especially CAP, the determination of the water content was investigated by Karl-Fischer titration. Pellets coated with one of the non-ionic polymers such as HPMC, PVA and Sepifilm LP 010 were tested in order to study the moisture barrier property of these film formers. The results showed that stored PVA-coated pellets had not taken up much water after 3 weeks. The water content in the pellets after 3 weeks of storage was not higher than 3 % w/w at the highest stress condition of 50 °C and 80 % r.h.. Pellets stored under room condition showed a water content of about 1 - 2 % w/w. There was no significant difference of the water content in PVA-coated pellets compared to HPMC-coated pellets or Sepifilm-coated pellets after storage. However, the water content of CAP-coated pellets was not determined because these pellets were not resistant to 0.1 N HCl.

The chromatographic method as HPLC was used to determine the content of free phthalic acid, which is the indicator for the chemical stability of CAP. Pellets coated with a formulation containing CAP and DEP showed a value of free phthalic acid which was not higher than the limit mentioned in the USP XXIII but higher than the limits mentioned in the USP XXIV or BP 1993. The high value of phthalic acid in the coated pellets may have resulted from hydrolysis of CAP (and/or DEP, in case this was used as plasticizer) during the coating process and during the storage period.

The effect of the storage conditions was studied in order to know the critical point of storage if the chemical study of CAP-coated pellets should be performed. The optical appearance of the pellets stored under different conditions (25 °C - 50 °C and 30 % r.h. - 80 % r.h.) showed that pellets coated with CAP cannot be stored over 40 °C and 60 % r.h. as a sticking occurred. The physical properties of the films would hereby be lost. The chemical stability of the enteric coated pellets can be investigated when the physical properties of the coated pellets were acceptable. The important physical property is the resistance against artificial gastric fluid (0.1 N HCl). The present study shows that the CAP-coated pellets prepared from different formulations and coating conditions were not resistant to 0.1 N HCl up to 2 h. Therefore the focus in this present work was particularly on the process or the variation of the formulations of the aqueous dispersions containing CAP instead of the study of the chemical interaction between a basic drug and acidic coats.

9. Zusammenfassung

Die Untersuchung der Stabilität einer mit Celluloseacetatphthalat (CAP) überzogenen Arzneiform ist von Interesse, insbesondere wenn die Arzneiform einen basischen Wirkstoff enthält. Die Wechselwirkung zwischen basischem Wirkstoff und saurem Polymer ist bekannt. Die Möglichkeit zur Verbesserung der Stabilität der Arzneiform, d.h. um die Hydrolyse der Celluloseacetatphthalat zu verhindern, wurde in dieser Arbeit untersucht. Das geeignete Modell sollte eine Schicht eines inerten Polymers zwischen basischem Kern und saurem CAP Polymer haben.

Um dieses Modell zu erzeugen, wurden Neutralpellets 800 - 1000 µm oder 1000 µm - 1180 µm als Träger benutzt. Diese Trägerpartikel wurden zunächst in einer Wirbelschichtanlage mit Wurster-Rohr mit einer HPMC-Lösung überzogen, um eine dünne Isolierschicht herzustellen. Dieser dünne Überzug dient als Schutzschicht gegen mechanische Belastung während des Aufsprühens weiterer, wässriger Dispersionen. Hierdurch kann die Auflösung der Zuckeroberfläche des Trägers verhindert werden. Auf diesem dünnen HPMC Überzug wurde eine weitere Schicht eines schwach basischen Wirkstoffes mit Hilfe von HPMC als Bindemittel erzeugt, die anschließend mit Celluloseacetatphthalat (CAP) überzogen wurde. Mittels dieses Modells konnte die chemische oder physikalische Wechselwirkung zwischen basischem Wirkstoff und der äußeren CAP Schicht beobachtet werden.

Das kugelförmige Modellpartikel (Neutralpellets) in dieser Arbeit trägt somit eine dünne Schicht von schwach basischem Wirkstoff, Nicotinamid. Durch diese dünne Schicht wird ein Effekt der Wechselwirkung dargestellt, welche durch den direkten Kontakt zwischen basischem Wirkstoff und dem sauren CAP Polymer entsteht. Die CAP Eigenschaft verändert sich, wenn dieser Wirkstoff in die Außenschicht diffundiert. Diese Diffusion kann durch eine Zwischenschicht verhindert werden. Außerdem kann die Zwischenschicht die Wechselwirkung zwischen basischem Wirkstoff und saurem Polymer wie CAP im Sinne einer Festphasenreaktion verhindern. Die Verwendung verschiedener nichtionischer Polymere für diese Zwischenschicht, wie Hydroxypropylmethylcellulose (HPMC), Ethylcellulose (EC) oder Polyvinylalkohol (PVA), erfolgte zur Feststellung, ob eines dieser Polymere zur Benutzung für eine Zwischenschicht geeignet ist. Als Vergleich wurde HPMC benutzt.

Zahlreiche Untersuchungen wurden durchgeführt, um eine passende Rezeptur für eine wässrige Dispersion von CAP und geeignete Überzugsbedingungen zu finden. Die Überzüge wurden in der Wirbelschichtanlage Aeromatic-MP 1 unter Einsatz eines Wurster-Rohres erzeugt. Eingesetzt wurden zwei kommerzielle CAP Produkte in Form von Sprühtrocknungspulver (Aquateric) und fertigen wässrigen Dispersionen (Aquacoat CPD). Verschiedene Weichmacher wurden den wässrigen CAP Dispersionen zugemischt. Ein Weichmacher war wasserlöslich (Triethylcitrat (TEC)), weitere zwei Weichmacher waren nicht wasserlöslich (Diethylphthalat (DEP) und Dibutylsebacat (DBS)).

Die Untersuchung der fertig überzogenen Pellets erfolgte mittels Raster-Elektronenmikroskopie (REM), um die Schichtdicke, die Strukturen und die Rauheit der Verfilmung festzustellen. Nach dem Aufbau der Schichten wurden die Gewichte und die Durchmesser der Pellets zur Errechnung der aufgetragenen Masse an CAP pro Quadratcentimeter gemessen. Die Quellung der überzogenen Pellets wurde in 0.1 N HCl mittels Bildanalyse untersucht, um die Filmeigenschaften festzustellen, die für die Magensaftresistenz Voraussetzung sind. In künstlichem Magensaft (0.1 N HCl) wurde nach Pharm.Eur. geprüft, ob die mit CAP überzogenen Pellets magensaftresistent sind. Die Freisetzung von Nicotinamid aus den verschiedenen überzogenen Pellets in 0.1 N HCl wurde durchgeführt, um die physikalische Veränderung durch Variieren der Rezepturen und Prozessbedingungen beobachten zu können. Die Pellets wurden nach der Freisetzung in verschiedenen Zeitabständen unter dem Lichtmikroskop darauf untersucht, wieweit die Umhüllungsfilme noch intakt waren.

Die Rezepturen für die Dispersionen zum Überziehen und die Parameter für die Überzugsprozesse mit Aquacoat CPD und TEC als Weichmacher wurden gemäss der Literatur modifiziert und hergestellt. Überdies wurde der Einfluß von Zusatzstoffen z.B. Magnesiumstearat, Talkum und EC auf die Filmbildung von CAP untersucht.

Um ökonomisch vorzugehen, wurde zunächst eine große Charge von Pellets mit Methylorange (MO) als Markiersubstanz und HPMC als Filmbildner hergestellt. Diese gelb gefärbten Pellets mit dünner HPMC-Schicht und darin gelöstem Methylorange wurden für Vorversuche als Ausgangsmaterial benutzt, um eine Prozessoptimierung durchführen zu können. Methylorange hat in basischem Medium eine gelbe Farbe und eine rote Farbe im schwach sauren Medium. Deshalb konnte die Diffusion des künstlichen Magensaftes (0.1 N HCl) in diese Schicht –und gegebenenfalls durch eine

darübergelegte Schicht aus CAP- durch Farbänderung von Methylorange in 0.1 N HCl über die Zeit beobachtet werden. Die Ergebnisse zeigten, daß die Farbe der - mit Methylorange und anschließend überzogen mit wässrigen CAP Dispersionen - sich von gelb zu gold-orange änderte. Dieses bedeutet, daß die Überzugsbedingung schon Einfluß auf die Eigenschaft des Methylorange hatte. Die Reduzierung der pH-Werte in der Umgebung von Methylorange durch freie Phthalsäure könnte für diesen Vorgang verantwortlich sein. Es ist zudem bekannt, daß die Überzugsbedingungen Einfluß auf die Hydrolyse des CAP haben und dieses zur Freigabe der Phthalsäure führt.

Eine gute Verfilmung konnte mit der wässrigen Dispersion aus CAP und dem Weichmacher Triethylcitrat (TEC) erreicht werden. Die Ergebnisse zeigten, daß die Farbe der gold-orange gefärbten Pellets sich spätestens nach 10 Minuten in 0.1 N HCl in rosa verändert hatte. Dagegen zeigte sich eine Verzögerung in der Methylorange-Freigabe in 0.1 N HCl bei der Freisetzungsuntersuchung der CAP-überzogenen Pellets insbesondere bei einer der hohen CAP-Schichtdicke von ca. 90 µm. Weitere Untersuchungen mittels FTIR und NMR zeigten, daß eine Salzbildung zwischen dem N-Atom in Methylorange und dem H-Atom der Phthalgruppe im CAP für diese Verzögerung verantwortlich sein könnte.

Die Benutzung hoher Luftströmung, um die Agglomeration der Pellets zu verhindern, führt zu hoher Staubbildung durch Sprühtrocknung der Dispersion. Dieses konnte beobachtet werden anhand der Differenz zwischen dem Gewicht des aufgetragenen Überzugsmaterials und des theoretischen Gewichts, abgeleitet aus der versprühten Menge Dispersion. Der Überzugsprozess mußte unterbrochen werden, um die Filter auszutauschen. Zur Vermeidung dieser Unterbrechung wurde ein Zyklon statt der Filter als Staubfänger getestet. Die Ergebnisse zeigten, daß die Überzugsprozesse nun kontinuierlich durchgeführt werden konnten. Der Strömungswiderstand des Zyklons ist indessen sehr hoch. Die Werte sind vergleichbar mit dem höchsten Widerstandswert der Filter, bei welchem der Überzugsprozess noch durchführbar ist. Der Widerstandswert des Zyklons wurde während des gesamten Überzugsprozesses überwacht.

Die Nicotinamid enthaltenden Pellets wurden auch mit der Rezeptur aus Aquacoat CPD und TEC überzogen. Die Überzugsrezepturen aus Aquateric und Aquacoat CDP mit DEP oder DBS als Weichmacher und die Überzugsparameter wurden auf Basis der Literatur und Produktinformationen der Herstellerfirma der Polymere modifiziert. Pellets,

mit verschiedenen Zwischenschichten (mit verschiedenen Farbindikatoren eingefärbt auf orange, rosa, grün und blau) und Placebopellets ohne Nicotinamid (weiß), aber mit HPMC beschichtet, wurden zusammengemischt und anschließend mit verschiedenen CAP Rezepturen überzogen. Somit konnten Pellets mit verschiedenen Zwischenschichten unter gleichen Bedingungen überzogen werden. Hierdurch konnte die Anzahl der Versuche bei verschiedenen Parametereinstellungen deutlich reduziert werden. Pellets ohne Zwischenschicht, aber mit Nicotinamid, wurden gleichfalls mit Placebopellets (ohne Nicotinamid) gemischt und dann mit CAP mit den gleichen Rezepturen und unter denselben Parameterwerten wie bei Pellets mit Zwischenschicht überzogen. Dieses Verfahren erlaubte die Untersuchung des Einflusses von Zwischenschichten und verschiedenen Komponenten. Die unterschiedlichen Farben (orange, rosa, grün und blau) wurden somit als Markierer für verschiedene Produkte benutzt. Dieses ermöglichte die spätere Auswahl der Pellets nach der Fertigung der Überzüge. Die Ergebnisse zeigten, daß Filme aus CAP und DEP viele Risse hatten, während Filme aus CAP und DBS Unebenheiten zeigten und porös waren. Die Quellung der Pellets überzogen mit CAP und DEP lag bei ca. 12 %, während die der Pellets überzogen mit CAP und TEC nicht gemessen werden konnte, weil sich von den in 0.1 N HCl liegenden Pellets nach einiger Zeit Teile gelöst hatten. Pellets, die Nicotinamid enthielten und eine HPMC Zwischenschicht hatten, zeigten eine hohe Quellung von ca. 25 %. Dieses könnte die Ursache für das Brechen der CAP Außenschicht sein. Pellets mit einer hydrophoberen EC- Zwischenschicht zeigten eine niedrige Quellung von ca. 0.5 %. Pellets mit der Kombination von EC und PVA in zwei Relationen in der Zwischenschicht hatten die sehr hohe Quellung von 8 – 43 %. Je höher der PVA-Anteil im Film war, desto höher war die Quellung. Es erfolgte eine sehr schnelle Nicotinamid Freigabe bei CAP überzogenen Pellets, welche HPMC oder eine Kombination von EC und PVA als Zwischenschicht hatten, insbesondere wenn diese Pellets mit Rezepturen aus CAP und DEP oder DBS überzogen waren. Ein Beispiel ist die Freigabe des Nicotinamids bis zu 80 % innerhalb der ersten 5 Min bei Pellets, die HPMC als Zwischenschicht hatten. Die Resistenz gegen Magensaft wurde höher, wenn die Dicke der aufgetragenen CAP Schicht erhöht war. Die Freigabe des Nicotinamid war bei den Pellets sehr hoch, die keine Zwischenschicht hatten. Innerhalb der ersten 5 Min wurden 90 % des Nicotinamid freigesetzt, ganz besonders wenn die Pellets mit den Rezepturen aus CAP und DEP oder DBS überzogen waren.

Die Untersuchung mit der Kombination aus CAP und HPMCAS diente zur Feststellung, ob die Elastizität des Films erhöht werden könnte. Die daraus resultierten Ergebnisse zeigten, daß die hergestellten Filme eine poröse Struktur hatten und die überzogenen Pellets nicht gegen 0.1 N HCl resistent waren.

Die Curing-Versuche unter verschiedenen Temperaturen und Feuchten ausserhalb der Wirbelschichtanlage wurden mit einer kleinen Rezepturauswahl an überzogenen Pellets durchgeführt. Es zeigte sich, daß unter den eingesetzten Bedingungen (40 – 80 °C und bis zu 75 % r.F.) keine Verbesserung der Filmbildung stattgefunden hatte. Filme aus CAP und DEP hatten, wie ohne Curing, überdies Risse, und Filme aus CAP und DBS zeigten noch Unebenheiten.

Der Wassergehalt in einer Arzneiform hat eine große Bedeutung, weil Wasser die Hydrolyse insbesondere von CAP beschleunigen kann. Deshalb wurde der Wassergehalt mittels Karl-Fischer Titration bestimmt. Pellets, die mit einem der nichtionischen Polymere, d.h. HPMC, PVA und Sepifilm LP 010 hergestellt waren, wurden auf den Wassergehalt nach der Lagerung untersucht, um die Eigenschaft der Feuchtigkeitbarriere dieser Filmbildner zu beurteilen. Das Ergebnis war, daß gelagerte, PVA- überzogenen Pellets nach 3 Wochen nicht viel Wasser aufgenommen hatten. Der Wassergehalt in den Pellets nach 3 Wochen Lagerung lag nicht über 3 % m/m bei der höchsten belastenden Bedingung von 50 °C und 80 % r.F. Pellets, die unter Raumbedingung gelagert wurden, hatten einen Wassergehalt von ca. 1 - 2 % m/m. Ein signifikanter Unterschied des Wassergehaltes zwischen den gelagerten PVA überzogenen Pellets, den HPMC-überzogenen Pellets und den mit Sepifilm überzogenen Pellets konnte nicht festgestellt werden. Der Wassergehalt der CAP überzogenen Pellets wurde, weil sie noch nicht resistent gegen 0.1 N HCl waren, nicht untersucht.

Mittels HPLC wurde der Phthalsäuregehalt bestimmt, welcher ein Indikator für die chemische Stabilität des CAP war. Die Pellets, die mit der Rezeptur aus CAP und DEP überzogen waren, zeigten keinen höheren als in der USP XXIII erlaubten Gehalt der freien Phthalsäure an, aber höher als die Grenze in den USP XXIV und BP 1993. Dieser hohe Phthalsäuregehalt könnte aus der Hydrolyse des CAP während des Überzugsprozesses oder der Lagerung (und/oder von DEP, wenn es als Weichmacher benutzt wird) resultieren.

Der Einfluß der Lagerungsbedingungen hinsichtlich relativer Luftfeuchte in Kombination mit der Temperatur wurde untersucht, um den kritischen Punkt bei der Lagerung zu bestimmen. Die optische Beurteilung der unter verschiedenen Bedingungen (25 – 50 °C und 30 – 80 % r.F.) gelagerten Pellets hatte gezeigt, daß CAP-überzogene Pellets nicht über 40 °C und 60 % r.F. gelagert werden können, weil eine Verklebung erfolgte. Dadurch gehen die physikalischen Eigenschaften der Filme verloren. Die chemische Stabilität der magensaftresistent überzogenen Pellets könnte untersucht werden, sofern die physikalische Eigenschaft „Magensaftresistenz“ akzeptabel wäre. Diese wichtige physikalische Eigenschaft wäre die Resistenz gegen künstlichen Magensaft (0.1 N HC) über mindestens 1 Stunden, besser zwei Stunden, mit einer Freisetzung von Wirkstoffmodell von unter 10 % m/m.

Die in dieser Arbeit erhaltenen Ergebnisse zeigen, daß der nach verschiedenen Rezepturen und Prozessbedingungen mit CAP überzogenen Pellets nicht resistent gegen 0.1 N HCl bis zu 2 Stunden waren. Deshalb wurden die Prozessbedingungen und die Rezepturen fokussiert und nicht die chemische Wechselwirkung zwischen basischem Wirkstoff und sauren Polymeren.

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Scientific Publications

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Presentations

1998 DAAD-Conference Potsdam/Germany, with acknowledgement by the General Secretary of the German Academic Exchange Service (DAAD), Dr. Christian Bode
Title: Stability of acid sensitive drugs within the carrier during the coating process with aqueous enteric polymer dispersions using a fluidized bed apparatus

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