Characterization of Different Shellac Types and Development of Shellac-Coated Dosage Forms

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Yassin Farag

aus Hamburg

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Für meine Annina

Reviewer of the dissertation:	Professor Dr. Claudia S. Leopold
	Professor Dr. Detlef Geffken
Reviewer of the disputation:	Professor Dr. Claudia S. Leopold
	Professor Dr. Sascha Rohn
	Dr. Werner Pauer
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Abstract

Shellac is the purified product of the natural material lac which is secreted by the small parasitic insect Kerria Lacca on various host trees in India, Thailand and South-eastern Asia. Shellac is non-toxic, physiologically harmless and therefore listed as GRAS by the FDA. This status allows its use in food products such as coating for citrus fruits or confectionaries. Besides its use in the color industry this is its main application.

Shellac for pharmaceutical applications is usually obtained by solvent extraction. With a careful selection of the raw material this refining process allows the production of shellac types with reproducible quality. However, this refining process results in shellac in its acid form which undergoes aging. This aging process leads to changes in the material properties and is the main reason for the decline in pharmaceutical applications.
Since the introduction of aqueous ammoniacal solutions shellac has regained importance. Aqueous solutions are easy to handle and allow the production of films that lack the aging instability.

In the present work different shellac types and batches were characterized with regard to their physicochemical properties and drug release from shellac-coated dosage forms. It could be shown that the samples differed significantly in their material properties and aging behavior as well as in the drug release profiles of the coated dosage forms. Besides the origin especially the age of the samples could be identified as a critical factor.

Subsequently, the influence of the aging process on the material properties was investigated. Therefore, shellac samples were artificially aged by thermal stress. Aim of this study was the identification of a suitable parameter for the detection of aged shellac. The determination of the acid value, which is required by the pharmacopoeias for the chemical characterization of shellac, was found to be unsuitable for this purpose. It could be shown, that the glass transition temperature is a more sensitive indicator for the detection of aged shellac.

Furthermore, the influence of process parameters during the production of shellac-coated dosage forms was investigated. It could be shown that the inlet air temperature of the fluid bed coating process has a large influence on the quality of the final product. Whereas high inlet air temperatures led to continuous coating films, a reduction of the temperature resulted in cracks in the coating film and thus a loss of film integrity with most samples. The temperature sensitivity of the coating process was found to be different for the investigated shellac types.

Finally, a new concept for the formulation of shellac-coated sustained release formulations is presented. A subcoat containing different substances that interact with shellac was applied to drug pellets which were subsequently coated with shellac. It could be shown that the application of modifying subcoats is an effective means to obtain sustained release from shellac-coated formulations. The choice of a suitable substance and concentration allows tailor-made release profiles.

Shellac is a very interesting material with a broad spectrum of applications. However, different shellac types may differ widely in their material properties. These differences are even more pronounced with aged shellac. This variability in the physicochemical and mechanical properties also affects the processibility of the material and has to be considered if shellac is used in pharmaceutical applications.
However, due to its regulatory status shellac may be of interest for coating applications especially for food products where the use of other coating materials is not allowed. Hence, the subcoat formulations presented in this work offer an interesting approach for the development of sustained release drug and dietary supplement formulations.

Zusammenfassung

Schellack ist die aufgereinigte Form des Harzes Lac, welches von dem kleinen, parasitischen Insekt Kerria Lacca auf verschiedene Wirtsbäume in Indien, Thailand und Südostasien sezerniert wird. Schellack ist ungiftig, physiologisch gut verträglich und deshalb als Lebensmittelzusatzstoff zugelassen. Diese Eigenschaft ermöglicht den Einsatz als Überzugsmittel für Lebensmittel wie Zitrusfrüchte und Süßwaren, worin Schellack neben der Verwendung in der Farbindustrie seine Hauptanwendung findet.

Schellack für pharmazeutische Anwendungen wird überwiegend durch Lösemittelextraktion gewonnen. Bei einer sorgfältigen Auswahl der Rohmaterialien erlaubt es dieses Aufreinigungsverfahren Schellack mit gleichbleibender Qualität herzustellen. Endprodukt dieses Verfahrens ist jedoch Schellack in seiner Säureform, die einem Alterungsprozess unterliegt. Dieser Alterungsprozess führt zu Veränderungen in den Materialeigenschaften, was einer der Hauptgründe dafür ist, dass die Verwendung von Schellack in pharmazeutischen Anwendungen stark zurückgegangen ist.
Seit der Einführung wässrig-ammoniakalischer Lösungen konnte Schellack wieder Bedeutung gewinnen. Wässrige Schellacklösungen lassen sich leicht verarbeiten und daraus hergestellte Filme zeigen nur geringe Alterungserscheinungen.

Im Rahmen dieser Arbeit wurden unterschiedliche Schellacksorten und -chargen hinsichtlich ihrer physikochemischen Eigenschaften sowie der Wirkstofffreisetzung aus schellack-überzogenen Arzneiformen untersucht. Dabei konnte gezeigt werden, dass sich die einzelnen Proben sowohl stark in ihren Materialeigenschaften und ihrem Alterungsverhalten als auch in den Wirkstofffreisetzungsprofilen der überzogenen Arzneiformen unterschieden. Neben dem verschiedenen Ursprung wurde dabei vor allem das Alter der Schellackprobe als kritischer Faktor identifiziert.

Im Folgenden wurde geklärt, welchen Einfluss der Alterungsprozess auf die Materialeigenschaften hat. Dazu wurden Schellackproben unter Stressbedingungen künstlich gealtert. Im Rahmen dieser Untersuchung sollte eine geeignete Kenngröße gefunden werden, um gealterten Schellack zu erkennen. Die Säurezahl, die vom Arzneibuch als einzige Kennzahl für die chemische Charakterisierung gefordert wird,

hat sich dabei als ungünstig erwiesen. Es konnte gezeigt werden, dass die Glasübergangstemperatur einen viel empfindlicheren Indikator für die Erkennung von gealtertem Schellack darstellt.

Des Weiteren wurde der Einfluss von Prozessparametern bei der Herstellung schellack-überzogener Arzneiformen untersucht. Hierbei konnte gezeigt werden, dass die Zulufttemperatur beim Überzugsprozess einen erheblichen Einfluss auf die Qualität der überzogenen Arzneiform hat. Während bei hohen Temperaturen intakte Überzüge hergestellt werden konnten, führte eine Absenkung der Temperatur bei den meisten Proben zur Ausbildung von Rissen im Überzug und damit zu einem Verlust der Filmintegrität. Es stellte sich heraus, dass die Temperaturabhängigkeit des Überzugsprozesses stark von der verwendeten Schellacksorte abhängt.

Schließlich wurde ein neues Konzept zur Entwicklung schellack-überzogener Retardarzneiformen entwickelt. Arzneistoffpellets wurden mit einem Zwischenüberzug versehen, der verschiedene Substanzen enthielt, die mit Schellack wechselwirken. Anschließend wurden die Pellets mit Schellack überzogen. Es konnte gezeigt werden, dass die Verwendung modulierender Zwischenüberzüge eine effektive Methode ist, eine verlängerte Wirkstofffreisetzung mit schellack-überzogenen Arzneiformen zu erhalten. Durch die Auswahl der entsprechenden Substanz sowie deren Konzentration können auf diese Weise Arzneiformen mit maßgeschneiderten Freisetzungsprofilen hergestellt werden.

Schellack ist ein Material mit vielfältigen Anwendungsmöglichkeiten. Einzelne Schellacksorten können sich jedoch deutlich in ihren Eigenschaften unterscheiden. Diese Unterschiede sind umso stärker ausgeprägt je älter die Schellackproben sind. Diese Variabilität in den Materialeigenschaften beeinflusst auch die Verarbeitbarkeit des Materials und muss bei der Verwendung von Schellack in Arzneiformen berücksichtigt werden.
Im Gegensatz zu den meisten anderen Überzugsmaterialien ermöglicht der Status als Lebensmittelzusatzstoff eine Anwendung von Schellack in Lebensmitteln. Die in dieser Arbeit vorgestellten Retardformulierungen eröffnen daher einen interessanten Ansatz für die Entwicklung verlängert freisetzender Arzneiformen und Nahrungsergänzungs-mittel.

Contents

1. Introduction

1.1. Coated dosage forms

Film coating has become a routine operation in the production of solid oral dosage forms. There are numerous reasons for the application of film coatings to drug formulations. Polymeric film coatings can be applied to pharmaceutical solids for decorative purposes to provide gloss [1]. The incorporation of dyes and pigments into the coating films allows coloration of the dosage form e.g. to facilitate product differentiation [2-4]. Film coatings are also applied to improve the mechanical stability and reduce abrasion of the dosage form during manufacturing, shipping and storage [5, 6]. Sensitive drug formulations are film-coated to protect the ingredients from light or humidity [7]. Film coatings can mask unpleasant taste as well as odor and facilitate swallowing [8] which will improve the patient's compliance during drug therapy.

Another important function of film coatings manifests itself once the dosage form reaches the GI tract. By selection of specific coating materials the film coating allows controlled release of the drug in the GI tract: So-called enteric coatings are applied to solid oral dosage forms to protect the drug from the acidic milieu of the stomach or vice versa. Sustained release coatings deliver the drug over a long time period and allow a reduction of daily intake frequency and thus improve the compliance of the patient. Especially for such coated controlled release formulations a consistent quality of the film coating is essential to maintain reproducible release profiles and to avoid the risk of dose dumping or loss of efficacy.

The large number of applications for film coatings, the variety of coating materials and the need for reliable coating processes explains the great research effort on coated dosage forms.

1.2. Film coating materials

For each desired application a variety of different coating materials with tailor-made physicochemical properties is available. Most commonly used are polymers such as polymethacrylates [9], povidones [10] and cellulose esters and ethers [11, 12]. Povidones and polymethacrylates are synthetic polymers which are obtained by emulsion polymerisation [13, 14]. The properties of the final polymer can be adjusted by selection of specific monomers. Cellulose derivatives are semisynthetic polymers gained either by esterification or etherification of natural cellulose. The type of substituent and the degree of substitution defines the properties of the final polymer. Besides these major film coating polymers there are few other materials used for film coating applications. One of them is shellac.

The chemical properties of the coating material define the functionality of the coating film and thus the drug release characteristics of the final dosage form.

Film coatings for taste masking or moisture protection are usually not intended to modify drug release. These coatings should maintain their barrier function during storage as well as during intake of the dosage form. Once the formulation reaches the stomach the coating should dissolve rapidly and release the drug. This type of coating is usually prepared with water soluble polymers [15] but also with water insoluble, basic polymers that dissolve in the acidic milieu of the stomach [16]. However, also the application of thin layers of enteric coatings has been approved for this purpose [17, 18]. Especially in moisture protective coatings the addition of pigments such as titanium dioxide or talc to the coating film further decreases the permeability of water vapor and thus enhances moisture protection [19, 20].

Enteric coatings are applied to solid oral dosage forms to improve the chemical stability of acid-sensitive drugs [21, 22], to decrease gastric irritation [23, 24] and to target the drug to the colon [25, 26]. Enteric coatings remain intact as long as the pH is below the release pH, above which the drug is released [27, 28]. For this application generally acidic polymers are used. They are protonated and thus insoluble in the acidic environment stomach but are permeable or dissolve at a higher pH.

For the application of sustained release coatings usually water insoluble polymers are used. After swelling of the coating film or dissolution of incorporated pore formers the coating film becomes permeable and/or the drug release occurs by slow diffusion of the drug through the coating layer [29, 30].

1.3. Film formation

Water soluble coating materials are usually applied from aqueous solutions. However, many coating polymers, especially those for modified release applications, are water insoluble and cannot be applied from aqueous solutions. This is critical because the use of organic polymer solutions for the coating of pharmaceutical dosage forms has several disadvantages such as regulatory requirements, explosion hazard and limits for solvent residues in the final product. Hence, during the last decades aqueous coating systems have gained importance.

Water insoluble polymers may be applied from aqueous polymer dispersions. These coating systems are either prepared by emulsion polymerization of monomers or by emulsification of a preformed polymer resulting in latex or pseudolatex formulations, respectively. In contrast to aqueous solutions in aqueous dispersions the polymer is colloidally dispersed in water. Aqueous dispersions show comparably low viscosities even at high polymer concentrations. However, polymer dispersions are sensitive to high electrolyte concentrations, pH changes, and high shear forces [31].

There is a fundamental difference in the film forming mechanism between polymer solutions and aqueous dispersions. Film formation from polymer solutions results from the evaporation of the solvent, which leads to an increase in the polymer concentration and to an interdiffusion of the polymeric chains (Fig. 1). At higher polymer concentrations, an intermediate gel-like stage is reached. Upon further evaporation of the solvent, a solid polymeric film is obtained [32, 33].

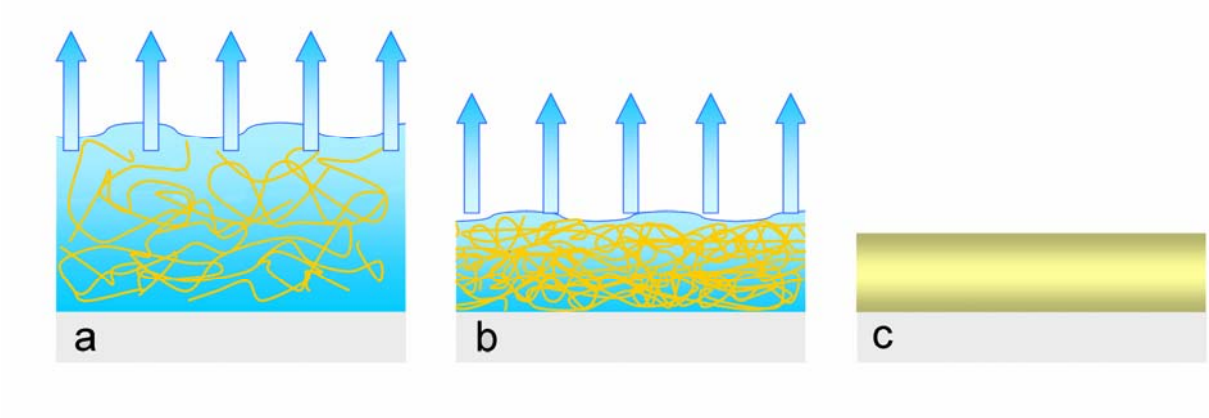

Fig. 1: Film formation from polymer solutions:
a) solvent evaporation; b) intermediate gel-like stage; c) solid film

Film formation from aqueous polymer dispersions is more complex (Fig. 2). As with the aqueous solutions, film formation starts with the evaporation of water from the coating formulation. In contrast to solutions, in aqueous dispersions latex particles are colloidally dispersed in water. As water evaporates the dispersed latex particles come into contact with each other and are forced into a closely packed, ordered array with water-filled voids. Further evaporation of water leads to particle deformation due to capillary pressure and interfacial tension and finally to coalescence of the particles. The film formation is completed by interdiffusion of polymer chains through the particle interfaces. This coalescence of the latex particles occurs only above a minimum film forming temperature. Below this temperature the particles do not coalesce resulting in a failure in film formation [34-38].

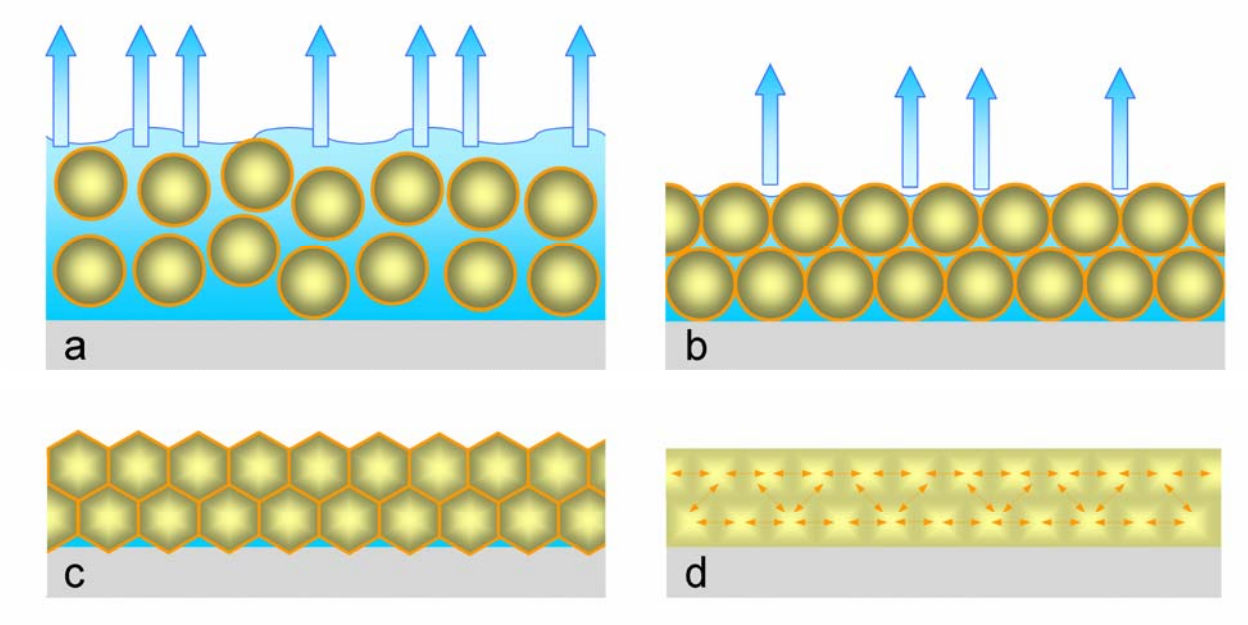

Fig. 2: Film formation from aqueous dispersions:
a) solvent evaporation; b) close-packed arrangement; c) deformation of latex particles
d) coalescence of latex particles above the MFT

1.4. Film coating process

Generally, there are three different techniques for the application of film coatings to pharmaceutical dosage forms: Pan coating, top spray fluid bed coating and bottom spray fluid bed coating which is also known as Wurster-based fluid bed coating. Because in the present work all coating experiments were performed in a Wurster coater, this process will be explained in more detail.

In the fluid bed process agitation, turbation and drying of the product is achieved by the inlet air flow [39].

In all modern coating processes the coating formulation is applied through a spraying nozzle. Whereas this spraying nozzle is located above the fluid bed in the top spray arrangement it is positioned on the bottom of the product chamber in the bottom spray arrangement, in the so-called Wurster insert. In contrast to the top spray arrangement, this configuration allows a well controlled product movement in a circulating fluid bed. The product flow in the Wurster process is schematically displayed in Fig. 3. The product is pneumatically accelerated towards the spraying nozzle by atomizing air and passes the spraying nozzle where the coating formulation is applied. Subsequently, the product leaves the Wurster insert, slows down and finally drops back into the fluid bed where the product dries and the circulation starts again.

The coating process consists of three phases. During the start up phase the inlet air preheats product and equipment. This heating prevents overwetting and facilitates film formation during the initial application of the coating formulation. During the coating phase the coating formulation is applied to the dosage form. The atomizing air transports droplets of the coating formulation from the spraying nozzle to the passing substrate. The droplets spread on the surface, dry by the inlet air and form the coating film. In the final drying phase residual solvent is evaporated to prevent sticking of the product. After that, the product is cooled down and equilibrated to ambient conditions [40].

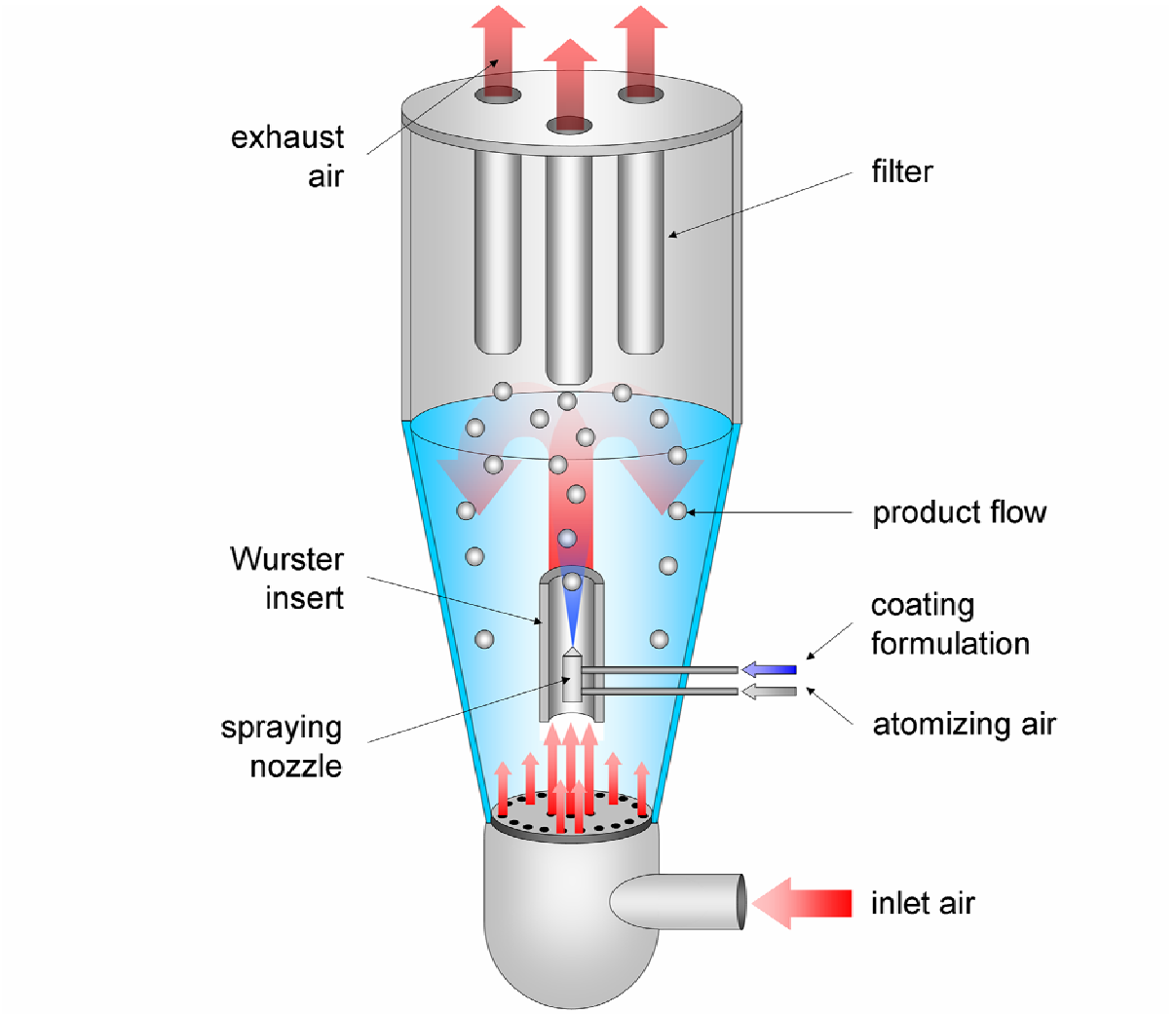

Fig. 3: Schematic description of the Wurster coating process

There are many parameters that affect the quality of the coated product. The diameter and length of the Wurster insert as well as its distance from the bottom plate influence the product movement. Inlet air pressure and atomizing air pressure must be balanced and adjusted to the coater's dimensions to assure an adequate product movement. The temperature of the inlet air defines its drying capacity and thus its moisture content. Nozzle diameter, spray rate and atomizing air pressure regulate the droplet size of the coating formulation. Hence, these parameters have to be related to each other as well as to the inlet air temperature and volume to avoid spray drying of the coating formulation on the one hand and overwetting and agglomeration of the product on the other hand [40-43].

Due to this complexity much effort is directed towards the optimization of the process parameters.

1.5. Shellac

Shellac is a natural product with interesting properties and an exceptional versatility. Shellac is the purified product of the natural resin lac which is the hardened secretion of the small, parasitic insect Kerria Lacca, popularly known as the lac insect. It is the only known commercial resin of animal origin. Lac has been known in India and China since ancient times. Its use can be traced back to recordings from India from more than 2000 years ago. The first mentioning in Europe can be referred to van Linschoten in 1596 who was sent to India by the king of Portugal [44].

1.5.1. Origin

The lac insect belongs to the family Kerriidae and superfamily Coccidae [45] to which also the scale insects and the mealybugs belong. The geographical distribution of this family is very wide and species have been collected from all continents except Europe. However, despite this wide distribution the main production of shellac takes place in South-eastern Asia especially India, Thailand and Myanmar. A number of species of the genus Kerria is known. However, Kerria Lacca is by far the most important species, producing the major percentage of commercial lac.

The lac insect lives on certain trees and bushes, the so-called lac hosts. Even though many of these lac hosts exist, only few are used for large-scale cultivation. The major hosts in India are the Palas tree (Butea monosperma), the Ber tree (Zizyphus mauritiana) and the Kusum tree (Schleichera oleosa). In Thailand the major host is the Rain tree (Samanea saman) [46].

Young larvae of lac insects are red and measure about half a millimetre in length and half as much in width. After emergence they settle down on the lac host and attach themselves to the host by piercing its bark. They suck the sap of the host and start secreting lac. Under this coating the larvae grow while they continue the secretion of lac from the inside. After eight to fourteen weeks the male insect emerges out of its lac cover, fertilizes the female and dies soon after. The female continues growing and increases lac secretion until the egg laying period [45-47]. There are two generations of lac insects and thus at least two crops per year.

The crop is collected by cutting down the lac-bearing twigs and scraping off the so-called sticklac. The yield and quality of lac may vary considerably depending on the insect species and the lac host. As the quality of the final product shellac is directly

dependent on the type of raw material, this great variety and the lack of cultivation can be critical for production of shellac with a consistent quality.

1.5.2. Refining process

The harvested sticklac is cleaned from wood and insect residues. A subsequent washing step with water removes soluble ingredients (e.g. laccaic acid) and leads to the intermediate product Seedlac (Fig. 4). Its color can vary from pale yellow to deep red depending on the insect strain and host tree.

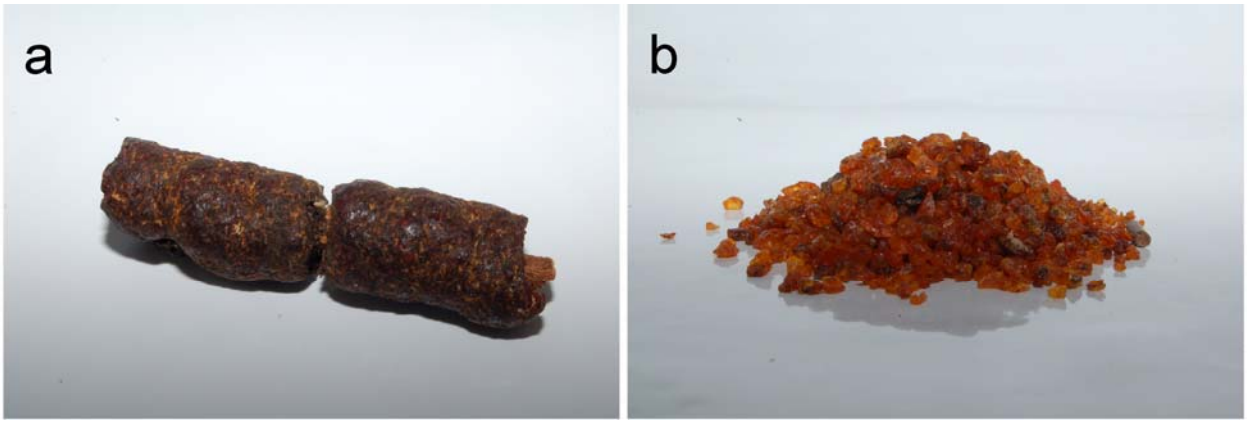

Fig. 4: a) raw material sticklac; b) intermediate product seedlac (pictures kindly provided by Stroever Schellack Bremen)

There are three different ways of refining seedlac, resulting in different shellac qualities (Fig. 5). Wax-containing shellac is obtained by the traditional melting filtration process where molten seedlac is pressed through a filter and cast to a film. After cooling the film breaks into the typical flakes [48]. This kind of shellac contains shellac wax and its color directly corresponds to that of the seedlac used.

The color of seedlac is mainly attributed to the presence of the dye erythrolaccin [49]. To obtain colorless shellac this dye either has to be eliminated or to be bleached. Bleached shellac is gained by dissolution of seedlac in aqueous alkali solutions followed by treatment with sodium hypochlorite. Shellac is then precipitated by addition of sulphuric acid. Solutions of bleached shellac are almost colorless which is advantageous for many applications. However, the bleaching process leads to changes in the molecular structure such as chlorination resulting in a higher reactivity and thus reduced stability. Shellac obtained by melting or bleaching processes is usually intended for technical use.

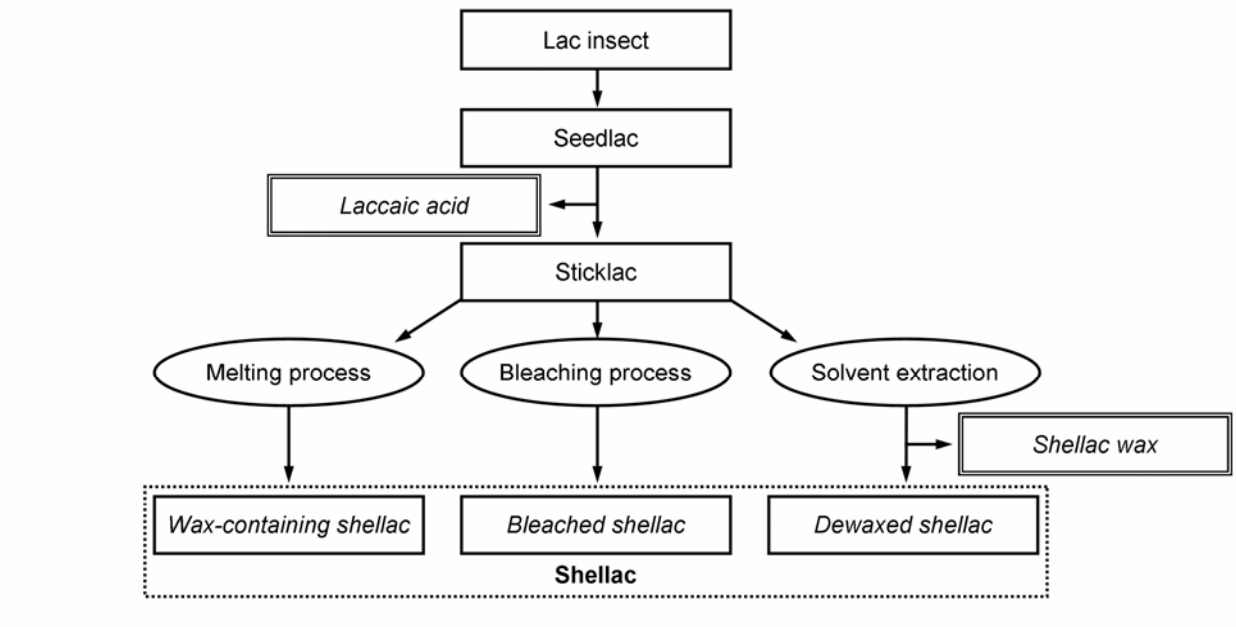

Fig. 5: Flow chart of the refining process of shellac

Shellac for pharmaceutical applications is usually dewaxed shellac that is refined by solvent extraction (Fig. 6): First, seedlac is dissolved in ethanol. Impurities and shellac wax are removed by filtration. Subsequently, the shellac solution is decolorized by addition of activated carbon. After removal of the activated carbon by a second filtration, the solvent is evaporated in a thin film evaporator and recovered. Removal of the solvent increases the concentration of the shellac solution until a hot molten shellac mass is obtained which is cast to a film. After cooling the film breaks into shellac flakes. Solvent extraction is a gentle process that does not affect the molecular structure. It allows the production of shellac with narrow specifications [50, 51].

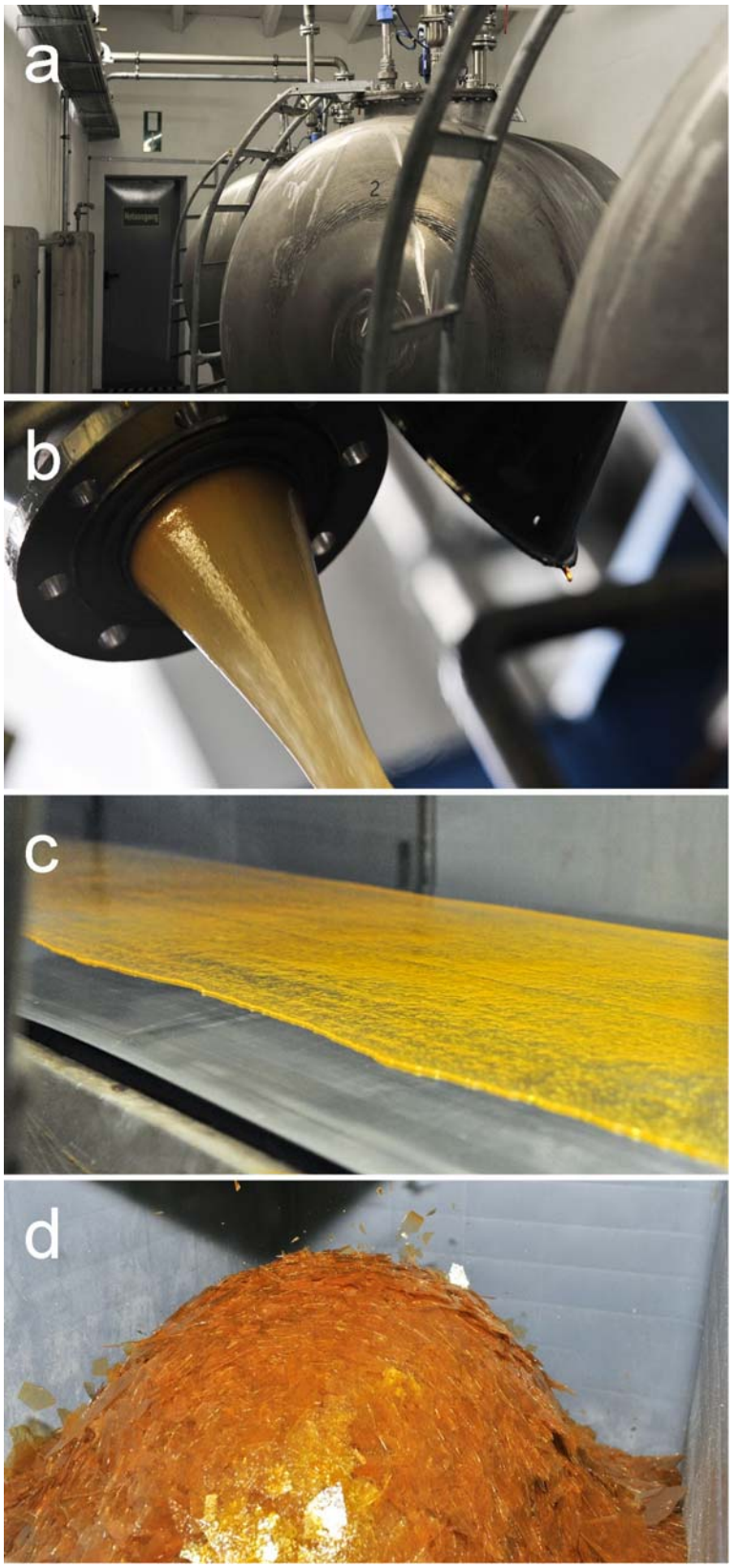

Fig. 6: Solvent extraction: a) tank with ethanolic shellac solution; b) discharge of molten shellac from a thin film evaporator; c) cooling of cast shellac film; d) shellac flakes (pictures kindly provided by Stroever Schellack Bremen)

1.5.3. Composition of shellac

Early studies on the chemical composition of lac can be referred to Hatchett in 1804 [52]. Since this time many researchers from all over the world performed studies on the composition of this complex material.

Shellac is a natural material with a complex mixture of esters and polyesters of polyhydroxy acids. The first systematic analysis of its composition was performed by Tschirch et al. in 1899 after fractionation of the material in different solvents [53]. Variations of this method have been used up to the present for separation of the shellac components [54-57]. The molecular structure of the ingredients was analyzed and revised several times [58] until the structure of the main components aleuritic acid [59] and shellolic acid [60] was clarified. It was found that depending on the shellac type aleuritic acid and homologues of shellolic acid make about 70 percent of the total shellac composition [61]. In later studies butolic acid [62, 63] and other sesquiterpenic acids related to shellolic acid [64-67] were identified as further components of the lac resin (Fig. 7). Besides the individual acids also several esters [68] as well as the position of the ester linkages [69] have been identified (Fig. 8). These findings have been confirmed and further specified by modern analytical methods such as liquid and gas chromatography [70, 71] or combined pyrolysis and mass spectrometry [72-74].

However, in spite of all this attention, the composition of shellac is still not completely understood. A reason for this might be the fact that the composition of shellac is highly variable depending on its origin and the type of refining [51].

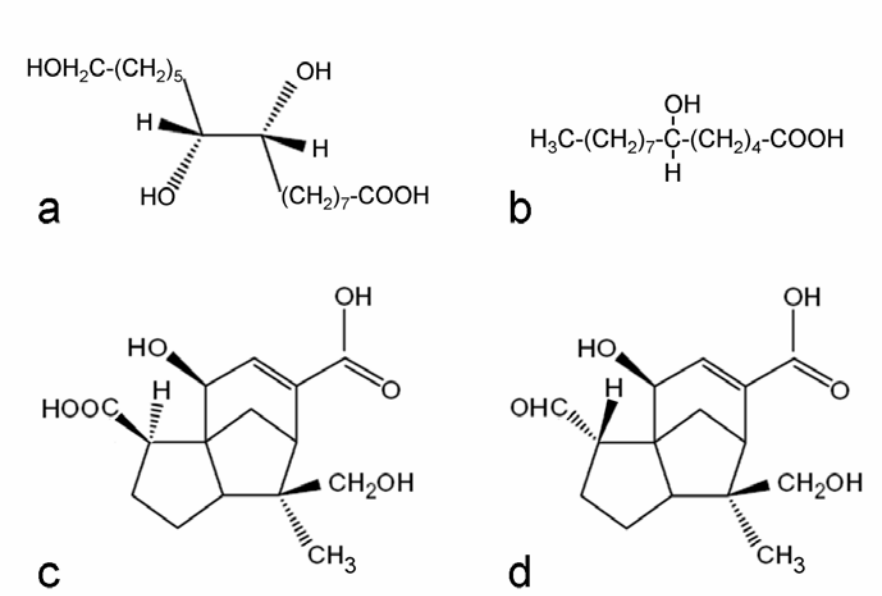

Fig. 7: Main components of shellac [56]: a) aleuritic acid; b) butolic acid c) shellolic acid; d) jalaric acid

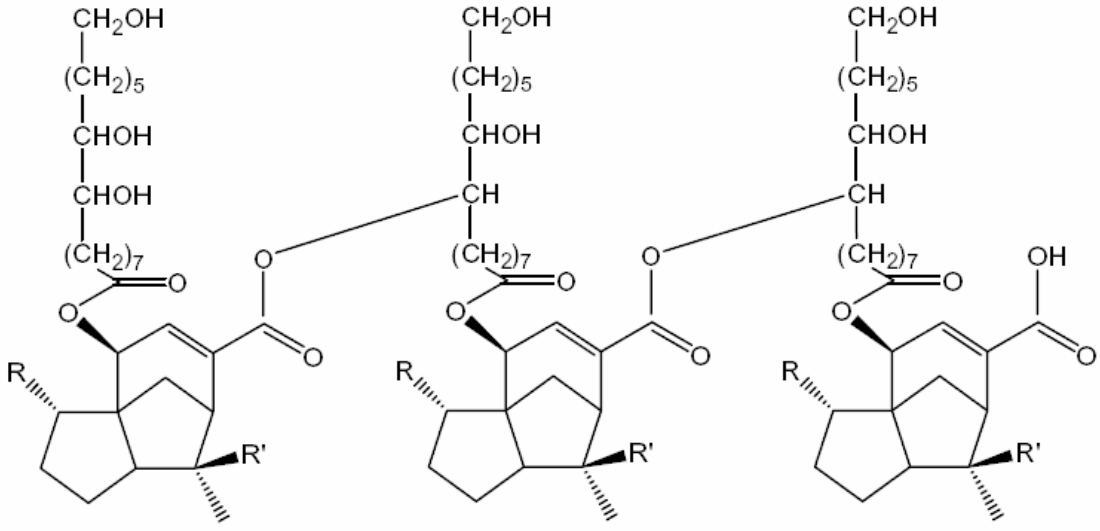

Fig. 8: Chemical structure of shellac according to Limmatvapirat et al. [75]

1.5.4. Properties of shellac

Shellac is a hard, brittle and resinous solid. It is practically odorless in the cold but evolves a characteristic smell on heating and melting. This smell can partially be referred to aleuritic acid which is known to be a starting material for the production of flavors [76, 77]. Its color is dependent on the type of seedlac and the refining process and can range from pale yellow to deep red. The color of the material is usually characterized by the Gardener [78] or Lovibond scale [79]. Shellac films provide high gloss [80], a low permeability for water vapor and gases [81] and good dielectric behavior [82].

Shellac is water insoluble. However, by addition of alkali translucent aqueous solutions can be obtained. Shellac is soluble in ethanol, methanol and partially soluble in ether, ethyl acetate and chloroform [46].

Even though few allergic reactions of the skin [83, 84] and the respiratory tract [85] are reported for shellac-containing products the material is generally regarded as non-toxic and physiologically harmless [86, 87].

The pharmacopoeias characterize shellac only by the acid value. The Ph. Eur. allows a range of the acid value between 65 and 80. The acid value of most dewaxed shellac types is about 70. Whereas the acid value of wax-containing shellac or bleached shellac can be considerably higher [46, 88], the acid value of aged shellac may be significantly lower [89].

In contrast to crystalline substances the amorphous material shellac has no sharp softening or melting point. Its glass transition temperature depends on the shellac type and varies between 30 and 50 °C for the acid form [51, 90]. It has been reported that glass transition temperatures of ammonium salts of shellac can be significantly higher [89].

Shellac undergoes aging (Fig. 9). Since most of the acids contain more than one hydroxyl group and some more than one carboxyl group it is believed that this aging is a result of selfesterification of the material [58]. This esterification is accompanied by a loss of solubility, a decrease in the acid value and an increase in the glass transition temperature [46, 89, 91]. This aging manifests itself in the so-called blocking of the material as the individual shellac flakes stick together. Several investigations deal with the prevention of shellac aging. It has been reported that proper storing conditions at temperatures below 27 °C and protection from light [88] as well as the addition of

antioxidants [91] prolong stability. It turned out that the stability of shellac can greatly be improved by salt formation with ammonia [92] or organic bases such as 2-amino-2-methyl-1-propanol [75, 93]. It is assumed that this salt formation leads to sterical hindrance and thus a reduced selfesterification.

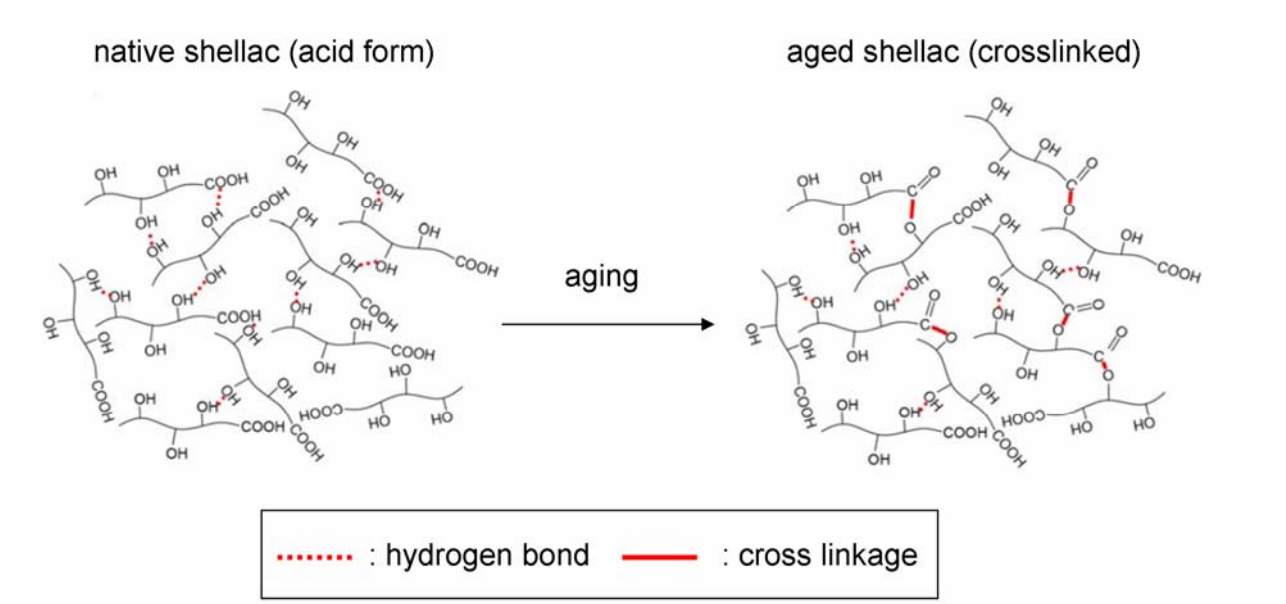

Fig. 9: Schematic description of aging of shellac; adapted from Limmatvapirat et al. [75]

1.5.5. Modification of shellac

Apart from the use of different salt forms modifications of shellac itself have been discussed to obtain the desired material properties. Shellac was partially hydrolyzed to achieve a higher solubility [94, 95]. However, it turned out that partially hydrolyzed shellac was less stable. Esterification was performed either with organic acids to improve enteric film properties [96] or with glycerol to obtain a better microencapsulating material [97, 98]. Shellac was treated with gamma radiation to enhance biodegradability [99], it was crosslinked with propanediamine [100] and t-butylacetoacetate [101] or graft polymerized with synthetic polymers to improve water resistance of shellac films [102-104] or the dielectric behavior of the material [105].

1.5.6. Applications of shellac

The use of shellac as a binding material in music records may probably be the best known application of the material [106]. Due to its brittleness shellac was soon substituted by synthetic polymers such as polyvinylchloride which shows a better mechanical stability. However, apart from music records there is still a great variety of applications for this versatile material. Some of these are listed in the following paragraphs:

Shellac has a long tradition as ingredient in colors and lacquers [107] where it has been used as protective layer on artistic objects [73, 108] and music instruments.

In dentistry shellac is used as a material for dental baseplates [48, 90] and impression trays [109]. Modified with fluoride and epoxy resins shellac has also been used as a varnish to reduce dental hypersensitivity [110, 111].

Shellac is listed as GRAS (generally recognized as safe) by the FDA. This regulatory status allows its use as additive in food products which is the most common application of shellac. Shellac is used as coating material on confectionaries [80, 112, 113] and fruits to apply gloss. Moreover, the application of shellac coatings on citrus fruits reduces the loss of water and volatile flavouring substances [114-116]. It has been reported that shellac coatings prevent early penicillum-induced postharvest decay by supporting populations of bacterial and yeast antagonists [117-119]. Also the application of shellac in the meat industry has been discussed. Cattle hides have been treated with shellac solutions during slaughter with the aim to reduce bacterial contamination of the meat [120].

The application of shellac as matrix material in so-called biocomposites [121] for the production of biodegradable composite materials may also be of interest as well as the application in paper-based packaging materials to improve water resistance [122].

1.5.7. Pharmaceutical applications

Shellac coatings for food applications are commonly applied from ethanolic solutions. This is critical, since the organic coating process requires special equipment for prevention of explosion and removal as well as recovery of the solvent. Various formulations have been developed to replace organic shellac coating systems. Aqueous formulations were prepared as dispersions by high pressure homogenization [123] or as pseudolatex [124]. Another attempt was done with shellac as material for powder polymer coating [125, 126], whereby the dosage forms are coated with micronized shellac powder and high amounts of plasticizer. However, as with the organic solutions all these alternatives contain shellac in its acid form, which undergoes aging. This aging is accompanied with a change of the physicochemical properties of the material and results in significant changes in the drug release profile of shellac-containing dosage forms. Because of this instability the use of shellac in pharmaceutical applications has declined.

Since the introduction of aqueous ammoniacal solutions, shellac regained importance for pharmaceutical dosage forms. Aqueous shellac solutions are easy to handle and show a low viscosity even at high shellac concentrations. Besides these technical advantages, the coating films prepared from these solutions result in the ammonium salt, which lacks the instability problems of the acid form [75, 92].

Due to its acidic character shellac is mostly used as an enteric coating [92, 127, 128]. However, shellac has a comparably high dissolution pH of about 7.3 [75]. This is unsuitable for a conventional enteric coating since it requires the addition of suitable additives to achieve fast release in the proximal small intestine. Organic acids [129] and hydrophilic polymers have been added to act as pore formers or swelling agents [130, 131] to enhance drug release. Shellac was modified to improve its solubility at lower pH. Partial hydrolysis by alkali treatment resulted in a better solubility [95] and improved mechanical stability of the shellac films. However, these films showed pronounced aging [94]. Another approach was the esterification of shellac with succinic acid [96]. This esterification with the dibasic carboxylic acid resulted in an increase in the acid value, which was accompanied by improved solubility.

Whereas the high dissolution pH of shellac is unsuitable for a conventional enteric coating it is of interest for colon targeting formulations [132-134]. The shellac coating layer remains intact during the passage of the stomach and the small intestine until it

reaches the colon with its higher pH. This allows the transport of drugs into the colon for a topical treatment of colonic diseases. Moreover, the peptidase activity in the colon is lower than in the upper GI tract allowing for an oral delivery of peptide drugs such as insulin [135].

Shellac has also been used as matrix former in sustained release tablet and pellet formulations [136, 137]. It could be shown that drug release was prolonged depending on the drug/shellac ratio. This sustained release effect could be further improved by a subsequent thermal treatment at different temperatures [138, 139].

Its low permeability for water vapor and gases qualifies shellac as a moisture protective coating for water sensitive formulations [140]. Moreover, its use as taste masking material has been discussed [18, 141, 142].

Another application of shellac is microencapsulation. It has been used in its natural form as the encapsulation material itself [143, 144], as additional coating on gelatin microspheres [145] or modified by esterification with glycerol to improve the encapsulation properties [97, 98, 146]. Microencapsulation has also been performed by precipitation of shellac with calcium ions to obtain water insoluble microspheres [147, 148].

This wide field of applications of this versatile material explains the great effort which is directed towards research on shellac.

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2. Physicochemical properties of various shellac types

Physicochemical properties of various shellac types

Abstract

Shellac in its acid form undergoes aging, resulting in the change of its physicochemical properties. Therefore, various shellac types were investigated as free films prepared from ammoniacal solutions and as micronized powder in its acid form. Due to its acidic character, shellac shows a pH-dependent solubility. The dissolution properties of shellac films prepared from ammoniacal solution were investigated at various pH values using a dissolution apparatus with basket holder. Micronized shellac in its acid form was analyzed using the intrinsic dissolution method (Ph. Eur.) with a paddle-over-disk apparatus. The dissolution properties of the investigated shellac types were correlated with their acid values and their thermal properties. Aging of shellac results in an increase in the glass transition temperature and a decrease in the acid value and the solubility. However, the extent of this change in physicochemical properties depends on the type of shellac, its origin, and type of refining process. Besides the acid value and the glass transition temperature, the intrinsic dissolution rate is an important parameter for the characterization of different shellac types.

2.1. Introduction

Shellac is the purified product of Lac, a natural resinous oligomer (MW ~ 1000 D) secreted by the parasitic insect Kerria Lacca on various host trees in India, Thailand and Myanmar. Shellac consists of polyesters of mainly aleuritic acid, shellolic acid and a small amount of free aliphatic acids [1, 2]. The composition varies depending on the insect species as well as the host tree from which the raw material is obtained.

After harvesting, the so-called “stick lac” is chopped and separated from wood and resin. A washing step extracts the water soluble dye laccaic acid leading to the raw material “seed lac”. There are three different processes used for refining, resulting in different shellac qualities: The melting filtration process, where melted seed lac is filtered through a cotton hose, leads to wax containing shellac. Bleached shellac is obtained by treating the dissolved polymer with sodium hypochlorite. The most suitable type of refining is the solvent extraction process. Hereby, the raw material is dissolved in alcohol, decolored by treatment with activated carbon, filtered and cast to a film. After cooling the film breaks into flakes giving shellac its typical appearance [3]. The solvent extraction process is a gentle process that does not change the chemical structure of the material. A careful selection of the raw material ensures shellac qualities with narrow specifications.

Due to its acidic character, shellac is mostly used as enteric coating. Other applications are sustained release [4], colon targeting [5] and microencapsulation [6].

Shellac is non-toxic, physiologically harmless [7] and is therefore listed as GRAS by the FDA. This makes shellac suitable even for use as food additive or in confectionaries. Shellac has excellent film forming properties, high gloss and is poorly permeable for gases and water vapor [8, 9].

Despite these advantages the use of shellac as a pharmaceutical excipient has significantly declined, because in the past shellac was mainly used as alcoholic solutions. Shellac films prepared from alcoholic solutions show pronounced hardening induced by a continuing polymerization process. This results in a loss of gastric resistance and a solubility decrease in intestinal fluids both leading to major changes in drug dissolution profiles. These are disadvantages compared to synthetic or partially synthetic polymers such as polymethacrylates and cellulose derivatives.

Nevertheless, it could be shown, that shellac films prepared from ammoniacalic solutions lack these material changes during storage [10, 11]. Thus, aqueous shellac solutions could regain importance in pharmaceutical applications.

Although shellac films prepared from aqueous solutions show a better stability, the raw material is still prepared by solvent extraction resulting in the instable acid form. Therefore, besides origin and type of refining process, the further processing to an aqueous formulation has major effect on the quality of the material.

In the present study different shellac batches of different age and origin are investigated with regard to their dissolution properties at different pH values and the dissolution rates correlated to the acid values and thermal properties.

2.2. Materials and methods

Materials

Shellac types: SSB 55 Pharma (batch 7174, manufacturing dates 07/2003; batch 109620, 04/2007; batch 110580, 11/2007); SSB MB Bys-Ber (batch 2918 A, 04/2007); SSB MB Bys-Pal (batch 2918 B, 04/2007); SSB 56 Pharma (batch 7249, 08/2003); SSB 57 Pharma (batch 7176, 07/2003); all Syntapharm, Mülheim an der Ruhr, Germany; Shellac 101 (batch 564, 12/2005), Renschel, Bremen, Germany; Platina Shellac (batch SSF-134-2004-05, 09/2005), Shraddha Seedlac Factory, Kolkata, India. All other reagents used were of analytical grade.

Methods

Preparation of the raw material

Ground shellac is prepared by milling shellac flakes in a Waring Blender fly cutter and sieving through a sieve (400 µm mesh). Ground shellac is used for the preparation of shellac solutions and for the determination of the acid values and glass transition temperatures.

For intrinsic dissolution studies, to achieve better compaction properties, and for the determination of the pK_a values, to achieve a faster dissolution, ground shellac is micronized using an Imperial Eastman air jet micronizer.

Preparation of aqueous shellac solutions

Ground shellac is dissolved in 1 % ammonium bicarbonate solution at 50 °C to obtain a final concentration of 10 % [m/V]. As the presence of excessive ammonium salt influences the dissolution properties of shellac films, the solutions are heated to 65 °C to remove the excessive ammonium salt by evaporation of free ammonia. Evaporated water is replaced. This process is repeated until a constant pH is reached. The pH of the final solutions is between 7.3 and 7.9. (Mettler Toledo MP 225 pH meter).

Acid values (AV)

The AV is determined by an acid-base titration method adapted from the European Pharmacopoeia (Ph. Eur.). Briefly, 0.4 g of ground shellac is dissolved in a mixture of diethylether and ethanol (1:1) and titrated with 0.1 M potassium hydroxide solution. Because of the dark color of the shellac solutions, instead of using a color indicator, the endpoint was determined potentiometrically (Mettler Toledo DL70ES Titrator). The AV is expressed as mg of potassium hydroxide per g of shellac. The average of five measurements is determined.

Preparation of free shellac films

Films were prepared by a casting and evaporation method: 20 ml of the shellac solutions are poured onto 10x10 cm Teflon plates. Solvent evaporation is carried out at 50 °C for 4-5 hours. After complete drying the films are carefully peeled off the plates and cut into 2x2 cm samples for dissolution testing using a sharp square formed punch. The thickness of the shellac films was determined to be 80-190 µm, measured at three spots per film using a Mitutoyo Digimatic Indicator. For thermal analysis circles with a diameter of 6 mm are prepared using a circular punch. The film samples are stored in a desiccator at room temperature over silica gel until use.

Glass transition temperatures (T_g)

Cast shellac films from aqueous solutions and ground shellac in acid form are investigated with DSC (Perkin Elmer, DSC 7, TAC 7/DX, liquid nitrogen cooling system). About 10 mg of film or powder are accurately weighed into standard aluminium pans with a punctured cap and measured twice under nitrogen atmosphere over a temperature range of -40 to 120 °C. Between the heating runs at 20 K/min an isothermal step of 1 min at 120 °C is introduced to remove excessive water. The T_g is determined from the second heating run by the Perkin Elmer Pyris software.

Dissolution profiles of free films

Phosphate buffers of different pH values (pH 7.0, 7.2, 7.4, 8.0) are prepared according to the method described in Ph. Eur. 2.9.3.: The required amount of 0.2 M sodium hydroxide solution is added to 250 ml of 0.2 M potassium dihydrogen phosphate solution. The pH value is measured using the Mettler Toledo pH meter. The 2x2 cm shellac films are accurately weighed and placed in the basket holder of a Sotax Premiere 5100 dissolution apparatus. Dissolution is performed at 37 °C and 150 rpm. The dissolution profiles are recorded spectrophotometrically at 223 nm in triplicate every two minutes using a Kontron Uvicon 930 spectrophotometer and 1 cm flow through cells at a flow rate of about 15 ml/min for 150 min.

Intrinsic dissolution

Intrinsic dissolution profiles are recorded using a Distek paddle-over-disk intrinsic dissolution kit. 80 mg of micronized shellac are weighed into a 9 mm die and compressed for two minutes at a compression force of 200 kg. The resulting sample discs are placed into the intrinsic dissolution vessels prefilled with 1000 ml of phosphate buffer (see above).

Dissolution is performed at 37 °C and 100 rpm. The dissolution profiles are recorded spectrophotometrically at 223 nm in triplicate every two minutes using a Perkin Elmer Lambda 25 spectrophotometer and 1 cm flow through cells at a flow rate of about 20 ml/min for 90 min.

The intrinsic dissolution rate is determined from the slope of the dissolution profile and expressed as mg shellac dissolved per cm^2 and min.

pK_a values

For determination of the pK_a values acid-base backtitrations are performed based on a method adapted from Parke and Davis [12]. Briefly, 0.2 g accurately weighed micronized shellac is dissolved in 8.0 ml of 0.1 M sodium hydroxide solution. Hydrolysis induced by the alkali treatment was observed, manifesting itself in a darkening of the solutions. As described in the literature [13], the effect of the hydrolysis on the pK_a values was found to be nonsignificant. Nonetheless, the samples are titrated immediately after complete dissolution and dissolution time periods are kept the same for all samples of a batch. Dissolution time periods for SSB 55 Pharma, SSB Bys Pal and SSB Bys Ber were about 20 min, for the older batches about one hour. Titrations

are done in 50 µl steps with 0.1 M hydrochloric acid and the titration profile is recorded potentiometrically. A blank curve is recorded by titration of 8.0 ml of 0.1 M sodium hydroxide solution without shellac. The shellac titration curves are subtracted from the blank curve and standardized referring to the sample weight. The pK_a could be determined from the pH value at a titration grade of 0.5. Eudragit® L and acetic acid served as reference substances.

2.3. Results and discussion

The acid value (AV) is found to be a good indicator for the quality of the shellac raw material. During storage polymerization induced by esterification takes place, resulting in a decrease in the AV. Therefore, the quality of the product can be estimated by comparison with the manufacturer's certificate of analysis.

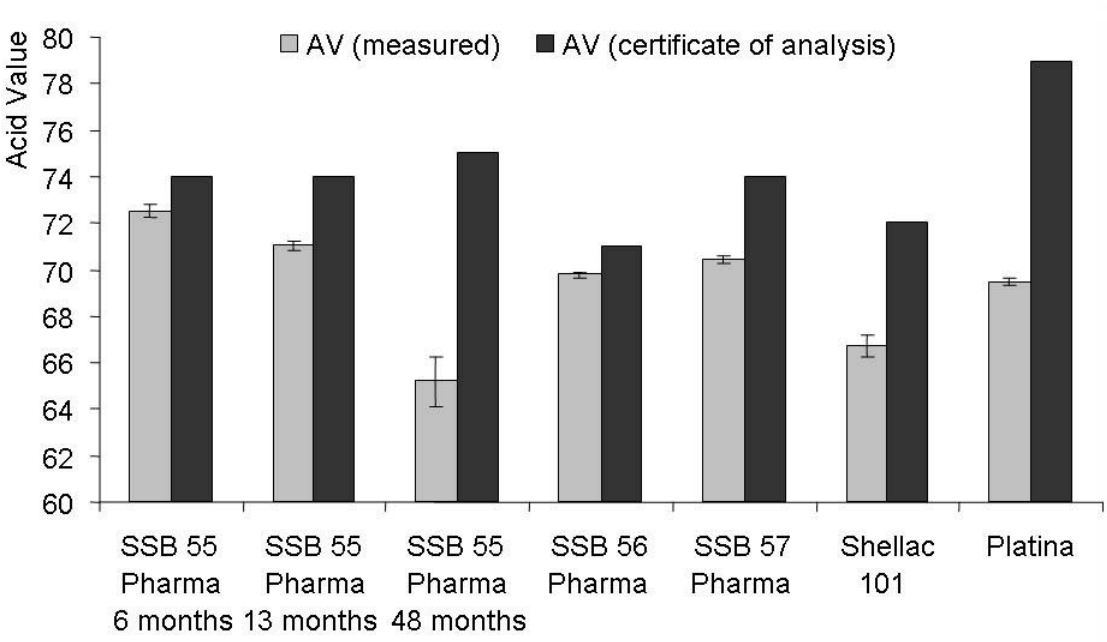

Fig. 1: Acid values of the investigated shellac types (means ± SD; n=5)

The AV is measured with seven different shellac batches of five shellac types. Compared to the manufacturer's certificate of analysis all measured AVs (Fig. 1) are decreased. The time-dependent decrease in the AV during storage is most significant with the three batches of SSB 55 Pharma. Whereas the youngest batch 110580 (6 months) already shows a decrease of 1.5 AV units, the decrease in the 13 months-batch 109620 turns out to be three AV units. The five year old batch 7174 on the other

hand shows a very pronounced decrease of almost ten AV units. The effect of aging on the AV within one batch is still under investigation.

The structural change in the material also affects the dissolution behavior in the testing solvent during AV measurement. Whereas the two younger batches dissolve completely within almost 15 min in the ethanol/ether mixture, it takes almost one hour for the oldest batch. Interestingly, the rate of AV decrease varies with the investigated shellac type. For instance, the youngest batch of SSB 55 Pharma shows a decrease of 1.5 AV units during only half a year of storage, whereas the decrease with SSB 56 Pharma is the same for a storage period of more than 4 years. Another significant decrease of almost ten AV units can be observed for Platina shellac. Interestingly, in contrast to the SSB 55 Pharma batch this decrease is not accompanied by a change in the dissolution behavior in the testing solvent.

The decrease in AV can easily be explained by the age of most of the batches and polymerization during storage. However, the rate of AV decrease and the resulting change in the material properties is different for the investigated shellac types.

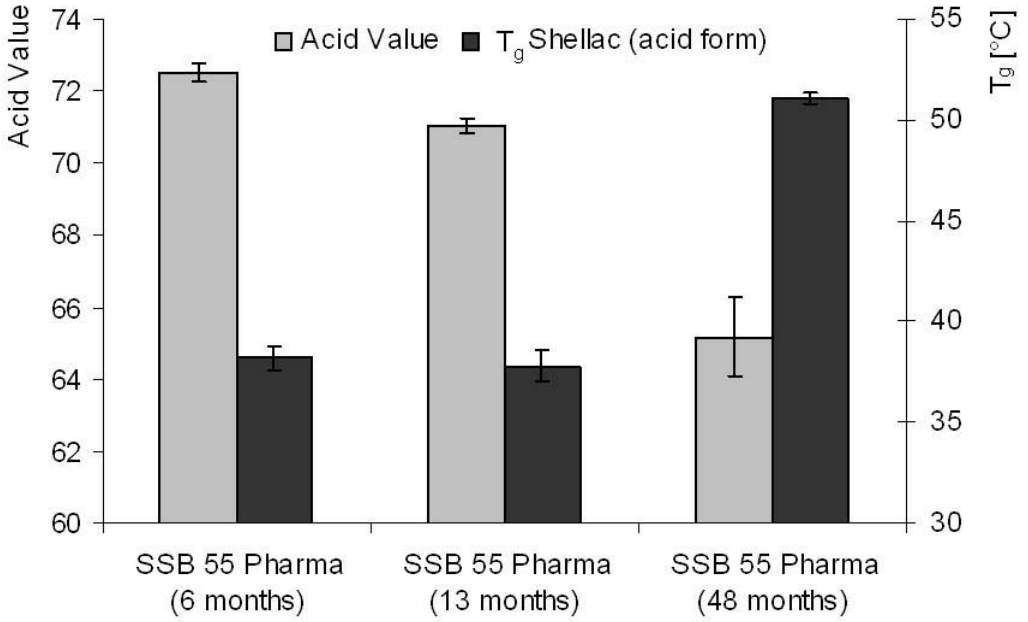

Fig. 2: Correlation of acid values and glass transition temperatures for three batches of SSB 55 Pharma (means ± SD; n = 5 (AV), n = 3 (T_g))

It can be demonstrated that the decrease in AV correlates with an increase in the glass transition temperature (T_g). As shown for the three batches of SSB 55 Pharma in Fig. 2, the T_g and AV remain almost unchanged for the younger batches, but change significantly with the older batch. During long term storage, polymerization and thus ester formation takes place resulting in the formation of additional bondings and therefore a tighter structure with higher T_g.

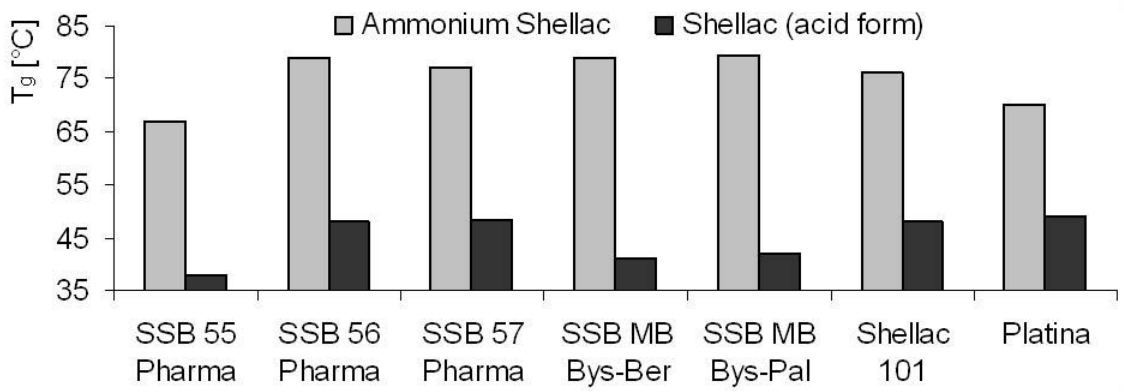

Fig. 3: Glass transition temperatures of the investigated shellac types in acid and ammonium salt form; (means ± SD; n = 3)

The T_g values of the ground shellac in its acid form shown in Fig. 3 vary from 37 °C to 49 °C. Again, the T_g values of the older batches are found to be higher compared to the younger batches of SSB 55 Pharma, SSB MB Bys-Ber and SSB MB Bys-Pal. In comparison, the T_g values of the cast films are significantly elevated due to salt formation with ammonium ions. The increase in T_g explains the brittleness of the unplasticized films prepared from aqueous solutions.

As already mentioned, the aging of shellac results in a change of dissolution properties. Aged shellac shows a reduction of gastric resistance and a decreased solubility in intestinal fluids. This can have consequences for shellac-coated dosage forms. Due to the already poor water solubility of shellac and its comparatively high dissolution pH of about 7.3 [14], a further reduction of the solubility might lead to incomplete drug release. On the other hand, acid labile drug substances could be degraded due to an increased permeability for gastric fluid caused by the loss of gastric resistance.

Various shellac films prepared from aqueous solutions are investigated with regard to their dissolution properties at various pH values. The basket holder was found to be a

suitable tool for the dissolution experiments. With the paddle stirring element the shellac films either begin to float and/or are attached to the sampling device of the dissolution apparatus. Particularly after longer dissolution periods, swollen shellac films are destroyed by shearing forces of the paddle.

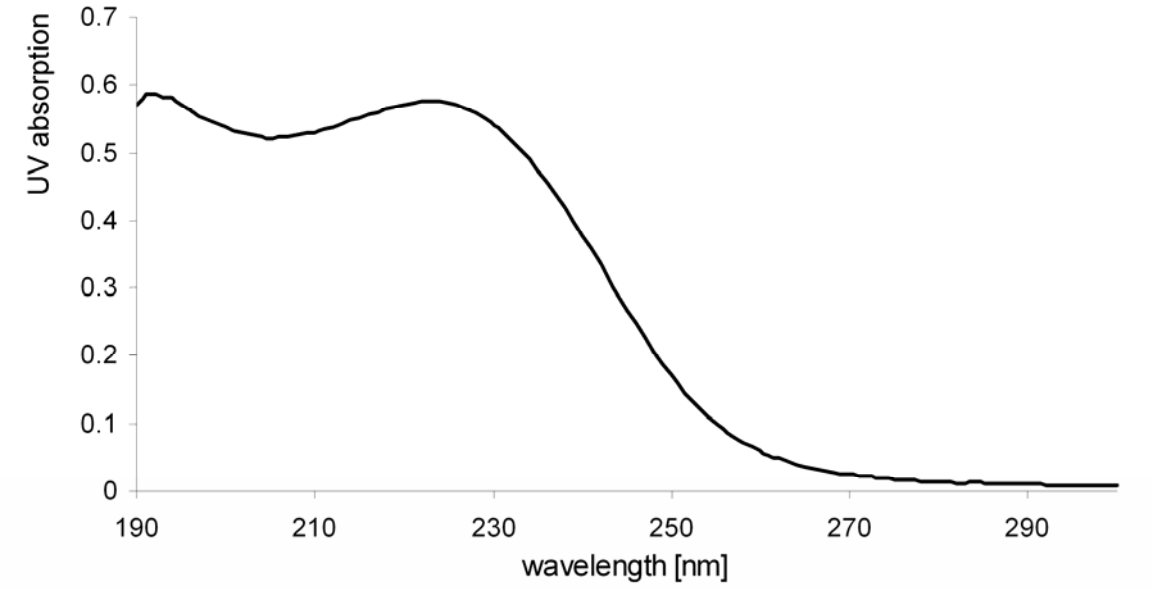

Fig. 4: UV spectrum of a solution of Shellac SSB 57 Pharma (50 µg/ml)

As shown in Fig. 4, shellac shows an UV maximum at a wavelength of 223 nm independently of the shellac type. The UV spectra of the investigated shellac types are found to be almost superimposed. This indicates that the differences between shellac types are caused only by different amounts of the various ingredients and not by their nature. The absorption coefficient $A_{1cm}^{1\%}$ is 103 - 122 depending on the investigated batch. Because only the raw material without additives is investigated, spectrophotometric detection is a suitable method for the recording of the dissolution profiles.

As shellac is a weak acid, the dissolution profiles are expected to be pH dependent. This pH dependence is confirmed for all samples. With increasing pH value the dissolution rate and the amount of dissolved shellac increases.

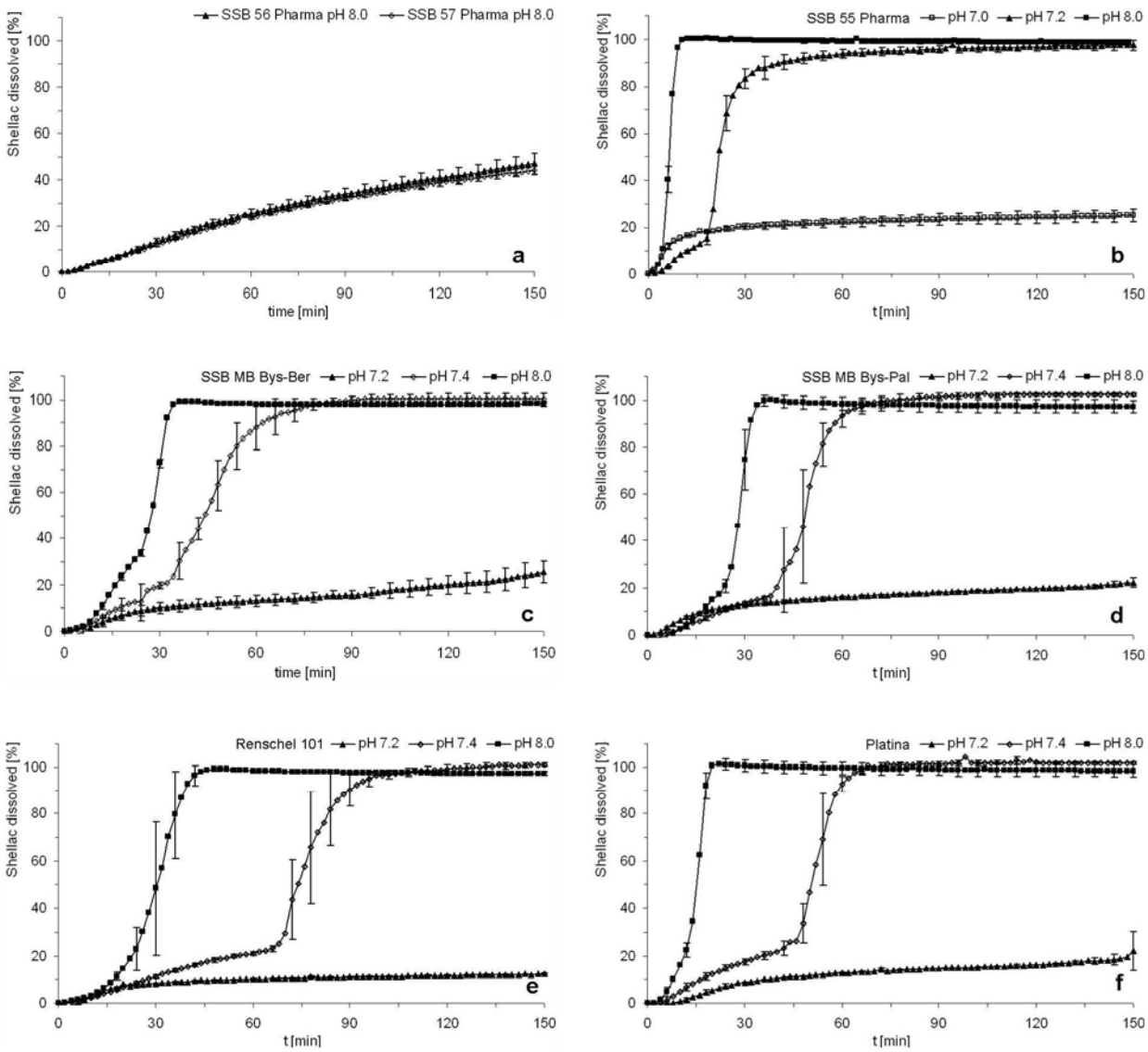

Fig. 5: Dissolution profiles of the investigated shellac types at various pH values
a) SSB 56 Pharma and SSB 57 Pharma, b) SSB 55 Pharma (batch 109620)
c) SSB MB Bys Ber, d) SSB MB Bys Pal, e) Renschel 101, f) Platina;
(means ± SD; n=3)

The recorded dissolution profiles are shown in Fig. 5. Except for the shellac batches of SSB 56 Pharma and SSB 57 Pharma (Fig. 5a), which do not dissolve completely even at pH 8.0, all samples of the investigated shellac batches show complete dissolution at pH values above 7.4. The shellac type SSB 55 Pharma already dissolves completely at a pH value of 7.2. Only the dissolution rate of the various shellac types differs. Whereas the complete dissolution of SSB 55 Pharma takes place in less than 30 min for all pH values above 7.2, the batches of SSB MB Bys Ber and SSB Bys Pal of the same age need almost one hour for complete dissolution. With the batches of Shellac 101 and

Platina Shellac an interesting phenomenon can be observed. Both batches show a step in the dissolution profile at a dissolved amount of almost 20 %. At this step a sudden increase in the dissolution rate occurs and the films dissolve completely within 15 min. This phenomenon can be explained due to a pronounced swelling and hence breaking up of the film structure. This water uptake can also be observed with the undissolved films, the color of which turns from translucent amber to off white.

However, the dissolution behavior of the films does not correlate with the observed decrease in the AV values. As observed during determination of the AV, Platina shellac, which shows a significant AV decrease of 10 units, dissolves at pH 7.4, whereas SSB 56 Pharma, showing only a slight AV decrease, does not dissolve completely even at pH 8.0. Although the AV decrease observed with SSB 55 Pharma amounted to 3 units, fast dissolution takes place already at pH 7.2. Obviously, the dissolution behavior does not only depend on the polymerization induced by esterification during storage.

Dissolution of the shellac films is an adequate method for characterization of the different shellac batches. However, from the sigmoid shape of the profiles an overall parameter describing the dissolution properties can hardly be determined. In contrast, intrinsic dissolution (ID) provides such an option. Hereby, the investigated substance is compacted by a punch in a die to achieve minimum porosity. The die containing the sample disc is placed in the dissolution apparatus providing a constant surface area to the dissolution medium. The ID rate follows a zero order kinetic if sink conditions are maintained and it only depends on the intrinsic properties of the material. The ID rate represents an appropriate material constant for the characterization of the different shellac batches.

ID experiments are performed for the batches of SSB 55 Pharma, SSB 56 Pharma and Platina shellac. Based on the results of the dissolution experiments with the shellac film samples the pH values for the ID experiments are chosen to be between 7.4 and 8.0. In preliminary experiments a compaction force of 200 kg held for two min is chosen for compression in a 9 mm die. Lower forces lead to insufficient compaction and a disruption of the sample during the dissolution experiment. Much higher compaction forces result in changes of the sample morphology, manifesting themselves in altered dissolution properties.

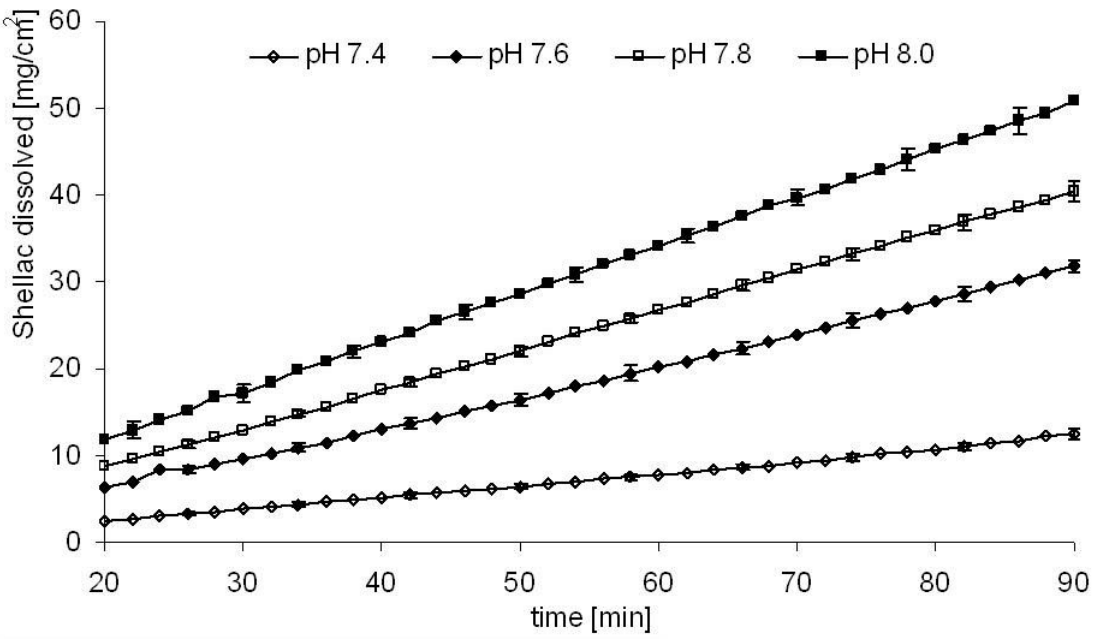

Fig. 6: Intrinsic dissolution profile of SSB 55 Pharma at various pH values (means ± SD; n=3) R^2 between 0.9999 and 0.9997

Fig. 6 shows the ID profile for batch 109620 of SSB 55 Pharma. For all samples ID profiles with a linear shape and good reproducibility are obtained. The ID rate of SSB 56 Pharma cannot be measured with these experimental parameters and is therefore not shown in Fig. 6. The poor solubility of the material does not allow maintaining sink conditions during the experiment. Therefore the ID profiles are not linear and the ID rate cannot be determined.

As in the dissolution experiments with the shellac films, a pH dependence of the ID rate can be observed (Fig. 7). The ID rate is increased at higher pH values. At pH 7.4 the ID rate is the equal with all investigated batches of SSB 55 Pharma. This is because this pH is close to the dissolution limit of shellac. Compared to the younger batches the pH dependency of the ID rate is less pronounced with the oldest batch. With the batches 106920 and 110580 of SSB 55 Pharma the ID rate/pH profiles do not differ significantly. The ID rate increases more than twice if the pH value is increased from 7.4 to 7.6. At higher pH values the ID rate does not increase to the same extent. However, there seems to be no linear relationship between the ID rate and the pH value. The similarity of the ID rate vs. pH profiles of the two batches indicates that polymerization does not affect the solubility during the first year of storage for this shellac type. However, after longer storage periods the ID rate vs. pH profiles are significantly changed.

For Platina shellac the ID rate at pH 7.4 is about twice that of the other batches at the same pH value. In contrast, at higher pH values the ID increase is not as pronounced as for the younger batches of SSB 55 Pharma.

Therefore, intrinsic dissolution is a suitable tool for the detection of polymerized shellac as well as the distinction of different shellac types.

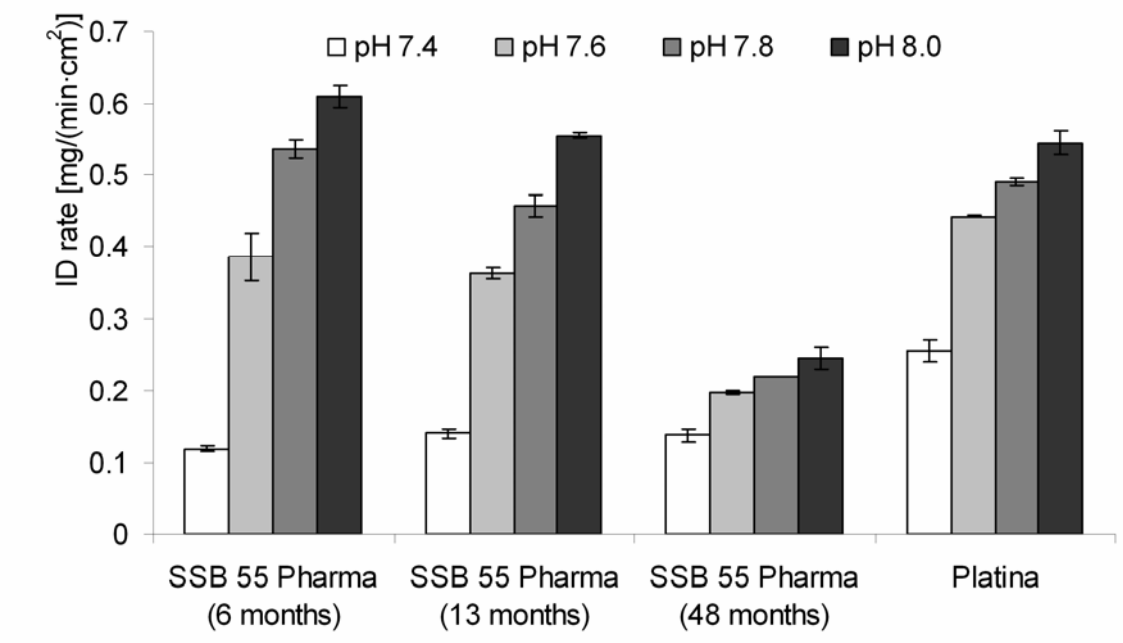

Fig. 7: Intrinsic dissolution/pH profiles of the investigated shellac types (means ± SD; n=3)

The pK_a value describes the acid strength and therefore the material's ability to dissociate. The pK_a values of the different shellac types vary between 5.8 and 6.1 (Table 1). These values do not correspond to the higher (about 1 pH unit) values found in the literature [13, 15, 16], while for Eudragit® L and acetic acid the published values are confirmed. A possible explanation for this discrepancy is the different source of the investigated shellac types. While the shellac types in this study are of Indian origin, most of the shellac types described in the literature are Thai shellacs, which are obtained by a melting filtration process and containing wax.

The pK_a range of about 0.3 units does not explain the differences in the dissolution behavior of the investigated shellac types, particularly not the almost complete insolubility of SSB 56 Pharma in the tested media.

Polymerization of shellac results in a loss of solubility while the pK_a value remains unchanged. Therefore, the determination of the pK_a value is unsuitable as a tool for the quality control of a single shellac type.

2.4. Conclusion

Even though matching the specifications of the pharmacopoeias, the physicochemical properties of the investigated shellac types such as the AV, T_g, pK_a value and dissolution profiles vary in a wide range. This is partly due to the different sources of the substance (insect species, host tree), the process of refining, but mostly a result of the different age. Dissolution experiments are found to be a suitable tool to characterize shellac. The intrinsic dissolution is an appropriate method for the characterization of the dissolution properties of shellac and therefore a useful tool for quality assurance of shellac-containing drug formulations.

Shellac raw material is provided in its acid form, which is subject to an unpredictable change in the chemical structure. For long term storage of the substance the use of ammoniacalic solutions or solid ammonium shellac is recommended.

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3. Investigation of drug release from pellets coated with different shellac types

Investigation of drug release from pellets coated with different shellac types

Abstract

Even though most commercially available shellac types meet the specifications of the pharmacopoeias, their physicochemical properties and thus drug release may vary considerably. So far a comparison of drug release from dosage forms coated with different shellac types has not been made. Drug release from pellets coated with different shellac types was investigated and the data correlated to the physicochemical properties of shellac. Theophylline pellets were coated with three different commercially available shellac types of Indian and Thai origin. The minimum coating level to achieve gastric resistance was determined for each shellac type. The drug release characteristics from the different formulations were correlated with the physicochemical properties of the shellac types such as pK_a, acid value and intrinsic dissolution rate.

Gastric resistance was achieved at comparatively low coating levels for all investigated shellac types. At pH 7.4 all investigated formulations showed complete drug release within 45 min. Drug release at pH 6.8 was prolonged and occurred by swelling and drug diffusion through the coating layer. However, the required minimum coating level and drug release profiles especially at pH 6.8 varied considerably. Of the investigated shellac types the Thai shellac stands out providing both gastric resistance at low coating levels and fast drug release at high pH 6.8.

Whereas a prediction of the release characteristic could not be made from the pK_a, the intrinsic dissolution rate turned out to be a good indicator for the drug release behavior.

3.1. Introduction

Shellac is the purified product of the resin lac. The small parasitic insect Kerria Lacca secretes lac on various host trees in India, Thailand and Southeast Asia to protect the brood from extreme temperatures and predators. The resin lac forms thick encrustations around the twigs. After harvesting, the obtained sticklac is chopped and cleaned from wood and insect residues. A washing step with water, which dissolves soluble ingredients (e.g. laccaic acid), leads to the intermediate product seedlac.

There are three different ways of refining shellac, resulting in different shellac qualities.

Wax-containing shellac is obtained by the traditional melting filtration process where molten seedlac is pressed through a filter and cast to a film. After cooling the film breaks into the typical flakes. The color of this type of shellac corresponds to that of the seedlac used.

Bleached shellac is gained by dissolution of seedlac in aqueous alkali solutions and followed by treatment with sodium hypochlorite. Shellac is precipitated after addition of sulfuric acid. Solutions of bleached shellac are almost colorless, which can be advantageous in many applications. However, the bleaching process leads to changes in the molecular structure such as chlorination resulting in a higher reactivity and thus reduced stability.

Shellac obtained by melting or bleaching processes is usually intended for technical use. Shellac for pharmaceutical applications is usually refined by solvent extraction: Seedlac is dissolved in ethanol. The obtained solution is filtered and decolorized by addition of activated carbon. After a second filtration step the solvent is evaporated and the resulting film breaks into flakes. Solvent extraction is a gentle process that does not affect the molecular structure. It allows the production of shellac with narrow specifications [1].

Shellac with a molecular weight of about 1000 Da mainly consists of polyesters of aleuritic acid and shellolic acid as well as a small amount of free aliphatic acids [2, 3]. The composition varies depending on the insect species as well as the host tree from which the raw material is gained.

Shellac is widely used in the dye industry as a component in lacquers and varnishes [4] because of its good film forming properties and water resistance. It is non-toxic, physiologically harmless [5] and is therefore generally recognized as safe (GRAS) by the FDA allowing its use as additive in food products where shellac already plays a

major role as coating material for citrus fruits [6] or confectionaries. The GRAS status opens the field also for modified release applications with the regulatory status of a food product or nutritional supplement such as vitamin formulations. In addition, its natural origin from renewable resources may be of certain ideological interest at least for marketing purposes.

In addition to the excellent film forming properties of the material shellac films provide a high gloss and a low permeability for water and gases [7]. This low permeability allows the use of shellac as protective coating or in taste masking applications [8-10].

Due to its acidic character, shellac is often used as enteric coating [11, 12]. Other applications are sustained release [13], microencapsulation [14], and colon targeting [15].

Despite all these advantages the use of shellac as a pharmaceutical excipient has declined. Since the properties of this natural material are strongly dependent on the raw material used, a consistent shellac quality requires a careful selection of the seedlac. Otherwise, there is a risk of batch to batch variations. In addition, shellac coatings prepared from alcoholic solutions as well as shellac raw material consist of shellac in its acid form which undergoes aging. This aging process is a result of polymerization and manifesting itself in a hardening of the material [16, 17]. Aging of shellac is accompanied by a loss of gastric resistance and a decrease in solubility in the intestinal fluids. This is a major disadvantage in comparison to synthetic and partially synthetic polymers such as polymethacrylates and cellulose derivates.

Since the introduction of aqueous solutions, shellac could regain importance. Although shellac is water insoluble, aqueous solutions can be obtained by addition of volatile alkali such as ammonium carbonate. These solutions are translucent and show a low viscosity even at higher shellac concentrations allowing for a quick mass increase of the coating film during the coating process. In addition to the technical advantages of aqueous compared to organic coating solutions, shellac films prepared from aqueous ammoniacal solutions show a good long term stability [11]. It has been reported that chemical stability may be even further improved by salt formation with other counter ions such as 2-amino-2-methyl-1-propanol [18].

Many publications are available on shellac and its use in pharmaceutical applications. However, in most publications the shellac-containing drug formulations are discussed without further specification of the type and origin of the shellac used. Due to its natural character and different origin the physicochemical properties and thus drug release may

vary. Nevertheless, a comparison of different shellac types and their effect on drug formulations has not yet been drawn.

The pharmacopoeias classify different shellac types only by the way of refining. A chemical characterization is done only by the determination of the acid value. As shown in previous studies the physicochemical properties of shellac may differ widely even if the pharmacopoeias´ specification for the acid value is met [16]. This requirement may be fulfilled even with aged shellac, which is completely unacceptable for pharmaceutical applications.

In the present study theophylline pellets were coated with different shellac types. The minimum coating level to achieve gastric resistance was determined. Drug release below and above the dissolution pH of shellac was investigated. The drug release characteristics were correlated with the physicochemical properties of the investigated shellac types.

3.2. Materials and methods

Materials

The following types of shellac were investigated: Marcoat™ 125 (Marcoat), ready to use shellac solution (25 % [w/w]) prepared from Bysakhi shellac of Indian origin (Emerson Resources, Norristown, PA, USA); SSB 55 Pharma (SSB 55); Kushmi shellac flakes of Indian origin (Stroever Schellack Bremen, Germany); Pearl N811F (Pearl), shellac flakes of Thai origin (Gifu Shellac, Gifu, Japan). All shellac types were refined by solvent extraction. The used theophylline pellets were immediate release matrix core pellets obtained by extrusion and spheronization containing 96.5 % theophylline (donation from Temmler, Ireland). Ammonium bicarbonate, potassium dihydrogen phosphate, sodium chloride, sodium hydroxide and hydrochloric acid were of analytical grade and purchased from Carl Roth, Karlsruhe, Germany

Methods

Processing of shellac raw material

Ground shellac was prepared by milling shellac flakes in a Waring Blender fly cutter (Waring, Torrington, CT, USA) and sieving it through a sieve (400 µm mesh). Ground shellac was used for preparation of shellac solutions and for determination of the acid value.

For determination of the pK_a value and the intrinsic dissolution rate micronized shellac was used. Approximately 10 g of ground shellac were micronized at 400 rpm for 3 min in a Fritsch Pulverisette 6 planetary mono mill (Fritsch, Idar-Oberstein, Germany) equipped with a 250 ml zirconium oxide grinding bowl prefilled with 30 zirconium oxide grinding balls (Ø 10 mm). The mean particle size (x_{50}) was 120 µm (x_{16}=60 µm; x_{84}=200 µm) determined from a 2 g sample with a HELOS laser diffraction spectrometer equipped with a RODOS dry dispersion system (all from Sympatec, Clausthal-Zellerfeld, Germany).

Acid value (AV)

The AV was determined by an acid-base titration method adapted from the European Pharmacopoeia (Ph. Eur.). Briefly, 0.4 g of ground shellac was dissolved in a mixture of diethylether and ethanol (1:1) and titrated with 0.1 M potassium hydroxide solution. Because of the dark color of the shellac solutions the endpoint was determined potentiometrically (Mettler Toledo DL70ES Titrator, Greifensee, Switzerland). The AV is expressed as mg of potassium hydroxide per g of shellac. The mean of five measurements was determined.

Preparation of aqueous shellac solutions

Ground shellac was dissolved in 1.5 % [w/V] ammonium bicarbonate solution at 50 °C to obtain a final concentration of 15 % [w/w]. As the presence of excess ammonium salt influences the dissolution properties of shellac films, the solutions were heated to 65 °C to remove the excessive ammonium salt by evaporation of the resulting free ammonia and carbon dioxide. Evaporated water was replaced. This process was repeated until a constant pH was reached. The pH of the final solutions was between 7.4 and 7.8. (Mettler Toledo MP 225 pH-meter, Greifensee, Switzerland).

Coating of theophylline pellets

Prior to the coating experiments the theophylline pellets were characterized with regard to their size and weight. The pellet diameter was determined using a Wild M3 microscope (Wild, Völkermarkt, Austria) equipped with a Zeiss AxioCam ICc and AxioVision software (Jena, Germany) by calculating the mean diameter of 500 pellets. The required shellac mass was calculated from the overall pellet surface and the desired coating level for the respective batch.

The Marcoat solution was diluted to a final concentration of 15 % [w/w] with demineralised water. The other aqueous shellac solutions were used as prepared. 50 g of immediate release theophylline pellets were removed from dust and coated with the aqueous shellac solutions in a Mini Glatt fluid bed coater (Glatt, Binzen, Germany) with Wurster insert (Ø 30 mm, 10 mm gap). The coating solutions were applied using a 0.5 mm two-way nozzle at a spraying rate of 0.4 g/min to achieve final coating levels of 0.5 mg/cm^2, 1 mg/cm^2 and 2 mg/cm^2, respectively. Atomizing air pressure was adjusted to 0.6 - 1.1 bar according to the weight gain of the pellets and the inlet air temperature was set to 60 °C at 14 m^3/h.
To avoid the effect of residual water, the pellets were stored in a desiccator over silica gel at least for 24 h before further processing.

Calculation of the coating level (CL)
The average coating level was determined as mass of shellac ($m_{shellac}$) applied to the pellet surface (A).

$$CL = \frac{m_{shellac}}{A} \qquad \text{(eq. 1)}$$

Before coating the theophylline pellets were characterized with regard to their average mass ($m_{uncoated\ pellet}$) and radius (r). The theophylline content ($c_{uncoated\ pellet}$) was determined spectrophotometrically at 275 nm after dissolution of approximately 150 mg of the uncoated pellets in 0.1 M NaOH (Lambda 25, Perkin Elmer, Waltham, MA, USA).
After coating, a sample of approximately 150 mg shellac-coated pellets (m_{sample}) was withdrawn and dissolved in 0.1 M NaOH using an ultrasonic bath. The theophylline content of this sample ($m_{theo\ sample}$) was determined as described above.
The mass of shellac in the sample may be calculated from the difference between the mass of the sample and the mass of the cores (m_{cores}) in the sample.

$$m_{shellac} = m_{sample} - m_{cores} \qquad \text{(eq. 2)}$$

$m_{shellac}$: mass of shellac in the sample [mg]
m_{cores}: mass of pellet cores in the sample [mg]
m_{sample}: mass of the sample [mg]

Due to the applied coating film, the relative mass of theophylline in the sample (= coated pellets) is decreased compared to the uncoated pellets. The mass of pellet cores in the sample can be calculated as follows:

$$m_{cores} = 100 \cdot \frac{m_{theo\ sample}}{c_{uncoated\ pellets}} \qquad \text{(eq. 3)}$$

$m_{theo\ sample}$: theophylline mass in the sample [mg]

$c_{uncoated\ pellets}$: theophylline content of uncoated pellets [%]

The surface area of the sample was calculated from the average radius and the number of pellets (n) which is determined from the mass of one uncoated pellet and the mass of cores in the sample:

$$n = \frac{m_{cores}}{m_{uncoated\ pellet}} \qquad \text{(eq. 4)}$$

n: number of pellets in the sample

$m_{uncoated\ pellet}$: average mass of one uncoated pellet [mg]

$$A = 4\pi r^2 \cdot n \qquad \text{(eq. 5)}$$

r: average radius of uncoated pellets [cm]

A coating level of 1 mg/cm^2 corresponds to a weight gain of 8 % (w/w) and a coating thickness of 10 µm determined microscopically from the average diameter increase of at least 500 pellets.

Dissolution experiments

Dissolution tests were performed according to the Ph. Eur. with approximately 150 mg pellets in 1000 ml dissolution medium. Gastric resistance was tested in simulated gastric fluid (pH 1.2) using the paddle apparatus (Sotax AT 7, Allschwil, Switzerland) at 100 rpm and 37 °C for 2 h. Drug release was measured in phosphate buffers (0.05 M) below (pH 6.8) and above (pH 7.4) the dissolution pH of shellac. The pellets remained on the bottom of the vessel throughout the dissolution test.

Dissolution profiles were recorded spectrophotometrically at 271 nm using 1 mm flow through Quartz cells.

pK_a values

For determination of the pK_a values acid-base backtitrations were performed based on a method adapted from Parke and Davis [19]. Briefly, 0.2 g of micronized shellac, accurately weighed, was dissolved in 8.0 ml of 0.1 M sodium hydroxide solution. Longer dissolution time periods led to hydrolysis of shellac by this alkali treatment, manifesting itself in a darkening of the solutions. It is described in the literature that the effect of hydrolysis on the pK_a values is nonsignificant [20]. Our experiments confirmed this assumption. However, the samples were titrated immediately after complete dissolution and dissolution time periods were kept the same for all samples. Titrations were done in 50 µl steps with 0.1 M hydrochloric acid and the titration profile was recorded potentiometrically. A blank curve was recorded by titration of 8.0 ml of 0.1 M sodium hydroxide solution without shellac. The shellac titration curves were subtracted from the blank curve and standardized referring to the sample weight. The pK_a value was determined from the pH value at a titration grade of 0.5.

Intrinsic dissolution rate (ID rate)

Since the coating with shellac was applied from aqueous ammoniacal solutions, the ID rate was also determined with the salt form for a better comparability. Therefore, 20 ml of shellac solution were poured onto Teflon plates and dried at 40 °C for 4-5 hours. The resulting film was carefully peeled off the plate and stored in a desiccator over silica gel at room temperature for at least 24 h. Afterwards the film was micronized as was done with the samples for the pK_a value determination.

80 mg of micronized sample were weighed into the die (9 mm diameter) of a paddle-over-disk ID apparatus and compressed for two minutes at a compression force of 200 kg. Dissolution was performed in intrinsic dissolution vessels at 37 °C and 100 rpm in 1000 ml phosphate buffer (pH 7.4). The dissolution profiles were recorded spectrophotometrically at 223 nm in triplicate using 1 cm flow through Quartz cells. The intrinsic dissolution rate was determined from the slope of the dissolution profile and expressed as mg shellac dissolved per cm^2 and min.

3.3. Results and discussion

Acid value (AV)

As described earlier the solvent extraction process provides shellac raw material in its acid form which is less stable and subject to aging. Except for Marcoat, which is already an ammoniacal aqueous solution, the AV was determined and compared to the manufacturer's certificate of analysis to confirm the shellac quality (Table 1). For SSB 55 and Pearl shellac flakes the AV complied with the certificate of analysis. Thus, these raw materials are suitable for further processing.

Preparation of aqueous shellac solutions

Shellac is generally classified by the Lovibond color index which is determined from a 20 % ethanolic solution of the material [21]. However, the color difference of the investigated shellac types was also apparent with the prepared aqueous solutions. The bright yellow color of the SSB 55 solution was much lighter than the darker Marcoat or the deep orange Pearl solution. This difference in the color may be a result of the different origin of the investigated materials but most likely due to the discoloration treatment with activated carbon during the refining process.

Coating experiments

Process times varied between 45 min for the 0.5 mg/cm^2 batches and 200 min for the 2 mg/cm^2 batches. Coating yields were at least 95 % and above for a CL of 0.5 mg/cm^2 and decreased with increasing CL to about 80 %. This decrease may be explained by the initially good adhesion of the coating solution to the pellet core. Later, once a continuous film is formed on the pellet surface, the adhesion of droplets to this smooth surface is reduced.

Dissolution experiments

The acidic character of shellac allows its use as an enteric coating. In Fig. 1 drug release profiles at pH 1.2 are shown. As expected, drug release was reduced with increasing CL with all shellac types. The minimum CL to achieve gastric resistance (< 10 % drug release within 2 h) was low compared to other coating polymers used for enteric coating. With Marcoat and Pearl gastric resistance could be achieved even at a CL of only 0.5 mg/cm^2. Pellets with a CL of 1 mg/cm^2 SSB 55 exceeded the drug

release limit only after 110 min. At a CL of 2 mg/cm^2 the amount of drug released within two hours was negligible with all shellac types.

Shellac has a comparatively high dissolution pH of about 7.3 [18]. This is disadvantageous if a fast release in the proximal small intestine is desired. Various attempts have been made to improve drug release from shellac-coated formulations at lower pH. One approach was the addition of pore formers or swelling agents such as hydrophilic polymers, water soluble plasticizers or aliphatic acids to the coating solution [22]. Another approach was the modification of shellac itself by partial hydrolysis [20]. Although the dissolution pH could be reduced, hydrolyzed shellac was found to be less stable than the unmodified material [23].

Because of the high dissolution pH drug release was measured not only at the standard pH of 6.8 for testing of enteric coated dosage forms (Ph.Eur.) but also at pH 7.4, which is above the dissolution pH of the material.

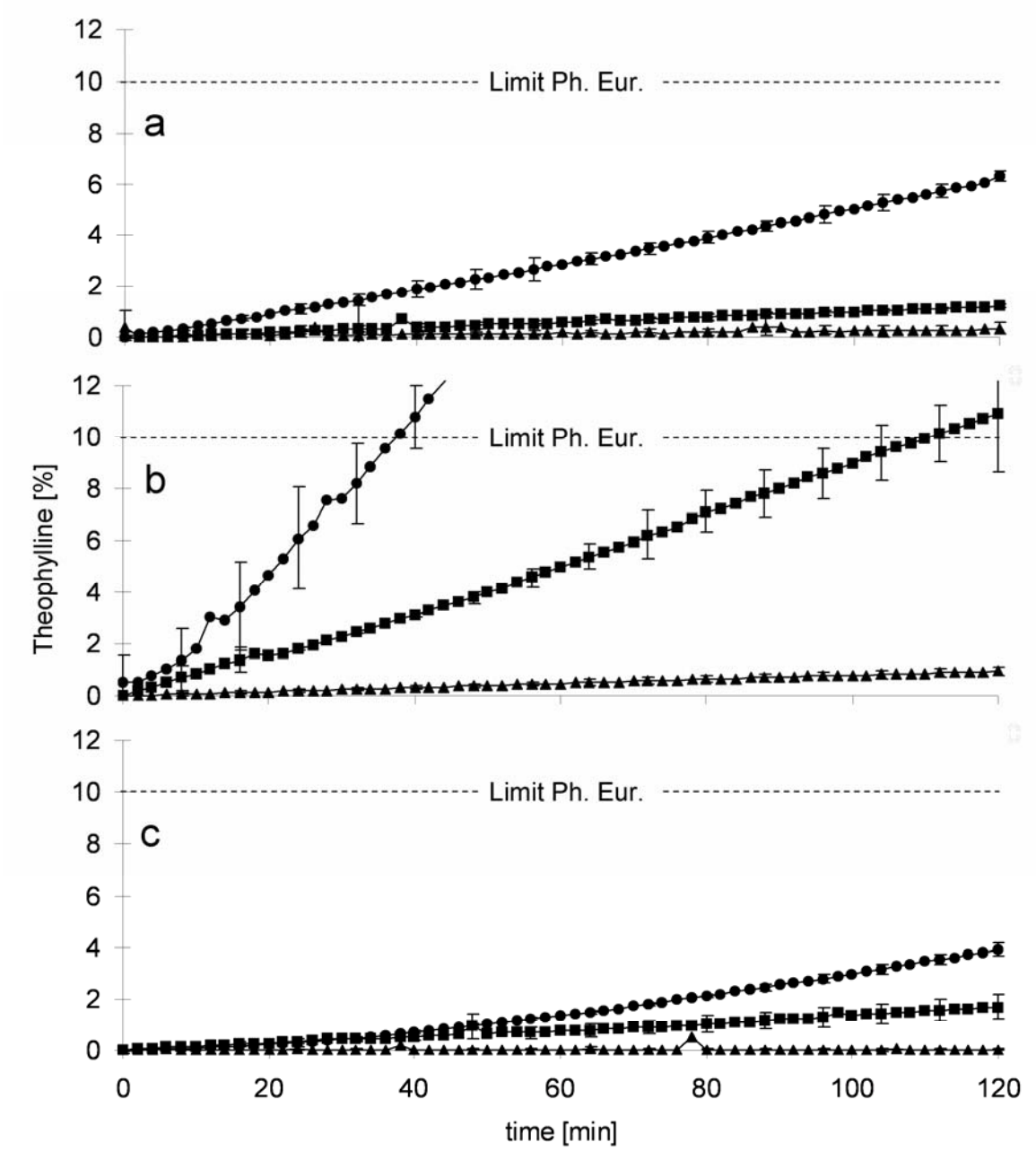

Fig. 1: Influence of the coating level on gastric resistance (means ± SD; n=3)
Coating level: ● 0.5 mg/cm^2 ■ 1 mg/cm^2 ▲ 2 mg/cm^2
a) Marcoat; b) SSB 55; c) Pearl

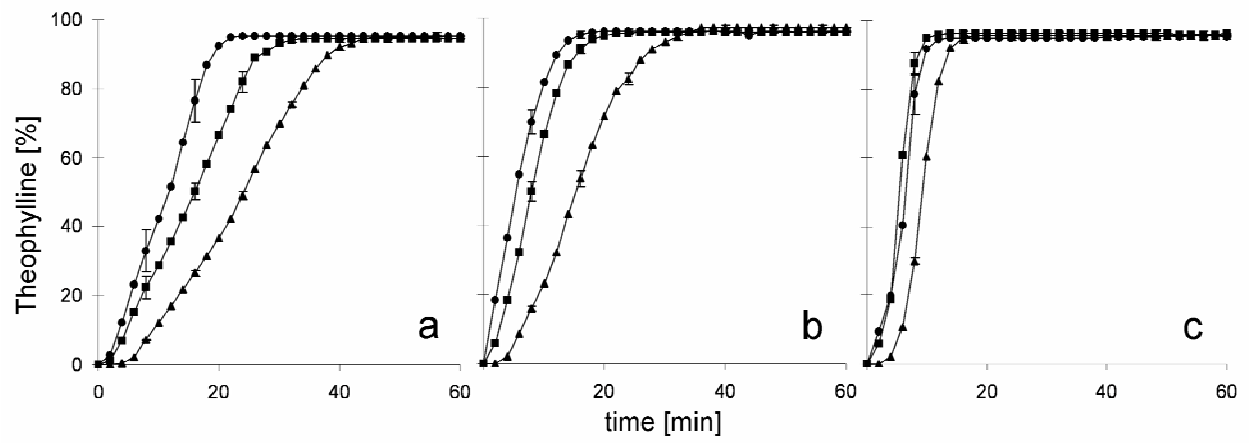

Fig. 2: Influence of the coating level on drug release at pH 7.4 (means ± SD; n=3)
Coating level: ● 0.5 mg/cm² ■ 1 mg/cm² ▲ 2 mg/cm²
a) Marcoat; b) SSB 55; c) Pearl

The results of the dissolution tests at pH 7.4 are shown in Fig. 2. With all formulations complete drug release was observed within 40 min. Fastest drug release was monitored with Pearl-coated pellets. Interestingly, drug release from pellets coated with this shellac type was almost independent of the CL. All formulations coated with the Thai shellac released the complete dose within a time period of 10-15 min.

In contrast, drug release from pellets coated with Marcoat and SSB 55 was much slower and clearly dependent on the CL.

Formulations with the lowest CL of SSB 55 showed drug release as fast as pellets coated with the highest CL of Pearl. A higher CL further delayed drug release. Formulations with 1 mg/cm^2 SSB 55 released the complete dose within 20 min, those with 2 mg/cm^2 within 35 min.

For formulations coated with Marcoat drug release was even slower and the dependence on the CL was more pronounced. However, all formulations released the complete dose within 45 min.

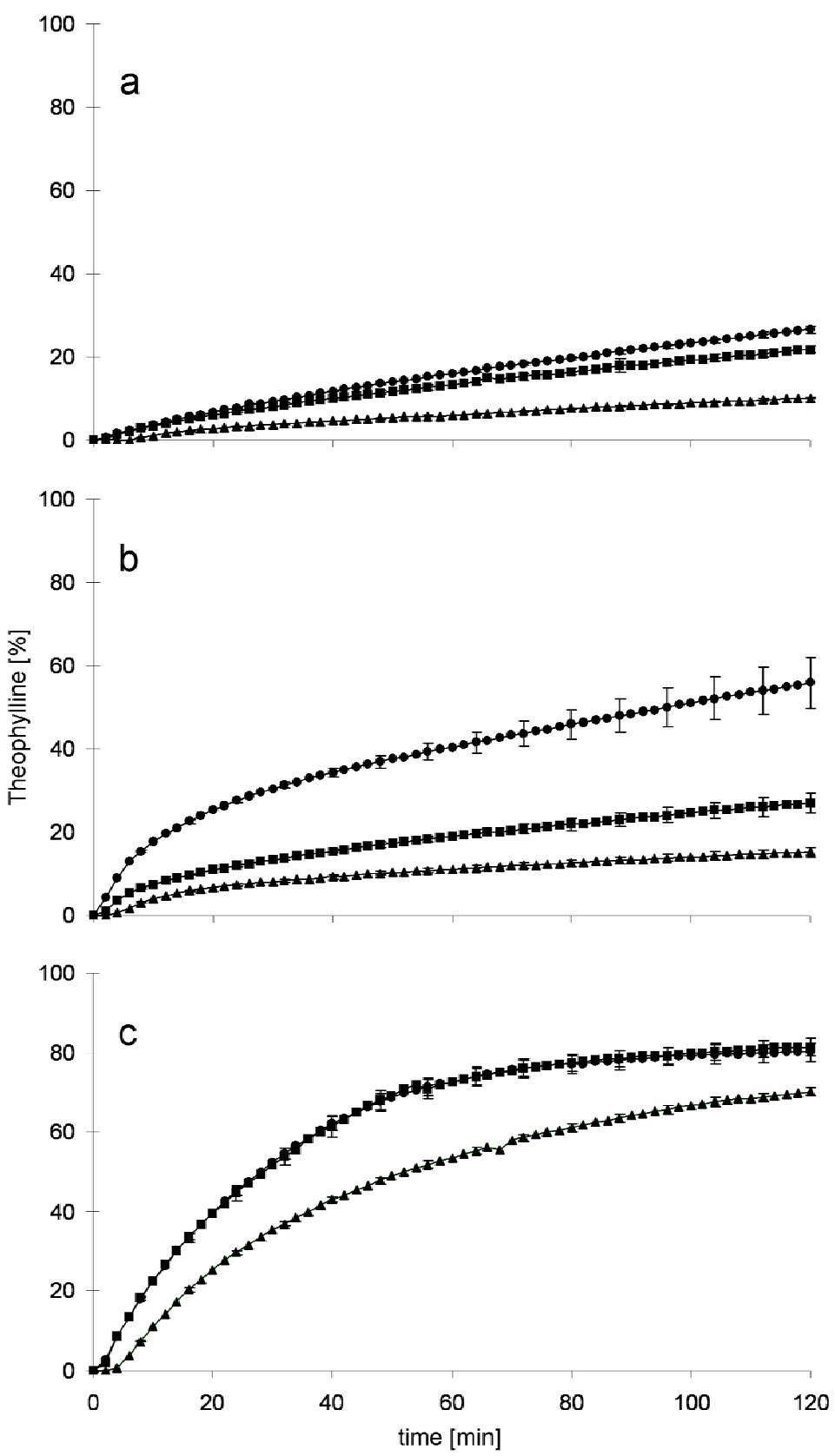

Fig. 3: Influence of the coating level on drug release at pH 6.8 (means ± SD; n=3)
Coating level: ● 0.5 mg/cm² ■ 1 mg/cm² ▲ 2 mg/cm²
a) Marcoat; b) SSB 55; c) Pearl

At pH 6.8 pronounced differences in the drug release profiles between the investigated shellac types were apparent (Fig. 3). This pH is below the dissolution pH of shellac. Therefore, drug release was not the result of shellac dissolution and subsequent liberation of the drug but of swelling of the shellac coating film followed by drug diffusion through the coating layer. Since film integrity was proven in the dissolution studies at pH 1.2, the drug flux through the coating film may be described by Fick's first law of diffusion [24]:

$$J = \frac{P_m}{d}(c_p - c_d) \qquad \text{(eq. 6)}$$

J: flux [g/(m^2·s)]

P_m: permeability coefficient [m^2/s]

d: film thickness [m]

c_p: concentration of dissolved drug in the pellet [g/m^3]

c_d: concentration in the dissolution medium [g/m^3]

After an initial lag phase where the coating layer swells drug release can be described by a zero order kinetic as long as undissolved drug is present in the pellet and sink conditions are maintained in the dissolution medium. This release kinetic was observed with pellets coated with Marcoat and SSB 55. After an initial lag phase all drug release profiles showed an almost linear shape. The flux can be determined from the slope of the drug release profiles divided by the total pellet surface area of the sample. Since the flux is inversely proportional to the coating thickness the drug release rate decreases with increasing CL.

Drug release from formulations with SSB 55 is fast in the initial phase. However, the slope of the linear part of the dissolution profile does not differ significantly from that of Marcoat at the same CL. This indicates that the permeability and thus the swelling characteristic of the coating layer are almost similar with both shellac types.

In contrast, drug release from Pearl-coated pellets differed significantly from pellets coated with the other shellac types. A linear shape of the drug release profile could not be observed with any of these formulations. In addition, the amount of released drug within the two hour test period was about twice that of the formulations with the other shellac types. For this shellac type drug release profiles of pellets with a CL of 0.5 and 1 mg/cm^2 were superimposed whereas with a CL of 2 mg/cm^2 drug release from the formulation was found to be marginally slower. It is hypothesized that swelling of the

Pearl coating layer is much more pronounced than that of the coating layers of the other shellac types resulting in a reduced barrier function especially with the lower coating levels. This leads to a higher permeability and thus increased drug release. In contrast, the thicker coating layer at a CL of 2 mg/cm^2 represents a stronger diffusion barrier.
However, pellets of all formulations remained intact during dissolution testing at pH 6.8 confirming drug diffusion through the coating layer as release mechanism.

Even though the high dissolution pH of shellac is too high for the application as an enteric coating, it allows for an application in sustained release or colon targeting formulations. The coating layer remains intact during the passage of the upper GI tract. Drug release is prolonged and results from diffusion through the coating film. Once the drug formulation reaches the distal colon, the higher luminal pH [25] causes dissolution of the coating and thus a fast release of the drug.

Correlation of the dissolution profiles with the physicochemical properties
The pK_a values determined in this study differ from those described in the literature. pK_a values found in publications from Thailand are about one unit higher [20, 26]. A possible explanation for this discrepancy is the different refining method of the investigated shellac types. Large differences in the pK_a values between differently refined shellac types have recently been reported [27]. The pK_a values determined in that study with shellac types refined by solvent extraction correspond to those presented in this study.
In Table 1 the physicochemical properties of the investigated shellac types are listed together with the data from drug dissolution studies. Interestingly, the pK_a value seems to be an unsuitable parameter for the prediction of the drug release profile. For instance, SSB 55 showed the lowest pK_a value implying a higher degree of dissociation and thus a faster drug release than formulations coated with Pearl with its higher pK_a. However, this theory could not be confirmed. The ID rate seems to be a more suitable indicator for the prediction of drug release characteristics from shellac-coated dosage forms. From pellets coated with Marcoat, which showed the lowest ID rate, drug release was slowest. Accordingly, with pellets coated with Pearl, which showed the highest ID rate, the fastest drug release at pH 7.4 and 6.8 was observed. This high ID rate also explains the independency of drug release from the coating level of formulations coated with Pearl shellac at pH 7.4. The shellac coating dissolved rapidly resulting in a very fast drug release and thus only minor differences between the different coating levels. In

comparison to Pearl, the ID rate of the other shellac types was much lower. Hence, dissolution of the coating layer was much slower and the drug release profiles were more dependent on the coating level.

Table 1: Overview of the physicochemical properties and the drug release performance of the investigated shellac types (means ± SD; n=3)

Shellac type			Marcoat	SSB 55	Pearl
Acid value: measured / certificate of analysis			/	73.1 ± 0.2 / 73	71.5 ± 0.1 / 71.2
pK_a value			/	5.89 ± 0.06	6.02 ± 0.04
ID rate [mg/(cm^2·min)]			0.088 ± 0.008	0.151 ± 0.006	0.335 ± 0.004
gastric resistance yes/no (dependent on the CL)	CL	0.5 mg/cm^2	yes	no	yes
		1 mg/cm^2	yes	no	yes
		2 mg/cm^2	yes	yes	yes
time for complete drug release at pH 7.4 (dependent on the CL)		0.5 mg/cm^2	20 min	10 min	10 min
		1 mg/cm^2	30 min	20 min	10 min
		2 mg/cm^2	45 min	35 min	15 min

3.4. Conclusion

From the data presented in this study it may be concluded that coating with shellac allows a reduction of the process time for the production of enteric coated dosage forms as gastric resistance can be achieved at comparatively low coating levels. At pH 6.8, drug release occurred by swelling and drug diffusion through the coating layer offering potential for the application in sustained release or colon targeting formulations rather than enteric coating formulations.

It has to be considered that different shellac types may differ significantly in their drug release profiles. For the prediction of drug release from shellac-coated pellets the intrinsic dissolution rate of the material turned out to be a more suitable indicator than the pK_a value.

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4. Mimicking the aging process of shellac by thermal treatment

Mimicking the aging process of shellac by thermal treatment

Abstract

Shellac raw material undergoes aging. The understanding of this aging process and its effect on the physicochemical properties of the material is important to establish specifications for pharmaceutical applications of different shellac types. The aging process of shellac raw material (SSB 55 Pharma) is mimicked by exposure to thermal stress. Alterations of the material properties are monitored by determination of the pK_a value, the acid value (AV), the ester value (EV), the saponification value (SV), the glass transition temperature (T_g), the intrinsic dissolution rate (ID rate) and the percentage insoluble solid (PIS) as well as by evaluation of changes in the MALDI TOF MS spectra.

It was found that aging of shellac is accompanied with an increase in the EV, the T_g and the PIS as well as a decrease in the AV and the ID rate. The pK_a value and the SV remain unchanged. A shift to higher m/z values cannot be observed with MALDI TOF MS.

Aging of shellac causes significant changes in the physicochemical properties of the material. The T_g was found to be a more sensitive indicator for a fast detection of these changes than the AV.

4.1. Introduction

Shellac is the purified product of the natural resin Lac. It consists mainly of esters of the main components aleuritic acid, butolic acid, shellolic acid and jalaric acid [1-3]. This versatile material has a wide field of applications mainly in the food industry for coatings on citrus fruits [4] and confectionaries but also as component in dyes and lacquers [5]. Shellac has good film forming properties. Shellac films show high gloss and a low permeability for water vapor and gases [6]. In pharmaceutical applications shellac is used as taste masking agent [7], moisture barrier [7], as excipient in enteric [8] or sustained release [9, 10] formulations. It has been described that coatings prepared from aqueous ammoniacal solutions show long term stability [11]. However, shellac raw material for pharmaceutical applications is usually obtained by a solvent extraction process resulting in the acid form which undergoes aging, which leads to changes in the physicochemical properties. This aging is even more pronounced, if shellac is not stored properly [12]. The extent of these changes may also vary in dependence on the shellac type used.

In the Ph. Eur. shellac is chemically characterized only by the acid value (AV) which is the most conventional parameter for quality control of shellac samples. However, it could be shown that depending on the investigated shellac type the pharmacopoeia's broad specifications may also be met by aged shellac which is completely unsuitable for pharmaceutical applications [13].

It has been reported previously that controlled artificial aging of shellac allows tailor-made release patterns from shellac-containing dosage forms [14]. However, if aging occurs uncontrolled it might have negative effects on drug release from shellac-containing formulations. This uncontrolled aging may take place not only during storage but also during processing of the material e.g. coating, when shellac is exposed to high temperatures and humidity. Thus, when working with shellac, particularly if it is used in controlled release formulations, knowledge about the aging behavior of the material and its effect on the physicochemical properties is very important.

In recent publications the influence of thermal treatment of shellac has been discussed. Kumar et al. performed extensive studies on the kinetics of shellac polymerization [15-19] and its influence on the gelation behavior of alcoholic shellac solutions. Bhatia et al. used specular reflectance spectroscopy to characterize thermally aged shellac [20] and

found anhydride formation as an important aging mechanism for thermal treatment at temperatures above 200 °C. However, the effect of aging on pharmaceutically relevant parameters has not yet been investigated.

In the present study the aging process of the shellac type SSB 55 Pharma with its well defined origin in comparison to other shellac types, is mimicked by exposure of the raw material to thermal stress.

4.2. Materials and methods

Materials

Shellac SSB 55 Pharma (Stroever Schellack Bremen, Germany). All other chemicals used were of analytical grade.

Methods

Sample preparation

Ground shellac is spread onto Teflon plates and molten at 110 °C in a drying oven over a period of 180 min. Samples are withdrawn every 30 min. After cooling the molten samples are micronized using a Fritsch Pulverisette 6 equipped with a 60 ml zirconium oxide grinding bowl and 30 zirconium oxide grinding balls (diameter: 10 mm) at 400 rpm for 3 min.

Acid Value (AV)

The AV is determined according to the Ph. Eur.: 0.3 g shellac is titrated potentiometrically in diethylether/ethanol (1:1, v/v) with 0.1 M KOH (Mettler Toledo DL70 ES Titrator).

Saponification value (SV) and Ester value (EV)

The SV is determined according to the Ph. Eur.: 1.5 g shellac powder is heated with 25.0 ml of 0.5 M alcoholic potassium hydroxide solution for 30 min in a 250 ml glass flask equipped with a reflux condenser. The hot solution is immediately titrated with 0.5 M hydrochloric acid. The endpoint is determined with phenolphthalein. A blank value is determined under the same conditions.

The EV is calculated as the difference between the SV and the AV.

Glass transition temperature (T_g)

The T_g is investigated with DSC (Perkin Elmer DSC 7, TAC 7/DX, Pyris Software, liquid nitrogen cooling system). Approximately 10 mg of shellac powder are filled into standard aluminium pans with a punctured cap and measured twice under nitrogen atmosphere (-40 to 150 °C, 20 K/min). The T_g is determined from the second heating run.

Percentage insoluble solid (PIS)

Dissolution of shellac in aqueous media plays a major role in the preparation of shellac solutions for pharmaceutical applications and for drug release from shellac-coated dosage forms under physiological conditions. Briefly, 0.5 g of shellac is dissolved in 50 ml 1 % aqueous ammonium carbonate solution for three hours and filtered through a weighed filter paper. The residue on the filter is washed with water, dried and weighed to determine the amount of insoluble solid.

Intrinsic dissolution rate (ID rate)

Intrinsic dissolution is performed with 80 mg of micronized shellac and a paddle-over-disk intrinsic dissolution kit (die diameter: 9 mm, compression force: 2 kN, compression time: 2 min) in 700 ml of phosphate buffer (0.05 M, pH 7.4; 37 °C, 100 rpm). The dissolution profiles are recorded spectrophometrically at 223 nm using 1 cm Quartz cells (Perkin Elmer Lambda 25).

pK_a value

Acid base backtitrations are performed according to a method adapted from Parke and Davis [21]. Briefly, micronized shellac is dissolved in 8.0 ml of 0.1 M NaOH. Titrations are done in 50 µl steps with 0.1 M HCl. The shellac titration curves are subtracted from a blank curve and standardized referring to the titration grade. The pK_a values correspond to the pH value at a titration grade of 0.5.

MALDI TOF MS

The MALDI TOF mass spectra were recorded with a Bruker Autoflex III mass spectrometer equipped with a smart beam laser. All mass spectra were recorded in the reflector mode using an acceleration voltage of 20 kV. The targets spots were prepared from ethanolic solutions (~ 1mg/mL) without salt addition using dithranol (10 mg/ml) as matrix.

4.3. Results and discussion

The exposure of shellac in its acid form to long term thermal treatment results in accelerated aging and thus changes in the physicochemical properties of the substance. In Fig. 1 the change of the AV, EV and SV is displayed. Long term thermal treatment results in a decrease in the AV: After 60 min of thermal treatment a significant decrease in the AV can be observed, after 150 min the AV reaches a minimum which remains almost unchanged until the end of the thermal treatment.

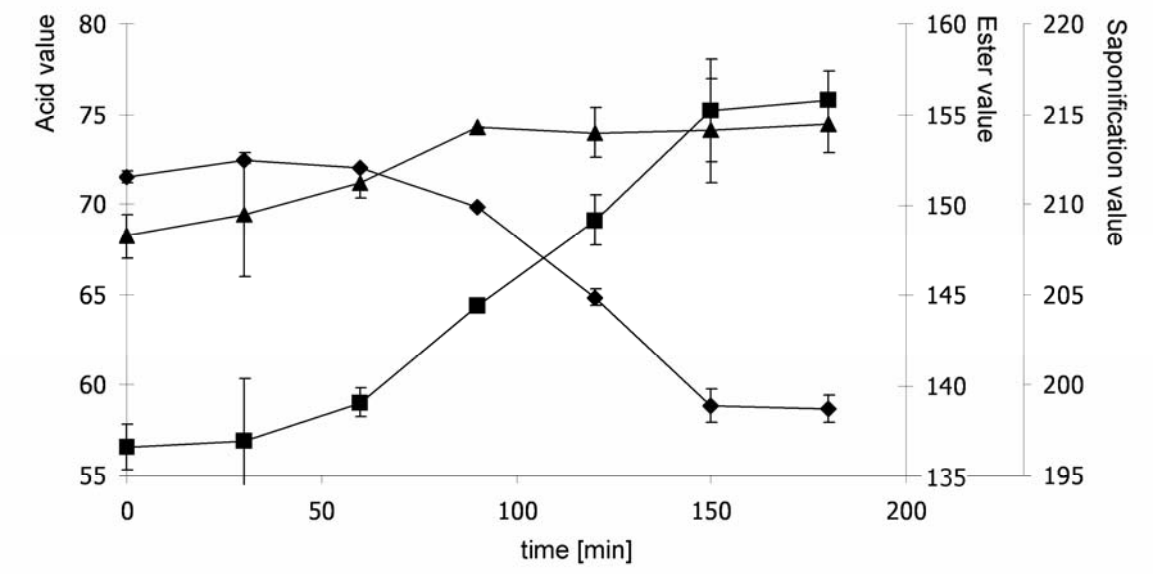

Fig. 1: Change of the acid value (◆), ester value (■) and saponification value (▲) of shellac samples during thermal treatment (means ± SD; n=3)

During determination of the SV even the water insoluble samples are completely dissolved under the experimental conditions (heated ethanolic KOH). Therefore, a determination of the unsaponifiable matter was unnecessary. The SV remains almost unchanged during this thermal treatment. As a consequence, the EV increases to the same extent as the AV decreases. Thus, the predominant aging mechanism is based on esterification.

The T_g is an indicator of the flexibility of a film and its ability to resist internal and external stress during manufacturing processes and storage. Films prepared from materials with a high T_g usually turn out to be brittle requiring the addition of a plasticizer for sufficient performance [22]. The solubility and dissolution of a coating film significantly affect drug release from coated dosage forms.
Since the determination of the AV is a simple and the most commonly used method to characterize shellac, the relationship between the AV and other physicochemical properties was investigated.
Such relationships are displayed in Figs. 2 a-c for the T_g, the PIS and the ID rate. In Fig. 2a the relationship between the T_g and the AV is shown. Initially, i.e. at high AV, a slight decrease in the AV of less than one unit results in an increase in the T_g of more than 5 °C indicating major changes in the material. In contrast, a decrease below an AV of 70 causes comparatively little changes in the T_g. A similar tendency could be shown for ID rate and PIS (Figs. 2b, c). Slight changes at the beginning have major effects on the data, whereas with reduced AVs below 70 only little changes are observed. Obviously, the initial esterification has a pronounced effect on the material properties of shellac.

These results also show that the AV is not the best indicator for aging of shellac especially in the initial phase. For a more sensitive characterization of the aging process the determination of the T_g is recommended.

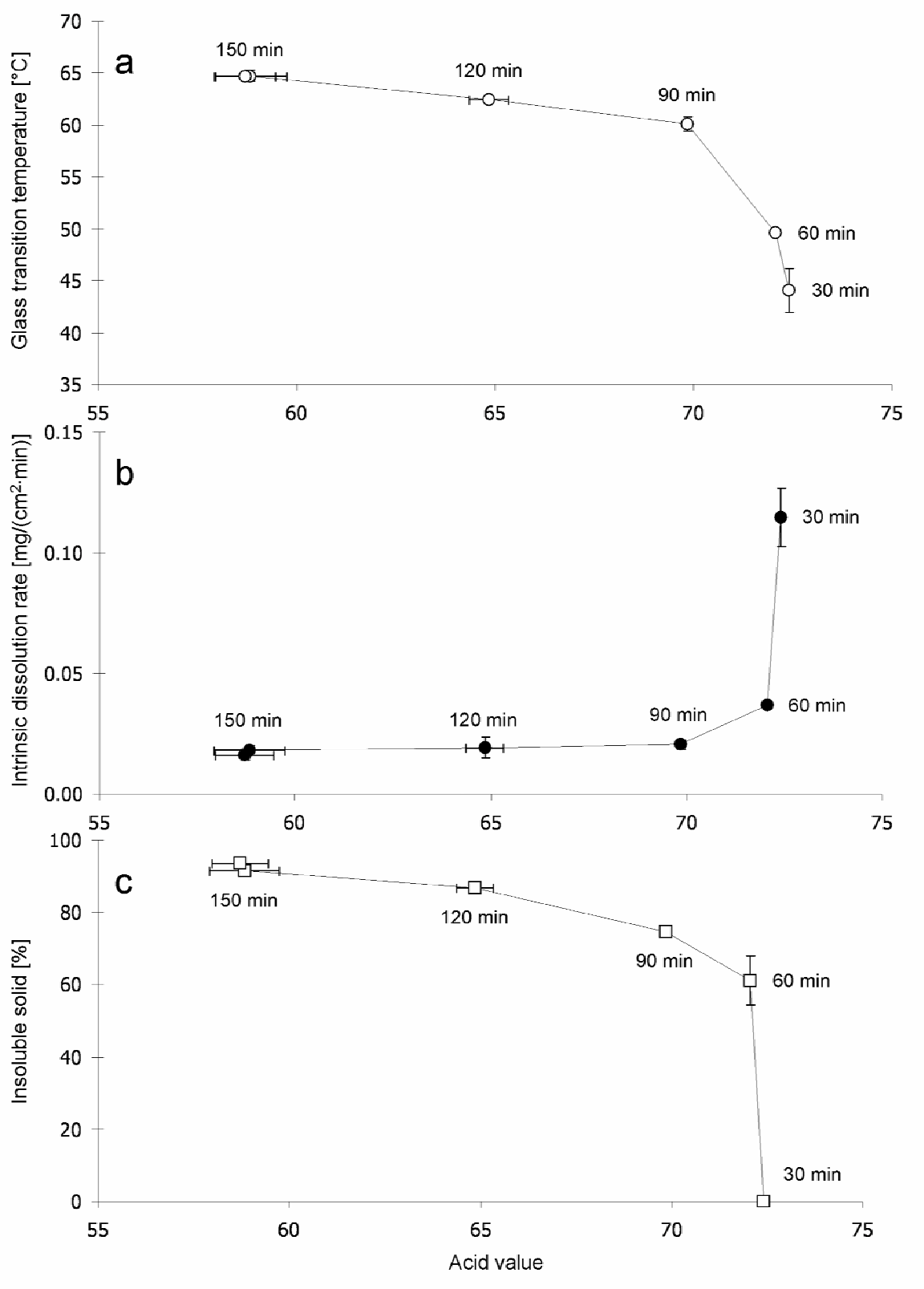

Fig. 2: Change of the physicochemical properties of shellac vs. acid value (means ± SD; n=3) a) glass transition temperature; b) intrinsic dissolution rate; c) insoluble solid

As shown in Fig. 3 the T_g allows more reliable information on the degree of polymerization and the dissolution properties of the sample because of its even curve profiles. In contrast to the correlations with the AV, the slopes of the curves are almost constant over the entire range of measured T_gs.

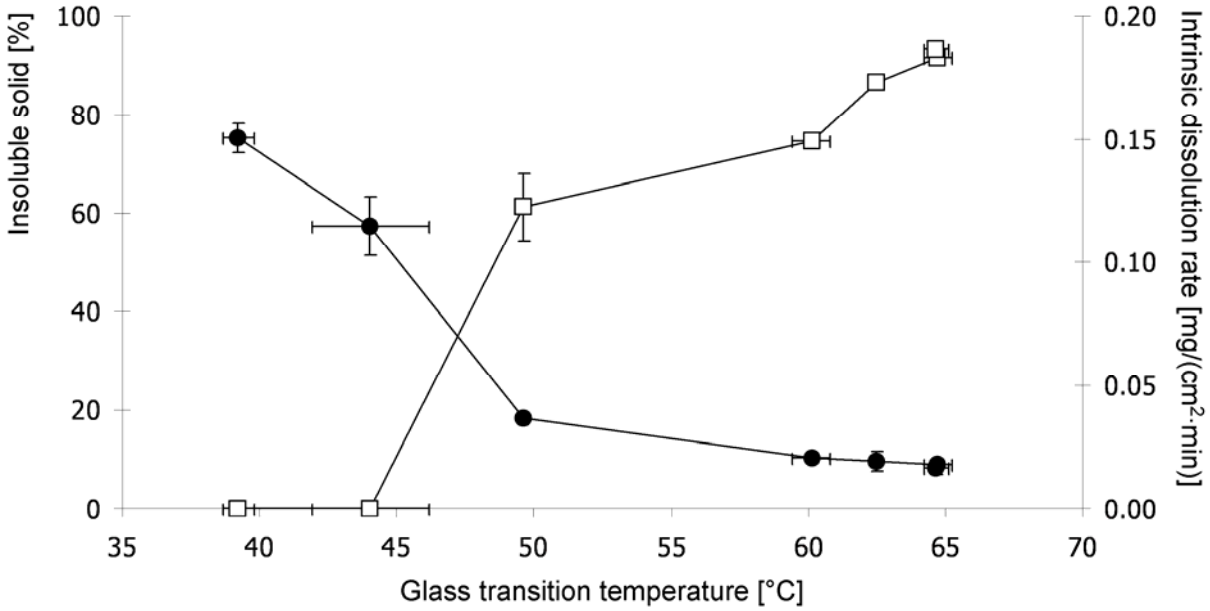

Fig. 3: Percentage insoluble solid (□) and intrinsic dissolution rate (●) of shellac vs. glass transition temperature (means ± SD; n=3)

It has been described previously that the pK_a value is independent of the degree of polymerization of the material [23]. In the present study, the pK_a value remains unaffected for at least 60 min of thermal treatment (Fig. 4). For longer thermal treatments the pK_a value appears to ease significantly. This is in contrast to the reduction in the solubility of aged shellac but may be explained by the incomplete dissolution of the substance in the medium before titration. The increase in insoluble solid and the constant pK_a value indicate that the change in solubility is not a result of a decreased dissociation but of a lower basal solubility of the aged material.

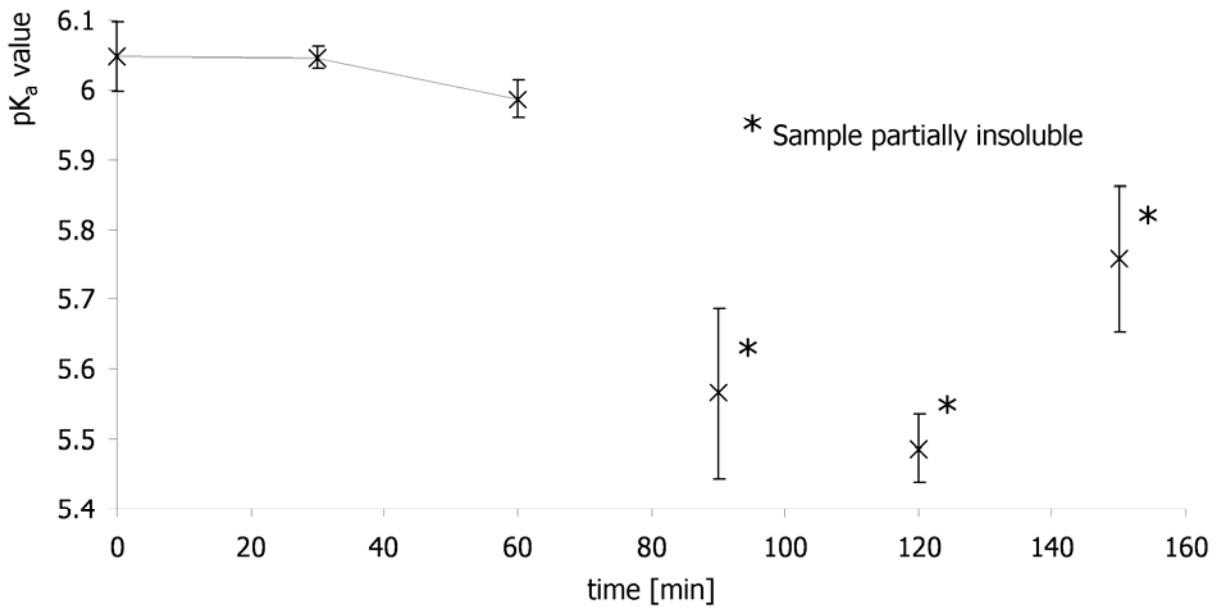

Fig. 4: Change of the pK_a value of shellac during thermal treatment (means ± SD; n=3)

Different mass spectroscopic methods have been described for analysis of the composition of shellac [24, 25] and the identification of aged shellac [26]. However, in these publications the samples were either pre-treated by saponification or pyrolysis to make them capable for GC analysis thereby causing a degradation of the material. Recent publications recommend MALDI TOF MS as powerful tool for the characterization of different shellac types. MALDI TOF MS allows an analysis without degradation of the samples and a good separation of the components of certain shellac types [27]. In Fig. 5 the MALDI TIOF mass spectrum of untreated shellac in a mass range of m/z 500 – 1500 is shown. As mentioned above, shellac is a natural material consisting of a complex mixture of esters. Thus, the mass spectra show a high variety of mol masses for the investigated shellac samples. Since MALDI TOF produces mainly $[M+Na]^+$ ions of the sample, the substances can be identified by adding the molecular weight of sodium to the molecular weight of the substance. The spectra can generally be divided into three sections of band areas representing the degree of esterification. In the mass range around m/z 600 mainly dimers can be found with the characteristic peaks of the esters of the main components aleuritic acid (A), jalaric acid (J) and shellolic acid (S) (AJ: m/z = 589; AS: m/z = 605). In the range from m/z 800 to 900 trimers can be found with the peaks of JAJ (m/z = 852), AJA (m/z = 876) and ASA (m/z = 892). Tetramers can be found in the third range around m/z 1150 with the characteristic peaks of JAJA (m/z = 1138) and SAJA (m/z = 1154).

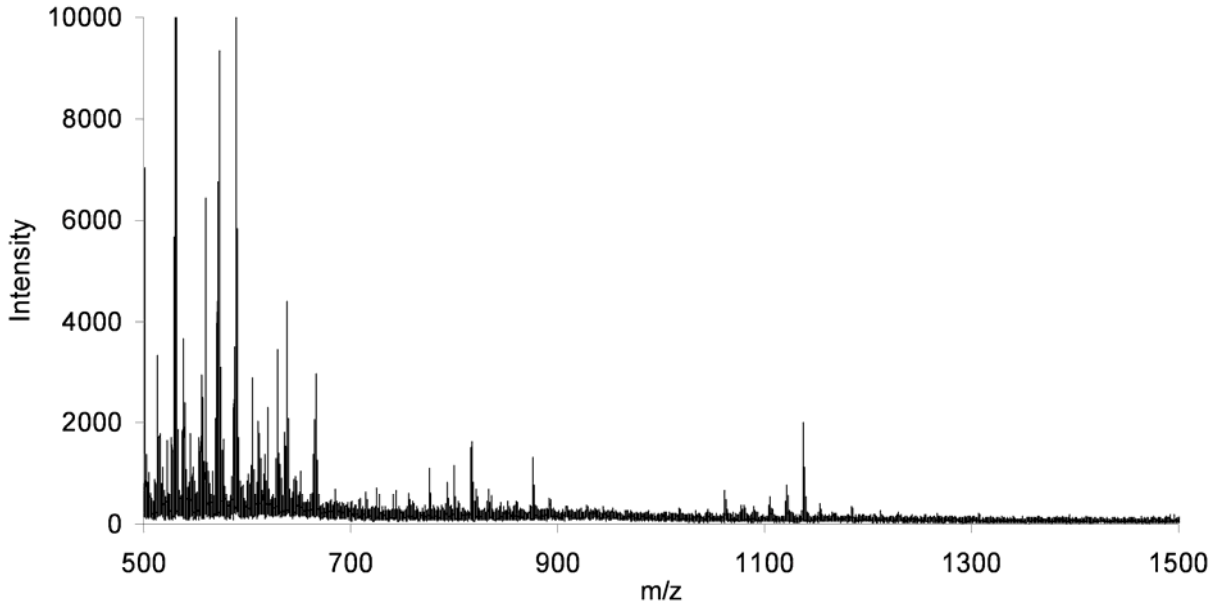

Fig. 5: MALDI TOF mass spectrum of untreated shellac

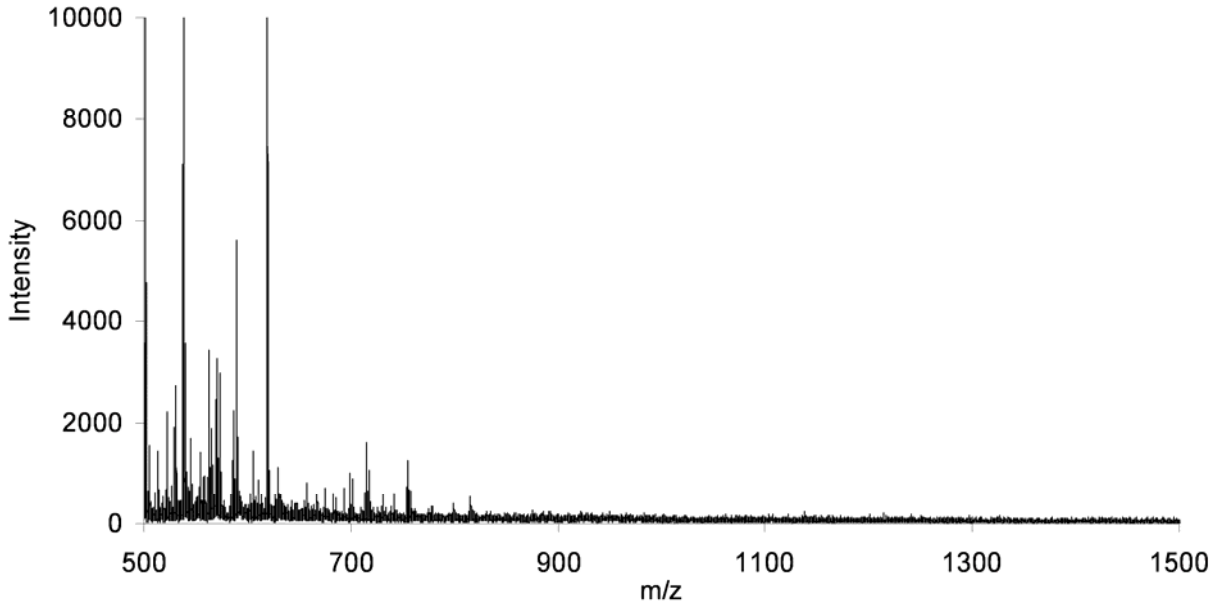

Fig. 6: MALDI TOF mass spectrum of shellac treated at 110 °C for 180 min

MALDI TOF MS was performed to demonstrate the polymerization of shellac during prolonged thermal treatment. It was expected that thermal treatment of the sample leads to an increase in the molecular masses and thus a shift of the peaks to higher m/z values. However, this shift could not be observed. In Fig. 6 the spectrum of shellac treated for 180 min at 110 °C is shown. As for the spectrum of the untreated shellac, in the lower m/z range characteristic bands of AJ and AS can be identified again. However, for m/z values above 800 the peaks are much less pronounced and not even the peaks of the trimers can be discriminated from the noise in the spectra. Most likely, thermal treatment causes the formation of a high variety of different esters, whose respective quantities are below the detection limit.

4.4. Conclusion

The understanding of the aging process and its effect on the physicochemical properties of shellac is important to establish specifications for the use of a certain shellac type. Aging of shellac is accompanied by a decrease in the acid value and the intrinsic dissolution rate as well as an increase in the T_g and the percentage insoluble solid. Whereas the ester value increases, the saponification value remains almost unchanged. This confirms esterification as the predominant aging mechanism. However, it was found that these changes are most pronounced in the initial phase where a slight decrease in the acid value causes significant changes in the material properties. Thus, for a more sensitive identification of aged shellac the determination of the T_g is recommended.

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5. Influence of the inlet air temperature in a fluid bed coating process on drug release from shellac-coated pellets

Influence of the inlet air temperature in a fluid bed coating process on drug release from shellac-coated pellets

Abstract

Since the introduction of aqueous ammoniacal solutions, shellac regained importance for pharmaceutical applications. However, as shellac is a material obtained from natural resources its quality and thus its physicochemical properties may vary depending on its origin and the type of refining.

In the present study theophylline pellets were coated with aqueous solutions of three different commercially available shellac types. The inlet air temperature of the coating process was varied and its influence on drug release from the coated pellet formulations was investigated. Film formation was correlated to the physicochemical and mechanical properties of the investigated shellac types.

Pellets coated at lower temperatures showed distinct cracks in the coating film resulting in a loss of the barrier function during dissolution testing. These cracks were non reversible by additional curing. The physicochemical and mechanical properties of the investigated shellac types varied significantly and could hardly be related to the drug release performance of the investigated formulations.

Obviously, with shellac a minimum inlet air temperature must be exceeded to achieve a coherent coating film. This temperature was dependent on the investigated shellac type.

5.1. Introduction

Shellac is the purified product of the natural material Lac which is secreted by the small parasitic insect Kerria Lacca on various host trees in India, Thailand and Southeast Asia to protect the brood from extreme temperatures and predators. Shellac is the only commercially used resin of animal origin.

Shellac with an average molecular weight of about 1000 Da is a complex mixture mainly of polyesters of the main components aleuritic acid, butolic acid, shellolic acid and jalaric acid with a small amount of free aliphatic acids [1-3]. However, its composition varies depending on the insect species as well as the host tree from which the raw material is gained.

Shellac is used in the dye industry as a component in lacquers and varnishes [4] because of its good film forming properties, high gloss [5] and water resistance. Shellac is non-toxic, physiologically harmless [6] and is therefore generally recognized as safe (GRAS) by the FDA. This allows the use as additive in food products where the material already plays a major role as coating material for citrus fruits [7] or confectionaries.

Due to its acidic character shellac is often used as an enteric coating material for pharmaceutical products [8, 9]. Moreover, its low permeability for water and gases [10] allows its use in other applications such as moisture protection and taste masking [11]. Also the use of shellac in sustained release [12] and colon targeting formulations [13] as well as coating material for microencapsulation [14] has been described.

Despite all these advantages, the use of this versatile material in pharmaceutical applications has greatly declined. Shellac coatings prepared from alcoholic solutions as well as shellac raw material consist of the acid form, which undergoes aging [15]. This aging leads to a hardening of the material resulting in changes in the release characteristics of shellac containing dosage forms. However, since the introduction of aqueous ammoniacal solutions, shellac could regain importance for pharmaceutical applications. It has been reported that shellac films prepared from aqueous ammoniacal solutions lack the instability problems of coatings prepared from organic shellac solutions [8]. Aqueous shellac solutions are translucent and show a low viscosity even at higher concentrations allowing for a fast increase in the film thickness during the coating process. In addition, the GRAS status of shellac allows its use in modified release formulations with the regulatory status of a food product or nutritional supplement such as vitamin formulations. This gives shellac an advantage over most

other release modifying film coating materials, which lack this status. Moreover, the natural origin from renewable resources may be of interest for marketing purposes.

In fluid bed coating processes agitation and drying of the product is caused by the inlet air [16]. The Wurster process is a variation of the fluid bed technology. The spraying nozzle is localized on the bottom of the product chamber in the so-called Wurster insert. During the process the product passes the spraying nozzle, which discharges the coating formulation. The product is moved upwards, passes the Wurster insert and drops back into the fluid bed.

Especially for the application of functional coatings knowledge about the process and the materials used is essential to assure functionality and a reproducible quality of the coating film.

In many publications the influence of coating process parameters on the product quality of coated dosage forms is described. Christensen et al. provided a detailed description of the Wurster process [17]. Thermodynamic models [18], studies on the interactions between coating formulation and core material [19] as well as the influence of various process parameters on the quality of the product [20, 21] helped to understand this complex manufacturing process. However, there is still need for further investigations.

It turned out that the inlet air temperature during the coating process is a key factor in the manufacture of coated dosage forms. Therefore, in the present study the influence of the inlet air temperature on drug release from shellac-coated pellet formulations is investigated.

5.2. Materials and methods

Materials

The following types of shellac were investigated: Marcoat™ 125 (Marcoat), a ready to use shellac solution (25 % [w/w]) prepared from Bysakhi shellac of Indian origin (Emerson Resources, Norristown, PA, USA); SSB 55 Pharma (SSB 55); Kushmi shellac flakes of Indian origin (Stroever Schellack Bremen, Germany); Pearl N811F (Pearl), shellac flakes of Thai origin (Gifu Shellac, Gifu, Japan). All shellac types were refined by solvent extraction. Theophylline pellets were donated by Temmler, Killorglin, Ireland.
Ammonium bicarbonate, potassium dihydrogen phosphate, sodium chloride, sodium hydroxide and hydrochloric acid were purchased from Carl Roth, Karlsruhe, Germany.

Methods

Preparation of shellac coating solutions

Ground shellac was dissolved in 1.5 % [w/V] ammonium bicarbonate solution at 50 °C to obtain a final concentration of 15 % [w/w]. As the presence of excess ammonium salt influences the dissolution properties of the final shellac films, the solutions were heated to 65 °C to remove the excessive ammonium salt in the form of free ammonia and carbon dioxide. Evaporated water was replaced. The heating process was repeated until a constant pH was reached. The pH of the final solutions was between 7.4 and 7.8. (MP 225 pH meter, Mettler Toledo, Columbus, Ohio, USA).

Preparation of theophylline pellets

Prior to coating the theophylline pellets were cleaned from dust and characterized for their average weight and diameter. The weight of a single pellet corresponds to the average weight determined from a sample of 500 pellets. The pellet diameter was measured using a Wild M3 microscope (Wild, Völkermarkt, Austria) equipped with a AxioCam ICc and AxioVision software (both from Zeiss, Jena, Germany).

Coating of theophylline pellets

The required shellac mass was calculated from the overall pellet surface and the desired coating level for the respective batch.

Marcoat solution was diluted to a final concentration of 15 % [w/w] with demineralised water. The other aqueous shellac solutions were used as prepared. 50 g of immediate release theophylline pellets were cleaned from dust and coated with the aqueous shellac solutions in a Mini Glatt fluid bed coater (Glatt, Binzen, Germany) with Wurster insert (Ø 30 mm, 10 mm gap) equipped with TEF 20 temperature sensors (LKM electronic, Geraberg, Germany) for the measurement of inlet air and product temperature (Software: Signasoft 6000, Peekel Instruments, Bochum, Germany). The coating solutions were applied using a 0.5 mm two-way nozzle at a spraying rate of 0.4 g/min to achieve a final coating level of 1 mg/cm^2. Atomizing air pressure was adjusted to 0.6 - 1.1 bar according to the weight gain of the pellets. For investigation of the temperature dependence of the process, theophylline pellets were coated at inlet air temperatures of either 20 °C, 40 °C or 60 °C and an inlet air volume of 14 m^3/h.

The pellets were stored in a desiccator over silica gel at least for 24 h before further processing.

Calculation of the coating level (CL) and coating yield (CY)

The average coating level was determined as mass of shellac per total pellet surface area as follows:

$$CL = \frac{w_{shellac}}{A} \qquad \text{(eq. 1)}$$

CL: average coating level [mg/cm^2]

$w_{shellac}$: amount of shellac in the sample [mg]

A: pellet surface area of uncoated pellets in the sample [cm^2]

The CL was calculated from the difference in theophylline content between coated and uncoated pellets and the average diameter as well as the weight of the uncoated theophylline pellets as reported in a previous publication [22]. Briefly, approximately 150 mg of shellac-coated pellets were dissolved in 250 ml of 0.1 M NaOH using an ultrasonic bath. After sufficient dilution the theophylline content of the sample was determined spectrophotometrically in 0.1 M NaOH at 275 nm (Lambda 25, Perkin Elmer, Beaconsfield, UK).

A coating level of 1 mg/cm^2 corresponds to a weight gain of 8 % (w/w).

The CY was calculated from the shellac mass and the mass of pellet cores in the sample as determined from the CL data as well as from the batch size and the mass of shellac applied to the batch.

$$m_{cores} = m_{sample} - m_{shellac} \quad \text{(eq. 2)}$$

$$CY = \frac{m_{shellac} \cdot m_{batch} \cdot 100\%}{m_{cores} \cdot m_{shellac-batch}} \quad \text{(eq. 3)}$$

m_{cores}: mass of cores in the sample [mg]
m_{sample}: mass of sample [mg]
$m_{shellac:}$ mass of shellac in the sample [mg]
CY: coating yield [%]
m_{batch}: batch size [mg]
$m_{shellac-batch}$: mass of shellac applied to the batch [%]

Dissolution experiments

Dissolution tests were performed according to the Ph. Eur. with approximately 100 mg pellets in 1000 ml dissolution medium. Gastric resistance was tested in simulated gastric fluid (pH 1.2) using the paddle apparatus (Sotax AT 7, Allschwil, Switzerland) at 100 rpm and 37 °C for 2 h. Drug release was measured in phosphate buffer (pH 7.4, 0.05 M) above the dissolution pH of shellac. The pellets remained on the bottom of the vessel throughout the dissolution test. Dissolution profiles were recorded spectrophotometrically at 271 nm using 1 mm flow through Quartz cells.

Curing of shellac-coated pellets

Approximately 5 g of shellac-coated pellets were placed into Petri dishes. The samples were cured in a drying oven at 60 °C for 2 h and at 80 °C for 2 h and 12 h, respectively.

Scanning electron microscopy

The surface of the coated pellets before and after dissolution testing was analyzed by scanning electron microscopy. The samples were coated with a thin carbon layer and analyzed using a LEO 1525 scanning electron microscope (LEO Elektronenmikroskopie, Oberkochen, Germany) and an accelerating voltage of 5 kV.

Preparation of free shellac films

Films were prepared by a casting and evaporation method. 20 ml shellac solution was poured onto Teflon plates. The solvent was evaporated at 40 °C for 4-5 hours. After complete drying the film was carefully peeled off the plates and cut into the desired shape for further investigation. The film samples were stored in a desiccator over silica gel at room temperature for at least 24 h before use.

Glass transition temperatures (T_g)

For determination of the T_g the cast shellac films were cut into circles with a diameter of 6 mm with a circular punch. The samples were analyzed with DSC (DSC 7, TAC 7/DX, liquid nitrogen cooling system, Perkin Elmer, Beaconsfield, UK). Approximately 10 mg of film sample were accurately weighed into standard aluminium pans with a punctured cap and measured twice under nitrogen atmosphere over a temperature range of -40 to 120 °C. Between the heating runs at 20 K/min an isothermal step of 1 min at 120 °C was introduced to remove excessive water. The T_g was determined from the second heating run with the Perkin Elmer Pyris software.

Mechanical properties of free shellac films

For mechanical characterization shellac films were cut in a dumbbell shape with the length of 25 mm and width of 4 mm. Film thickness was measured with a Digimatic Indicator (Mitutoyo, Kawasaki, Japan). The mechanical properties of free shellac films were investigated with a texture analyzer (Inspect mini, Hegewald and Peschke, Nossen, Germany) at a test speed of 10 mm/min. Tensile strength, elastic modulus and elongation at break were determined with at least five samples and calculated as shown below [23]:

$$\text{Tensile strength} = \frac{F}{A} \text{ [MPa]} \quad \text{(eq. 4)}$$

$$\text{Elastic Modulus} = \frac{F \cdot l}{A \cdot \Delta l} \text{ [MPa]} \quad \text{(eq. 5)}$$

$$\text{Elongation at break} = \frac{100 \cdot \Delta l}{A \cdot l} \text{ [\%/mm}^2\text{]} \quad \text{(eq. 6)}$$

F: Maximum force applied during the test [N]

A: Initial cross sectional area of the sample [mm^2]

l: Initial length [mm]

Δl: Change in length [mm]

5.3. Results and discussion

During the coating process the process parameters were kept constant with exception of the atomizing pressure which varied according to weight gain of the pellets to maintain an adequate product flow through the Wurster insert.

Pellets coated at lower inlet air temperatures were found to be less electrostatically charged. This was advantageous during discharge of the final product from the chamber of the coater. Whereas pellets coated at 60 °C tended to stick to the Wurster insert and the coater's wall, pellets coated at 20 °C were easily removed from the product container. Due to the low temperature the moisture uptake of the inlet air was reduced, resulting in increased humidity of the product and thus less electrostatic charge. In addition, the CY was found to be higher at lower inlet air temperatures. Whereas the CY was about 88 % for the batches coated with an inlet air temperature of 60 °C it increased to 95 % and above for batches coated with an inlet air temperature of 20 °C. This can be attributed to a reduced tendency of spray drying of the coating formulation at lower inlet air temperatures. Moreover, coating at lower inlet air temperatures has several advantages such as the processing of thermolabile drugs and a reduction of energy costs.

However, the dissolution profiles of the theophylline pellets coated at low inlet air temperatures differed significantly from those coated at 60 °C (Fig. 1). With decreased inlet air temperature drug release was enhanced. All pellets coated at 20 °C showed complete drug release at pH 7.4 within 10 min or less. However, there were distinct differences between the drug release profiles of the investigated shellac types. Whereas formulations coated with Pearl showed fast drug release almost independent from the inlet air temperature, with the other two shellac types a clear temperature dependence was observed. Fast drug release at high pH is desired for enteric-coated formulations. At first sight it seems that such a release profile may be obtained with shellac by reduction of the inlet air temperature.

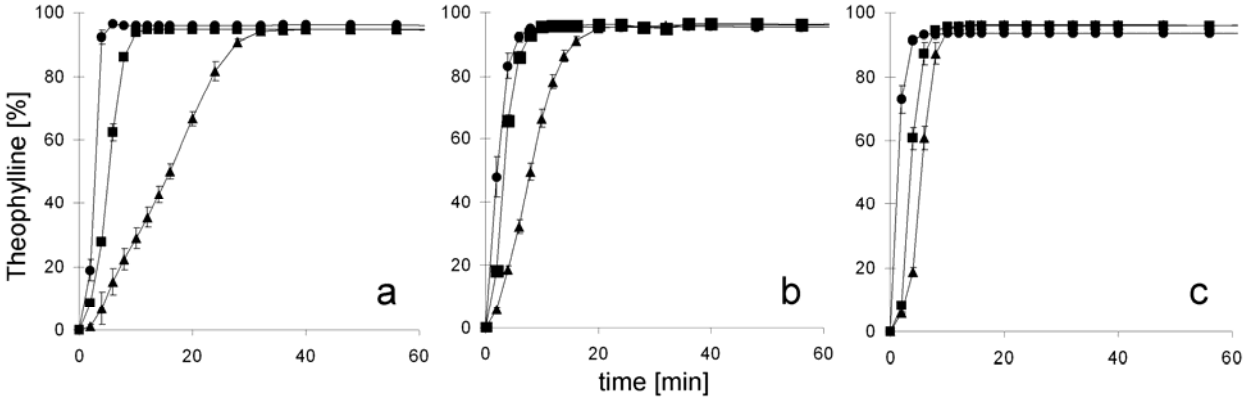

Fig. 1: Influence of the inlet air temperature on drug release from shellac-coated pellets at pH 7.4 (means ± SD; n=3) a) Marcoat b) SSB 55 c) Pearl
Inlet air temperature: ●20 °C ■ 40 °C ▲ 60 °C

However, drug release experiments at pH 1.2 showed that a reduction of the inlet air temperature resulted in a loss of gastric resistance of most of the pellet formulations (Fig. 2). Whereas with pellets coated with Marcoat and Pearl gastric resistance was observed down to an inlet air temperature of 40 °C, with SSB 55 only the formulation coated at an inlet air temperature of 60 °C showed gastric resistance. All formulations coated at an inlet air temperature of 20 °C showed pronounced drug release at pH 1.2.

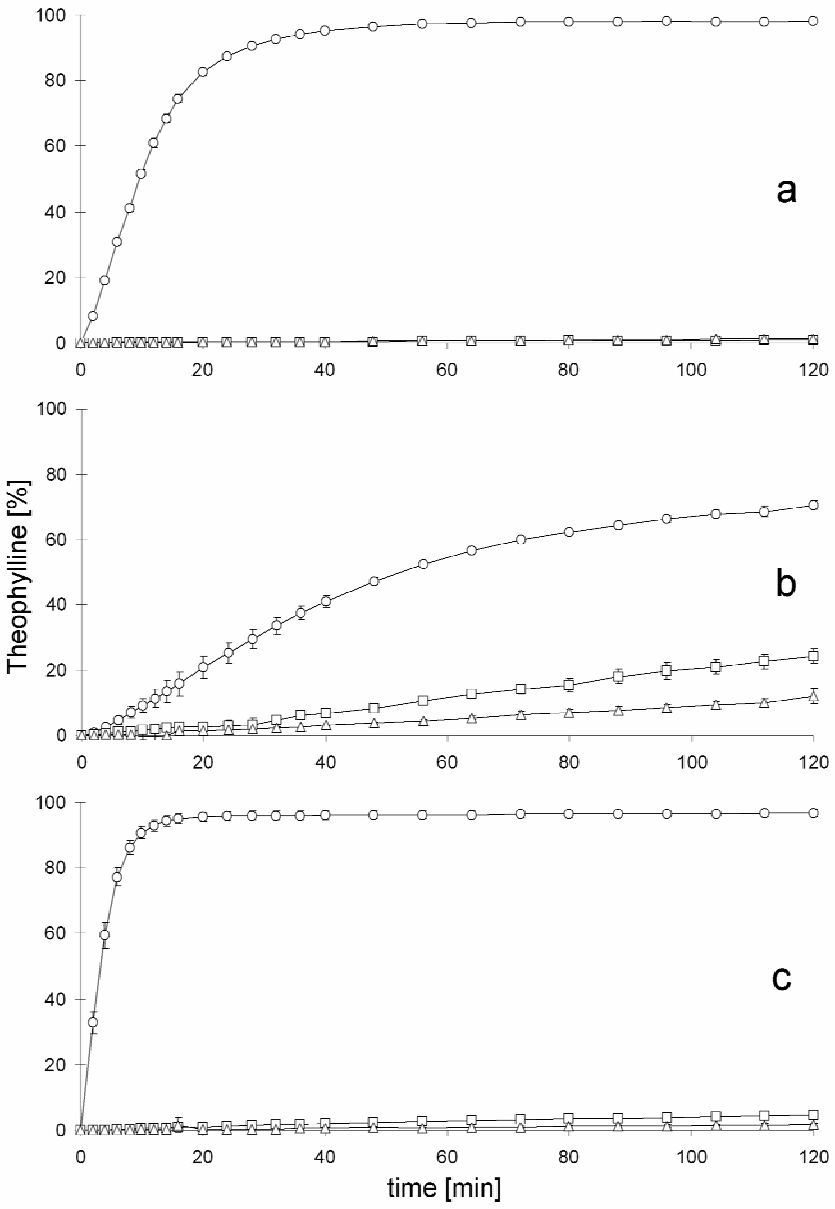

Fig. 2: Influence of the inlet air temperature on drug release from shellac-coated pellets at pH 1.2 (means ± SD; n=3) a) Marcoat b) SSB 55 c) Pearl
Inlet air temperature: ○ 20 °C □ 40 °C △ 60 °C

SEM pictures (Fig. 3) showed a smooth continuous coating layer of pellets coated at 60 °C. In contrast, pellets coated at 20 °C showed cracks all over the coating surface. These cracks represent defects in the barrier and are obviously the reason for the loss of gastric resistance. SEM pictures of pellets after dissolution testing proved this theory. Whereas the inner pellet core was completely dissolved, the empty shell of the coating layer remained undissolved.

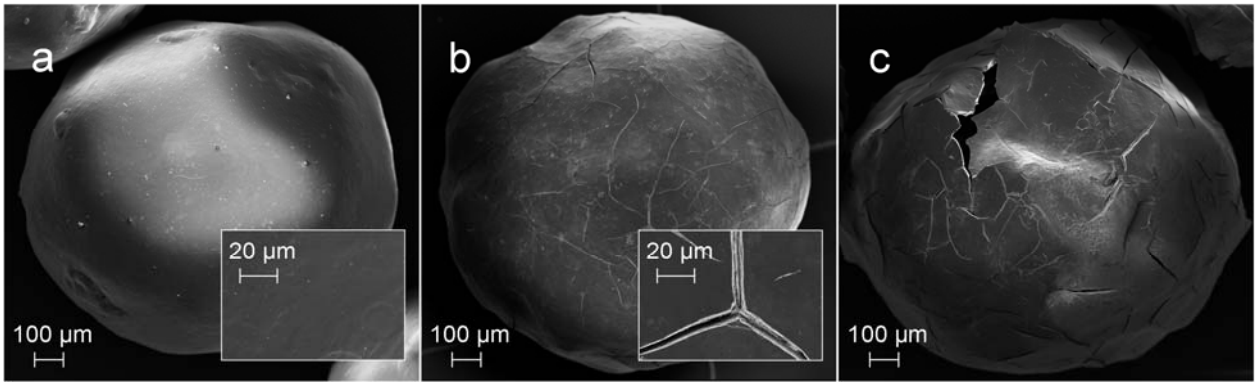

Fig. 3: SEM pictures of pellets coated with Marcoat at different inlet air temperatures before and after dissolution testing at pH 1.2
a) 60 °C; b) 20 °C; c) 20 °C (after dissolution testing)

Most likely, an interaction of several factors led to these coating defects. Dalton et al. reported a higher moisture uptake for granule formulations during fluid bed granulation at lower temperatures [24]. With regard to the product temperature another factor comes into focus. From the difference between the inlet air temperature and the product temperature the water removal efficiency can be estimated (Fig. 4). Dry inlet air passes through the wet product and absorbs water. The resulting evaporative heat loss leads to a temperature decrease in both inlet air and product. The more water evaporates the lower the product temperature becomes. Whereas the difference between the inlet air temperature and the product temperature was 13 K at an inlet air temperature of 60 °C, this difference was decreased to 6 K at 40 °C and to less than 2 K at 20 °C. Accordingly, water absorption and thus the drying capacity were decreased at lower inlet air temperatures. Whereas about 4.8 g water were absorbed per kg dry air at an inlet air temperature of 60 °C this absorption was decreased to about 2.4 g/kg at 40 °C and 0.8 g/kg at 20 °C. Since the spraying rate was kept the same for all batches it may be concluded that a major portion of the water remained in the product at lower inlet air temperatures [25]. A combination of these factors - high humidity, low drying capacity

and high moisture uptake by the product - led to higher water content in both, pellet core and film coating. The remaining water is partially incorporated into the coating film leading to a temporary increase in the film thickness. It has been reported that these conditions may cause an increased surface roughness of the films [20].

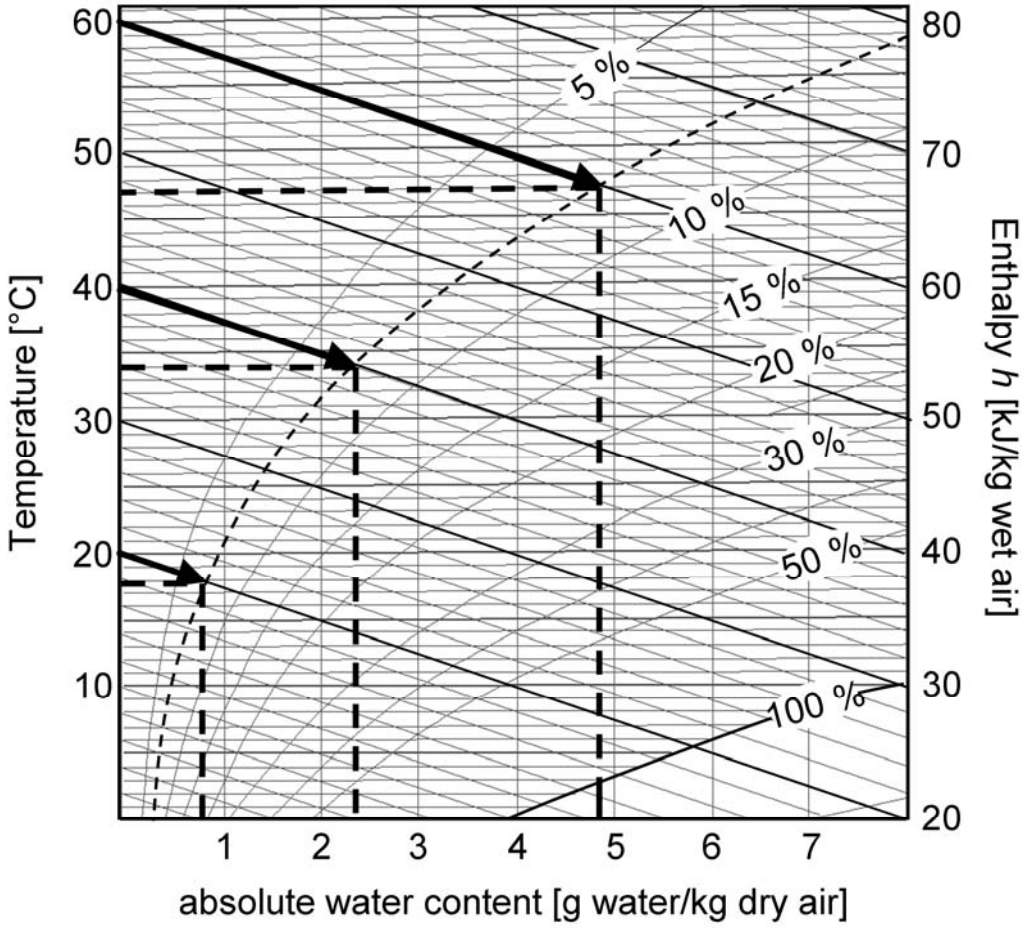

Fig. 4: Modified Mollier h,x for the demonstration of the drying capacity at the used inlet air temperatures

In addition to the process parameters during coating the storing conditions affect the properties of the final product. It has been described for tablets that they undergo significant dimensional changes during a coating process [26]. These changes were even more pronounced during storage and equilibration at ambient conditions. Aulton et al. investigated the effect of storage conditions on the mechanical properties of HPMC films [27]. Storage at high humidity led to water uptake into the film samples and thus plasticization. In the present study the samples were stored over silica gel. Under these conditions the opposite effect occurred. The water was removed from the film causing two effects, a loss of plasticization and a decrease in film thickness. Whereas the acid

form of shellac has a comparatively low T_g [28], the T_g of the salt form is higher with values of about 65 °C and above [15] depending on the shellac type. The removal of the residual water led to an increase in the T_g resulting in a loss of film flexibility. Together with the above mentioned decrease in the film thickness and the dimensional changes of the pellet core the resulting internal stress [29, 30] most likely led to the cracks and the loss of gastric resistance.

Curing of pellets coated at low inlet air temperature

A loss of the barrier function as a result of low inlet air temperatures is a phenomenon well known from coatings applied as aqueous dispersions. If coating is performed below the minimum film forming temperature (MFT), coalescence of the polymer particles and thus film formation does not take place [31]. However, with coatings prepared from aqueous dispersions film formation can be induced by a subsequent curing step with temperatures above the MFT.

However, it has to be emphasized, that the investigated pellets were coated with aqueous solutions and not aqueous dispersions of shellac. Nevertheless, an additional thermal treatment of the shellac-coated pellets was performed to clarify if a final curing step removes the defects in the film.

The pellets were cured at two different temperatures: At 60 °C, the temperature of the initial coating process, and at 80 °C, a temperature above the T_g of the shellac salt form. The results of the dissolution experiments are shown in Fig. 5. Obviously, the cracks in the coating film were nonreversible. Drug release at pH 1.2 was decreased with pellets cured at higher temperatures and for longer curing periods. However, after 12 h of curing at 80 °C still 40 % of the dose was released within 2 h. Most likely, the curing process led to a decrease in number and the size of the cracks resulting in a decrease in drug release at pH 1.2. However, even after this long term curing a certain amount of cracks remained. SEM pictures of cured pellets support this hypothesis (Fig. 6). It is obvious from these pictures that although the edges of the cracks became smoother with increasing temperature, the cracks themselves still remained.

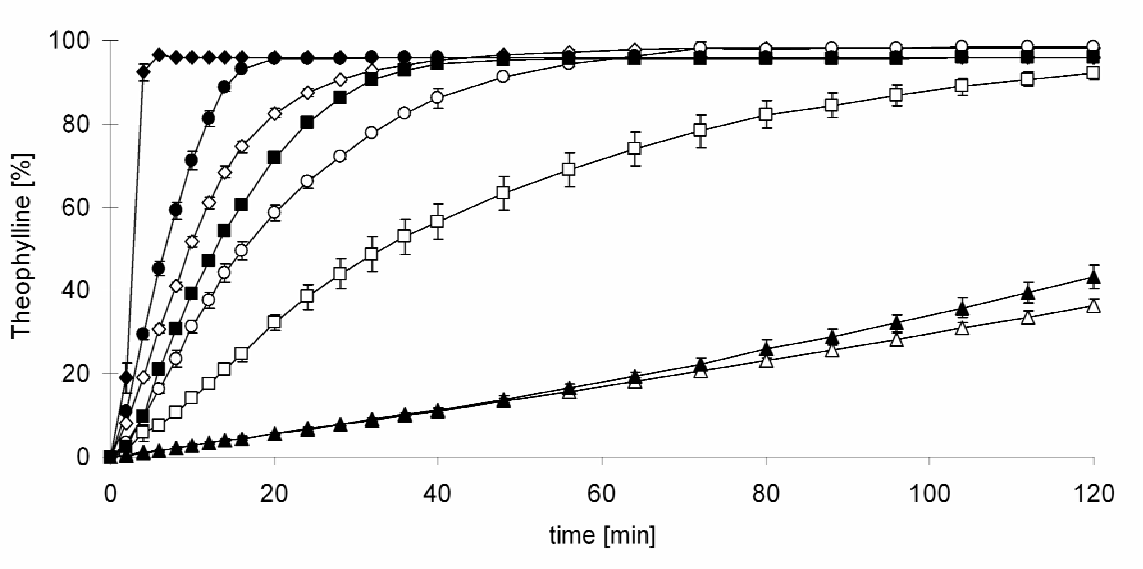

Fig. 5: Influence of curing conditions on drug release profiles of pellets coated with Marcoat at 20 °C (means ± SD; n=3)
pH 1.2: ◇ uncured; ○ 60 °C, 2 h; □ 80 °C, 2 h; △ 80 °C, 12 h
pH 7.4: ◆ uncured; ● 60 °C, 2 h; ■ 80 °C, 2 h; ▲ 80 °C, 12 h

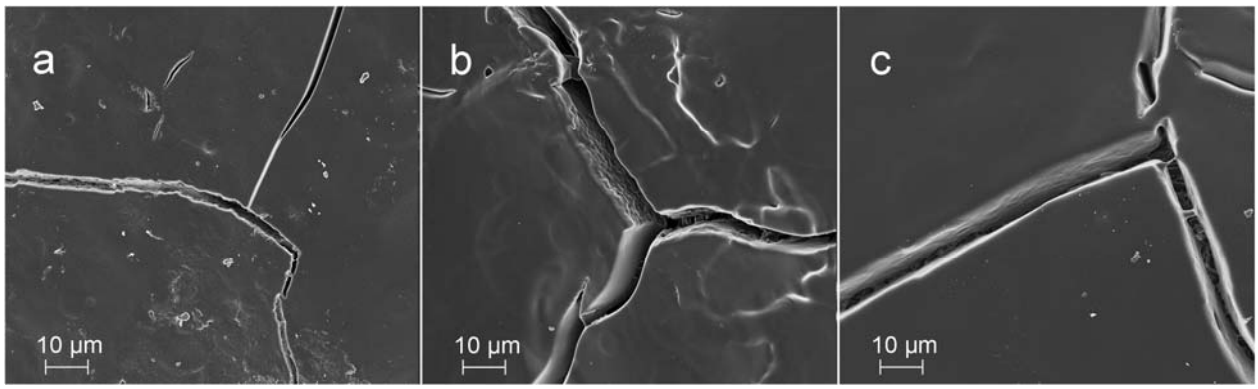

Fig. 6: SEM pictures of pellets coated with Marcoat at 20 °C treated under different curing conditions.
a) 60 °C, 2 h; b) 80 °C, 2 h; c) 80 °C, 12 h

In addition to the failure of the curing process regarding the film integrity the thermal treatment led to changes in the material properties of the coating layer. This is apparent in the dissolution profiles at pH 7.4: Drug release was decreased even at this pH induced by artificial aging as a result of the thermal treatment. Prolonged thermal treatment of shellac led to polymerization and thus decreased solubility.

After 12 h of curing at 80 °C the dissolution profiles at pH 1.2 and 7.4 were almost superimposed. The coating layer was completely insoluble even at pH 7.4. Drug release took place only by diffusion through the cracks, independent of the pH.

Correlation of the dissolution profiles with the physicochemical properties of shellac

The T_g values of the investigated shellac types ranged from 66 to 82 °C (Table 1). These values are high compared to data found in the literature [28, 32, 33]. However, this discrepancy can easily be explained by the type of investigated shellac. In most publications the T_g of the acid form of shellac is determined. As described in a previous study [15], the T_g of shellac ammonium salt is significantly higher.

Ideally, coating films have a high tensile strength, a large elongation at break and a high elastic modulus. Such films provide a good mechanical stability without being brittle [27]. The investigated shellac films show high values of tensile strength and elastic modulus. However, the low elongation at break proves the brittleness of the unplasticized material.

Table 1: Overview of the physicochemical and film forming properties of the investigated shellac types (means ± SD, T_g: n=3; mechanical testing: n=5)

Shellac type		Marcoat	SSB 55	Pearl
T_g [°C]		67.7 ± 0.7	65.9 ± 0.8	77.5 ± 0.8
mechanical properties	Tensile strength [MPa]	7.14 ± 0.64	5.43 ± 0.58	5.89 ± 0.55
	Elastic modulus [MPa]	1820 ± 211	1107 ± 124	1344 ± 286
	Elongation at break [%/mm^2]	0.308 ± 0.033	0.241 ± 0.051	0.266 ± 0.036
continuous coating film (in dependence on temperature)	20 °C	no	no	no
	40 °C	yes	no	yes
	60 °C	yes	yes	yes

In Table 1 the physicochemical properties of the investigated shellac types are listed together with the film forming properties. It is obvious that a prediction of the film formation is impossible on the basis of the physicochemical properties. The T_g could be related to the flexibility of the shellac coating and thus to the ability to resist internal stress and to form a continuous film even at low inlet air temperatures. However, a relationship between the T_g values of the shellac types and their film forming properties

could not be found. Even though SSB 55 has the lowest T_g, the coatings prepared from this shellac type tended to break at higher temperatures than films of Pearl, which shows an 11 °C higher T_g.

Generally, two possible measures to avoid cracking of film coatings are suggested: reduction of the stress build-up and increase in the cohesive strength of the film [34]. The latter has been shown for synthetic polymers by increasing their molecular weight. However, this modification is not possible for the natural material shellac. Hence, only the addition of a plasticizer can be used to reduce the internal stress build-up and thus to avoid cracking of the film coating. In the present study with the modification of the inlet air temperature and the resulting increase in the drying capacity a third option is provided to achieve a uniform coherent coating without addition of a plasticizer. However, it has to be considered that too high inlet air temperatures can lead to spray drying of the coating formulation and thus incomplete film formation [17]. Hence, for each formulation individual process parameters have to be established.

5.4. Conclusion

In the present study the influence of the inlet air temperature on drug release from shellac-coated pellets was investigated. It was found that even though coating was performed with aqueous solutions, a minimum inlet air temperature had to be exceeded to obtain a continuous coating film. Below that temperature cracks in the coating film appeared resulting in changes in the release profiles and especially loss of gastric resistance. It could be shown that the temperature dependence of the coating process was different for the investigated shellac types. This temperature dependence can hardly be predicted from the physicochemical and mechanical properties of the shellac types. In contrast to coatings from aqueous dispersions these coating defects were found to be nonreversible by a subsequent curing step.

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6. Development of shellac-coated sustained release pellet formulations

Development of shellac-coated sustained release pellet formulations

Abstract

Shellac regained importance for pharmaceutical applications since the introduction of its aqueous ammoniacal solutions. Because of the comparatively high dissolution pH of this material, further additives are required if shellac is used as enteric coating material. However, this dissolution bahavior of shellac may be of interest for sustained release or colon targeting applications. To obtain sustained drug release from shellac-coated pellet formulations different modifying subcoats were investigated with regard to their ability to prolong drug release resulting from interactions with the shellac coating film. Different subcoats containing calcium chloride, citric acid or Eudragit® E, respectively, were applied to immediate release theophylline pellets which were subsequently coated with shellac. Drug release from the resulting pellet formulations was measured. The mechanism of interaction between the modifying subcoat ingredients and the shellac coating was investigated using IR spectroscopy. All formulations with modifying subcoat prolong drug release. Whereas the effect of calcium chloride was a result of ionic interactions with shellac, the effect of citric acid was a reduction of the degree of dissociation of shellac. The influence of Eudragit® E can be explained by the solubility characteristics of this basic polymer. The application of modifying subcoats is an easy and effective means to achieve sustained release from shellac-coated dosage forms. The choice of a suitable substance and the adjustment of its concentration allow tailor made sustained release profiles.

6.1. Introduction

Shellac is the only pharmaceutically used resin of animal origin. It is the purified product of the natural material Lac which is secreted by the small parasitic insect Kerria Lacca on various host trees in South Eastern Asia [1, 2]. It consists mainly of esters of aleuritic acid, butolic acid, jalaric acid and shellolic acid [3-5].

Shellac has good film forming properties. The films provide high gloss [6] and low permeability for water vapor and gases [7, 8]. Shellac is non-toxic, physiologically harmless and therefore listed as GRAS (Generally Recognized As Safe) by the FDA [9]. This regulatory status allows the use of shellac as additive in food products where the material already plays a major role as coating for confectionaries and citrus fruits [10, 11]. Since the introduction of ammoniacal aqueous solutions shellac could regain importance for pharmaceutical applications. Shellac coatings can easily be applied from aqueous solutions and they do not show the instability problems of coatings prepared from organic solutions [12, 13]. Due to its acidic character shellac is mostly used as enteric coating [14, 15, 13].

However, shellac has a comparatively high dissolution pH of about 7.3 [12] which is unsuitable for the application in conventional enteric coated dosage forms. Because of this high dissolution pH the addition of excipients is necessary to achieve a faster drug release in the small intestine. Nevertheless, it has been suggested previously that this characteristic qualifies shellac for application in colon targeting formulations [16, 17]. The shellac coating layer remains intact during the passage of the stomach and the small intestine until it reaches the colon with its higher pH. This allows the transport of drugs into the colon for a topical treatment of the colonic diseases. Moreover, the peptidase activity in the colon is lower than in the upper GI tract allowing for the oral delivery of peptide drugs such as insulin [18].

Besides colon targeting also sustained release formulations have been developed. Pearnchob et al. investigated drug release from shellac containing matrix tablets. These formulations were prepared either by compression of powder or granules. These tablets provided sustained drug release depending on the drug/shellac ratio [19]. This concept was further modified by Kanokpongpaiboon et al. by treating shellac containing matrix tablets with additional annealing at different temperatures. This thermal treatment leads to artificial aging, changes in the solubility characteristics of the material and ultimately to a pronounced sustained release behavior [20].

The aim of the present study was to achieve sustained drug release from coated pellet formulations using shellac as the coating material. Since shellac is an acidic material, its dissociation is pH-dependent and the carboxylate groups may interact with cationic structures. These interactions were induced by application of subcoats consisting of citric acid, calcium ions or the cationic polymer Eudragit® E. Drug release from these formulations was investigated and the mechanism of interaction was analyzed.

6.2. Materials and methods

Materials

Shellac (SSB 55 Pharma), Stroever Schellack Bremen, Germany; Kollidon® 30, BASF, Ludwigshafen, Germany; Eudragit® E, Evonik Röhm, Darmstadt, Germany; all other chemicals used were of analytical grade.

Methods

Preparation of coating solutions for subcoat application

Ten different subcoat formulations were prepared. The composition of each formulation is listed in Table 1. The ingredients were dissolved at room temperature under moderate stirring in the respective solvent. The amount of solid was 10 % [w/w] for all subcoat formulations.

Preparation of shellac coating solutions

Ground shellac was dissolved in 1.5 % [w/V] ammonium bicarbonate solution at 50 °C to a final concentration of 15 % [w/w]. As the presence of excess ammonium salt influences the dissolution properties of shellac films, the solutions were heated to 65 °C to remove the excessive ammonium salt in the form of free ammonia and carbon dioxide. Evaporated water was replaced. The heating process was repeated until a constant pH was reached. The pH of the final solutions was 7.5 (Mettler Toledo MP 225 pH-meter, Columbus, Ohio, USA).

Table 1: Composition of the coatings of the investigated pellet formulations (CL: Coating level)

No.	Subcoat								Shellac
	Ingredient 1	[%]	Ingredient 2	[%]	Kollidon [%]	Solvent	[%]	CL [mg/cm^2]	CL [mg/cm^2]
1	/	/	/	/	/	/	/	/	2.5
2	/	/	/	/	10	H_2O	90	1	2.5
3	Citric acid	1	/	/	9	H_2O	90	0.5	2.5
4		1	/	/	9	H_2O	90	1	2.5
5		1	/	/	9	H_2O	90	1.5	2.5
6		0.5	/	/	9.5	H_2O	90	1	2.5
7	$CaCl_2$	1	/	/	9	H_2O	90	0.5	2.5
8		1	/	/	9	H_2O	90	1	2.5
9		1	/	/	9	H_2O	90	1.5	2.5
10	Eudragit® E	1	/	/	9	Ethanol	90	1	2.5
11		1	Citric acid	0.5	8.5	H_2O	90	1	2.5

Coating of theophylline pellets

The subcoat was applied to 50 g of immediate release theophylline pellets in a Mini Glatt fluid bed coater (Glatt, Binzen, Germany) with Wurster insert (30 mm diameter, 15 mm gap) using a 0.8 mm two-way nozzle, an atomizing air pressure of 1.5-1.7 bar and a spraying rate of 1 g/min. Final coating levels of the subcoat were 0.5, 1 and 1.5 mg/cm^2 (Table 1). Inlet air temperature was set to 60 °C for the aqueous coating solutions and 20 °C for the ethanolic solution. Inlet air pressure was adjusted to 0.3 bar. The outer shellac coating was applied under the same conditions with 45 g of the subcoat layered pellets. The final shellac coating level was 2.5 mg/cm^2.

Characterization of coated pellets

After each coating step the pellets were characterized for their coating level, diameter and weight. These values were used as quality control criteria of the coating process as well as the basis for calculation of the required shellac mass for the final shellac coating level.

The average coating level of subcoat and shellac coating was calculated from the difference in theophylline content of coated and uncoated pellets. A sample of 150 mg pellets was dissolved in 250.0 ml 0.1 M NaOH using an ultrasonic bath. After sufficient dilution with 0.1 M NaOH the theophylline concentration was determined

spectrophotometrically at 275 nm using a Lambda 25 spectrophotometer (Perkin Elmer, Beaconsfield, UK).

The weight of a single pellet corresponds to the average weight determined from a sample of 500 pellets. The dimension of the pellets was determined by image analysis using a SteREO Discovery.V8 stereomicroscope equipped with an AxioCam ICc and AxioVision software (all from Zeiss, Jena, Germany). The average radius was determined from at least 500 pellets.

Dissolution of shellac-coated theophylline pellets

Dissolution tests were performed at 37 °C with approximately 150 mg pellets in 1000 ml simulated gastric fluid (pH 1.2) and phosphate buffer (pH 6.8; 7.4) using a paddle apparatus at 100 rpm (AT 7, Sotax, Allschwil, Switzerland). Dissolution experiments were run for 2 h at pH 1.2 and 7.4 and for 10 h at pH 6.8. Drug release was recorded spectrophotometrically at 271 nm using a Lambda 25 spectrophotometer equipped with 1 mm flow through Quartz cells.

Preparation of film samples

Film samples for IR investigations were prepared by a casting and evaporation method: Films of shellac in its acid form and Eudragit® E were each prepared from 10 % [w/w] ethanolic solutions. The combination of Eudragit® E and shellac in a 1:1 molar ratio referring to their functional groups was dissolved in ethanol to a final concentration of 10 % [w/w] solid. The solutions were filtered and cast onto Teflon plates. After evaporation of the solvent at room temperature the films were carefully peeled off and cut into the desired shape.

Preparation of calcium shellac

Calcium shellac was prepared by addition of 1M calcium chloride solution to the aqueous shellac coating solution. Calcium shellac precipitates from the solution. The addition of calcium chloride was continued until a colorless, translucent solution was obtained. The precipitate was filtered, rinsed with water and dried at 60 °C. Finally, the material was ground in a fly cutter and stored over silica gel until further investigation.

FT-IR spectroscopy

In order to determine possible interactions between the subcoat and the shellac coating IR spectroscopy was performed using a Tensor 37 FT-IR spectrometer (Bruker, Ettlingen, Germany) equipped with a MIRacle™ ATR unit (Pike Technologies, Madison, Wisconsin, USA). The respective film or powder samples were fixed to the reflection plate of the ATR unit. The spectrum was calculated from 16 measurements using the OPUS software.

6.3. Results and discussion

Eleven different shellac-coated pellet formulations were prepared and tested for drug release. The formulations contained either no subcoat, a subcoat without modifying substance as blank or a subcoat with different substances at different subcoat coating levels.

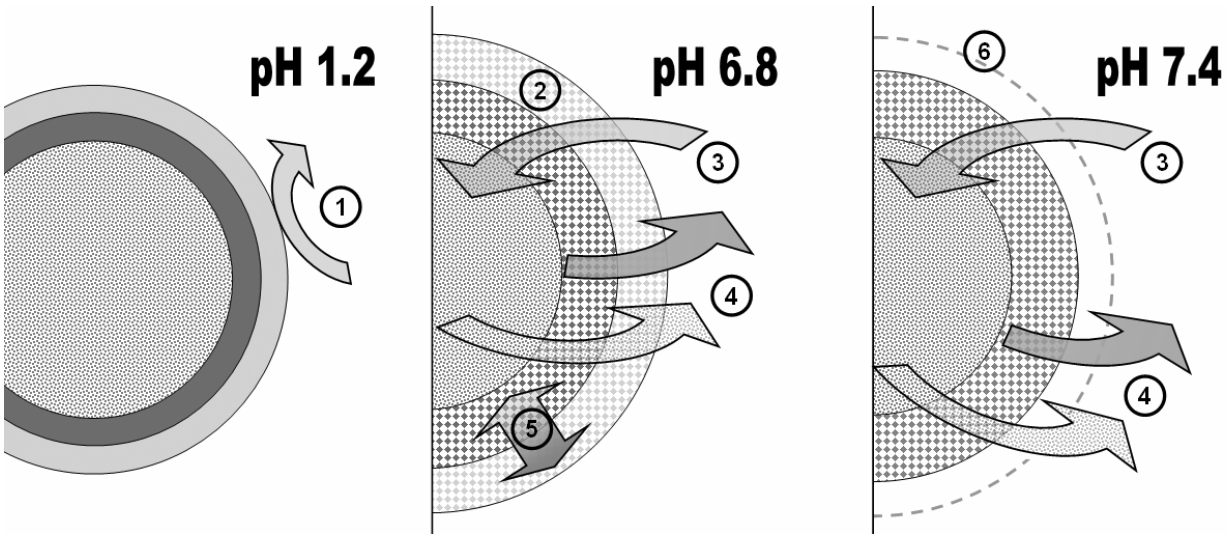

Fig. 1: Drug release mechanism from shellac-coated drug pellets with subcoat at different pH: 1) gastric resistance; 2) swelling of shellac coating; 3) penetration of water into the subcoat and the pellet core; 4) dissolution and release of drug and subcoat; 5) interactions between subcoat and shellac coating; 6) dissolution of shellac coating

The mechanism of drug release at the investigated pH values is shown schematically in Fig. 1. Shellac as acidic material does not dissolve at pH 1.2 maintaining its barrier function and providing gastric resistance. Dissolution testing was also done at pH 6.8, the standard buffer for testing of enteric-coated dosage forms. However, this pH is below the dissolution pH of shellac. At pH 6.8 the material only swells resulting in a reduced barrier function of the coating and allows for water penetration into the pellet core. Drug and subcoat material dissolve and diffuse through the coating layer. The pK_a of shellac is known to be about 6 [1, 21]. Even though the material does not dissolve at pH 6.8, a small amount of its carboxylic groups is dissociated and may interact with the subcoat material. Final dissolution tests were performed at pH 7.4 which is above the dissolution pH of shellac. The shellac coating dissolves followed by liberation of subcoat material and drug release.

Dissolution experiments at pH 1.2 confirmed gastric resistance and film integrity. None of the prepared formulations showed drug release of more than 4 % of the dose within 120 min of dissolution testing at pH 1.2. Therefore, all formulations fulfilled the specification of the pharmacopoeias for gastric resistance.

Drug release experiments at pH 6.8 showed a pronounced effect of the subcoat materials on the drug release performance of the investigated pellet formulations. It could be shown, that this effect can be attributed to the embedded substances and not to the presence of a subcoat itself (Fig. 2). In comparison to the formulation without subcoat, drug release from pellets with a blank subcoat (without modulating substance) was altered only negligibly. This slight slow down in drug release can be explained by the presence of the blank subcoat which represents a diffusion barrier. Other reasons are the time needed for dissolution process of the subcoat material and possibly a competing release of drug and subcoat material. However, all these factors are negligible compared to the release-modifying effect of the modulating substances present in the other subcoat formulations.

In Fig. 2 the effect of the investigated modulating substances on drug release at pH 6.8 is shown. All formulations displayed in this figure have a coating level of the subcoat of 1mg/cm^2. This allows a direct comparison of the effect of the modulating substances.

The greatest effect could be shown for the formulation containing citric acid. Citric acid is a tricarboxylic acid with three readily dissociable protons: pK_{a1} = 3.13, pK_{a2} = 4.76

and pK_{a3} = 6.40 [22]. After placing the pellets in the dissolution medium the shellac coating begins to swell allowing for diffusion of dissolution medium into the pellet core. The dissolution medium dissolves the subcoat material and the embedded citric acid is liberated. At pH 6.8 the citric acid in the subcoat dissociates resulting in a local pH decrease in the pellet core. Since shellac has a high pK_a, this reduced pH leads to reduced dissociation of shellac, a reduction of film swelling and thus a sustained drug release from the pellet formulation.

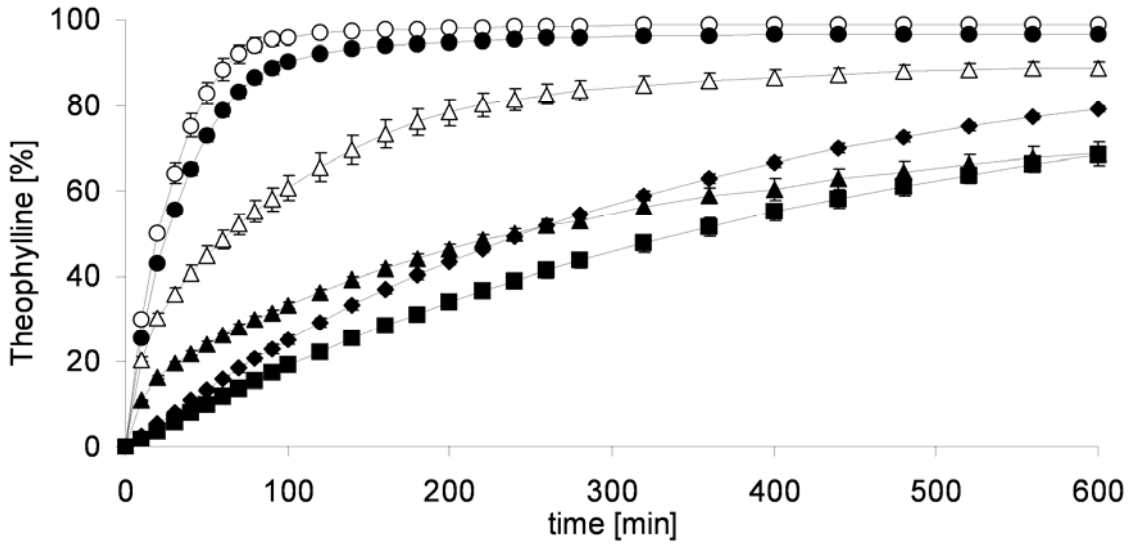

Fig. 2: Drug release from shellac-coated pellets with subcoat (CL: 1mg/cm^2) at pH 6.8 (means ± SD; n=3)
○ no subcoat ; ● blank subcoat (PVP)
■ citric acid (10 %); ◆ calcium chloride (10 %);
△ Eudragit® E (10 %); ▲ Eudragit® E/citric acid (10 %/5 %)

This mechanism also explains the sustained drug release observed with shellac-coated ascorbic acid pellets [23]. Drug release in that study was performed in water. In addition to the insolubility of shellac in this medium, the ascorbic acid pellet core suppressed a possible swelling of the coating layer. Hence, drug release could only take place through the coating defects mentioned in that publication.

It is well known, that calcium ions interact with many functional groups. This could result in reduced absorption of drugs in the GI tract as e.g. antibiotics [24]. Also, changes in drug release from drug formulations in the presence of calcium ions have been reported [25]. Calcium ions accelerated drug release from xanthan matrix tablets due to a change in the swelling bahavior of the matrix material. In the present study calcium ions

were used to achieve the opposite effect, a sustained release. Shellac forms water insoluble salts with calcium ions. This precipitating effect has been used previously for the preparation of calcium shellac microspheres [26, 27]. In the present study the calcium ions were embedded into the subcoat material. After swelling of the shellac coating layer the dissolution medium penetrates into the pellet and dissolves the calcium chloride subcoat. The liberated calcium ions interact with the shellac coating leading to precipitation of calcium shellac. This local precipitation in the coating layer leads to a decrease in film swelling, increased barrier function and thus sustained drug release.

Eudragit® E is a basic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate. The polymer is insoluble in saliva but dissolves in the acidic medium of the stomach. Therefore, it is generally used for taste masking applications. Eudragit® E films are insoluble at pH 5 or higher. Below pH 5 the polymer dissolves rapidly by salt formation [28]. In the present study Eudragit® E is combined with PVP in the subcoat. The amount of just 10 % Eudragit® E in the subcoat guarantees that no continuous Eudragit® E film is formed which might inhibit drug release at higher pH.

In comparison to citric acid and calcium chloride the prolonging effect of the Eudragit® E subcoat is found to be less pronounced. In contrast to the other modulating substances Eudragit® E is water insoluble and the pH of the dissolution medium is too high for dissolution of this basic polymer. Thus, no interaction between free base of Eudragit® E and the shellac coating could take place. However, in comparison to the blank subcoat drug release is prolonged. Combined with PVP the insoluble Eudragit® E most likely forms a denser matrix than PVP alone providing a more effective diffusion barrier.

The addition of citric acid to the Eudragit® E subcoat lowers the pH in the pellet core allowing for protonation of the basic polymer. This addition was intended to clarify whether protonation of the basic polymer led to an interaction with the shellac coat and a possible formation of an interpolymer complex. In fact, dissolution experiments showed that a combination of Eudragit® E and citric acid further decreases drug release. However, a comparison with a formulation containing citric acid alone at the same concentration as in the Eudragit® E-citric acid combination subcoat revealed almost identical dissolution profiles (Fig. 3). This proved that the decrease in drug release must be attributed mainly to the pH reduction caused by citric acid and not to an interaction of Eudragit® E and the outer shellac coating.

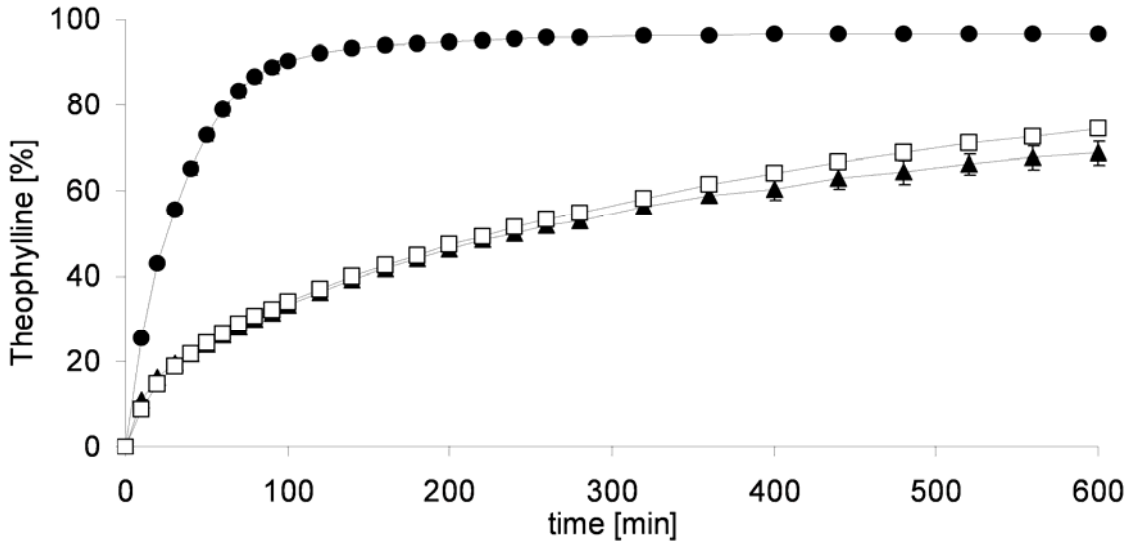

Fig. 3: Drug release from shellac-coated pellets with subcoat (CL: 1mg/cm^2) at pH 6.8 (means ± SD; n=3)
● blank subcoat (PVP);
□ citric acid (5 %); ▲ Eudragit® E/citric acid (10 %/5 %)

The formation of interpolymer complexes has been well studied for combinations of the basic polymer chitosan and acidic polymers such as sodium carboxymethylcellulose [29], polyacrylic acid [30] or Eudragit® L and Eudragit® S [31]. In these studies the interaction of basic and acidic polymer could be identified via IR spectroscopy by the formation of a new band in the area of 1560 cm^{-1}, which could be attributed to the interaction of the carboxylate group of the acidic polymer and the protonated amino group of the glucosamine in chitosan.

In Fig. 4 the IR spectra of shellac and Eudragit® E as well as the combination of both in a film and in a physical mixture are shown. In the film as well as in the physical mixture characteristic bands of the individual substances can be identified. However, in contrast to the physical mixture a band appears at 1568 cm^{-1} in the spectrum of the film of the combination shellac and Eudragit® E. This indicates an interaction of the carboxylate group of shellac and the protonated amino group of Eudragit® E. However, this interaction does not seem to significantly affect drug release from the pellet formulations. A possible explanation is the low solubility of both compounds at pH 6.8 although according to their pK_a values they are both charged to over 90 % at this pH.

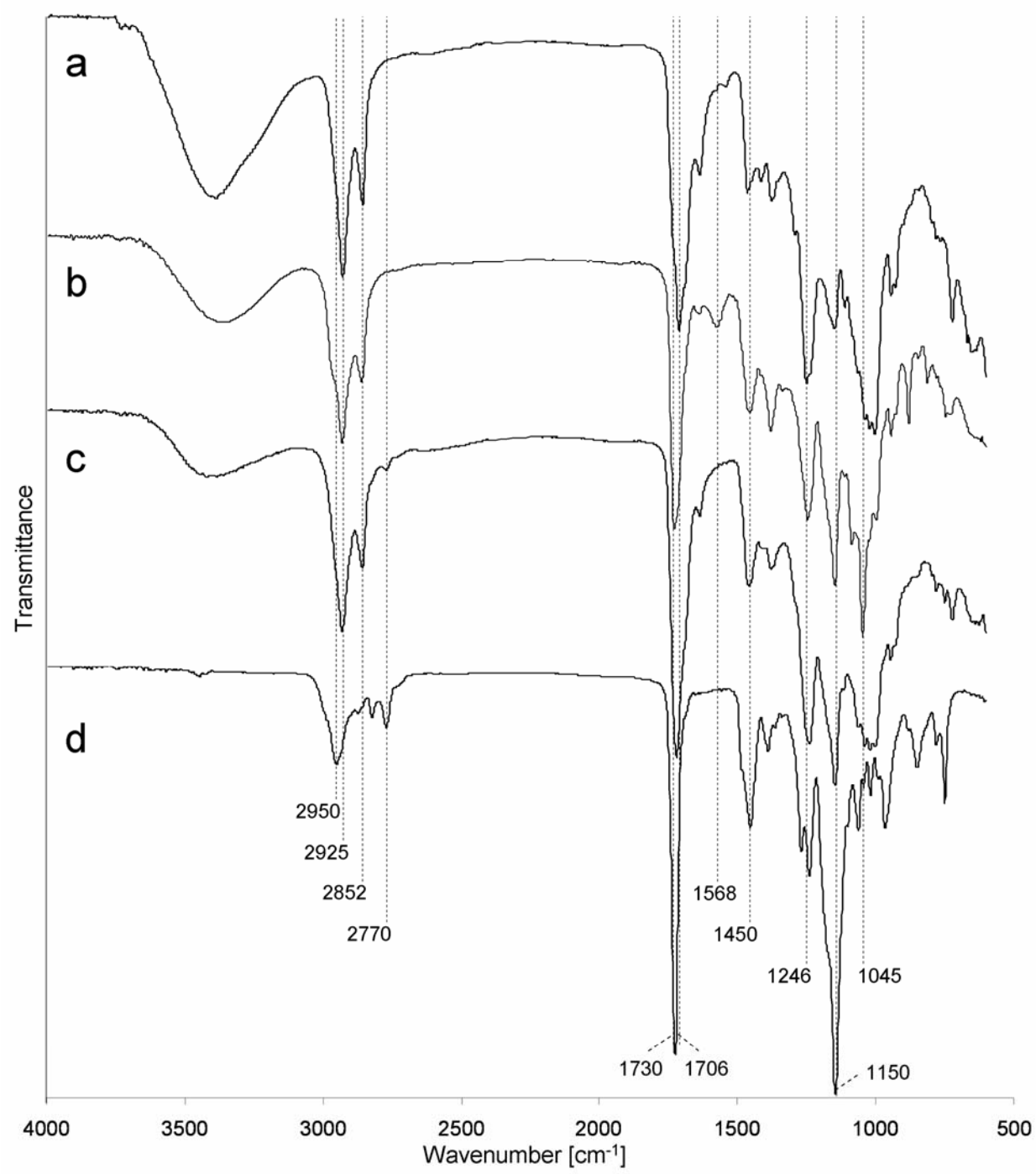

Fig. 4: IR spectra of a) shellac; b) Eudragit® E/shellac (1:1 molar ratio) film; c) Eudragit® E/shellac (1:1 molar ratio) physical blend; d) Eudragit® E

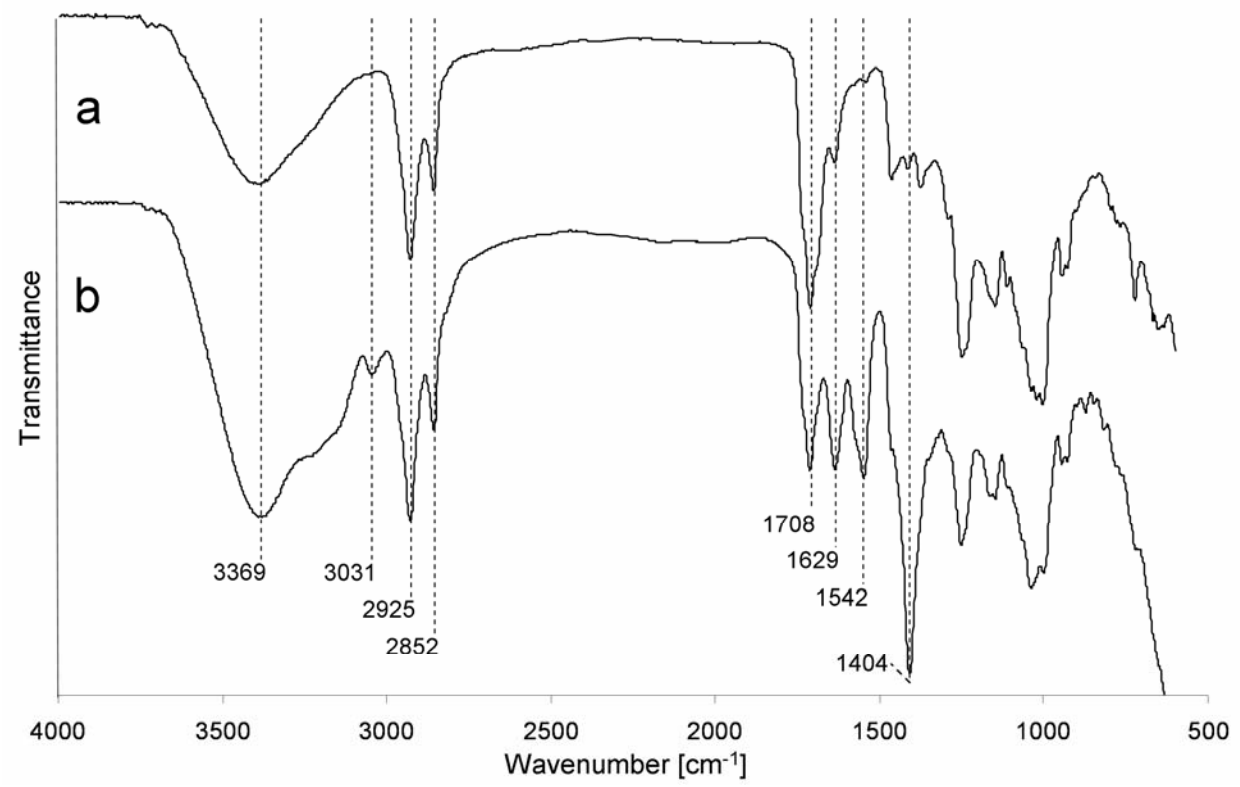

Fig. 5: IR spectra of a) shellac; b) calcium shellac

In Fig. 5 the IR spectra of shellac in its acid form and calcium shellac are shown to clarify the interaction between calcium ions and shellac. Whereas the location and intensity of the C-H stretching vibrations (2925 and 2852 cm^{-1}) remain almost unchanged, distinct changes appear in other areas of the spectrum of calcium shellac. The band in the area between 3700 and 3000 cm^{-1} is a result of O-H stretching vibrations. This band has a shoulder in the spectrum of the calcium salt and is located next to a small new band at 3031 cm^{-1}. This indicates an interaction of calcium ions with the carboxylate groups as mechanism of salt formation. The intensity of the bands at 1629, 1542 and 1404 cm^{-1} is significantly increased with calcium shellac compared to its acid form. It has been reported previously that a shift of the carbonyl band (asymmetric C=O stretching vibration) to areas around 1560 cm^{-1} can be attributed to an interaction between calcium ions and carboxylates [32, 33]. The bands at 1629 and 1404 cm^{-1} may be referred to the asymmetric and symmetric C=O stretching vibration, respectively, of the carboxylate. From changes in the spectrum it may be concluded that the mechanism of interaction is a salt formation of calcium ions and the carboxylate groups

of shellac. However, the presence of the carbonyl band at 1708 cm^{-1} in the calcium shellac spectrum indicates that not all carboxylic groups are involved in this salt formation.

Since the bands at 1629, 1542 and 1404 cm^{-1} also appear in the shellac acid spectrum it can be assumed that a small part of the material is deprotonated in the film.

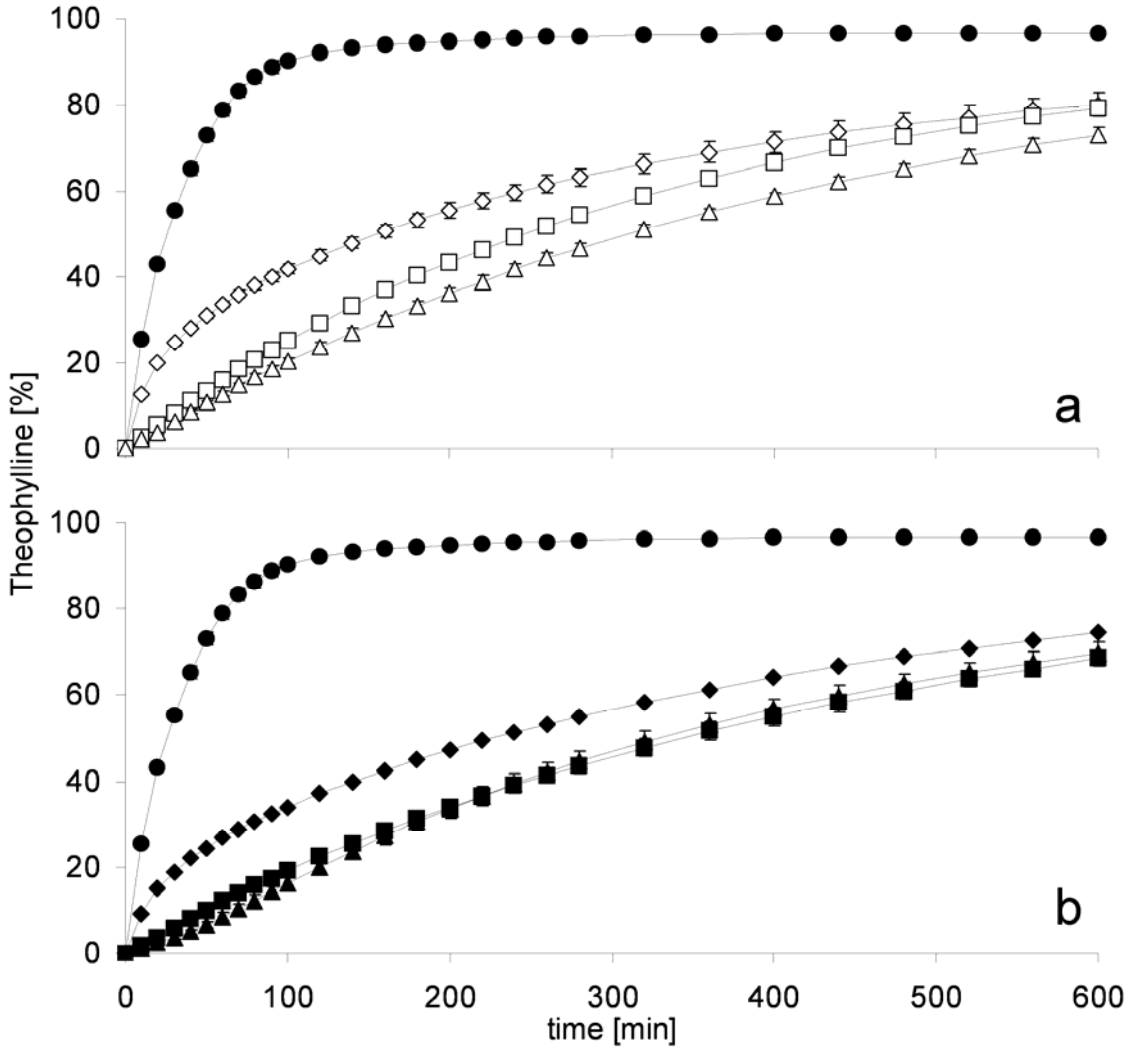

Fig. 6: Drug release from shellac-coated pellets with different subcoat coating levels at pH 6.8 (means ± SD; n=3)

● blank subcoat (PVP)

calcium chloride (10 %) CL: ◇ 0.5 mg/cm² □ 1 mg/cm² △ 1.5 mg/cm²

citric acid (10 %) CL: ◆ 0.5 mg/cm² ■ 1 mg/cm² ▲ 1.5 mg/cm²

In Fig. 6 drug release from pellet formulations with different coating levels of the citric acid and the calcium chloride subcoat is shown. As the concentration of modulating substance in the subcoat was kept constant for these formulations the total amount of the substance is proportional to the subcoat coating level.

Formulations with a calcium chloride subcoat at a coating level of 0.5 mg/cm^2 already show distinct sustained drug release. After an initial fast release, the precipitating effect of the calcium ions leads to a reduction of the release rate until after about 100 min a constant release rate is obtained. This release characteristic can be explained by the subcoat thickness. The 0.5 mg/cm^2 subcoat is not thick enough and drug can be released before the interaction between the subcoat and the shellac coating manifests itself in a decrease in drug release. Higher amounts of calcium ions in the subcoat further reduce the release rate. In contrast to the formulation with 0.5 mg/cm^2 the formulations with a higher amount of calcium ions show sustained drug release without this initial fast release. Before drug dissolution in the pellet core, calcium ions are dissolved from the subcoat and interact with the swollen shellac film. The thicker the subcoat the more pronounced is the decrease in drug release.

Formulations with a citric acid subcoat show almost the same release pattern as the formulations with calcium chloride subcoat. As with the calcium chloride the formulation with 0.5 mg/cm^2 citric acid subcoat shows an initial fast release, which slows down consistently in a comparable manner. However, in contrast to calcium chloride there is no significant difference between the 1 mg/cm^2 and the 1.5 mg/cm^2 citric acid subcoat formulations. This can be explained by the mechanism of interaction with the shellac coating. Calcium chloride interacts with shellac by precipitation, citric acid by decreasing the pH and a reduced dissociation of the shellac coating. During the dissolution experiment, in addition to the drug, material from the subcoat diffuses through the swollen shellac coating layer. This leads to a mass reduction of both materials in the pellet core with ongoing dissolution testing. Calcium ions on the one hand interact with dissociated carboxylate groups of shellac. This interaction remains effective as long as sufficient calcium ions are present in the pellet core. Thus, the more calcium ions the denser the shell of precipitated calcium-shellac and the slower drug release. Citric acid on the other hand interacts with shellac coating in a more general way. Here, a reduced dissociation instead of salt formation decreases drug release as long as a low pH is maintained in the pellet core. The presence of dissociated and undissociated acid creates a buffer medium in the pellet core that ensures a constant pH which is almost

independent of the citric acid concentration. Hence, above a certain coating level no further change in drug release was observed.

At pH 6.8 the shellac coating layer of all pellet formulations remained intact during the dissolution experiments. This confirms drug diffusion through the intact coating film as release mechanism.

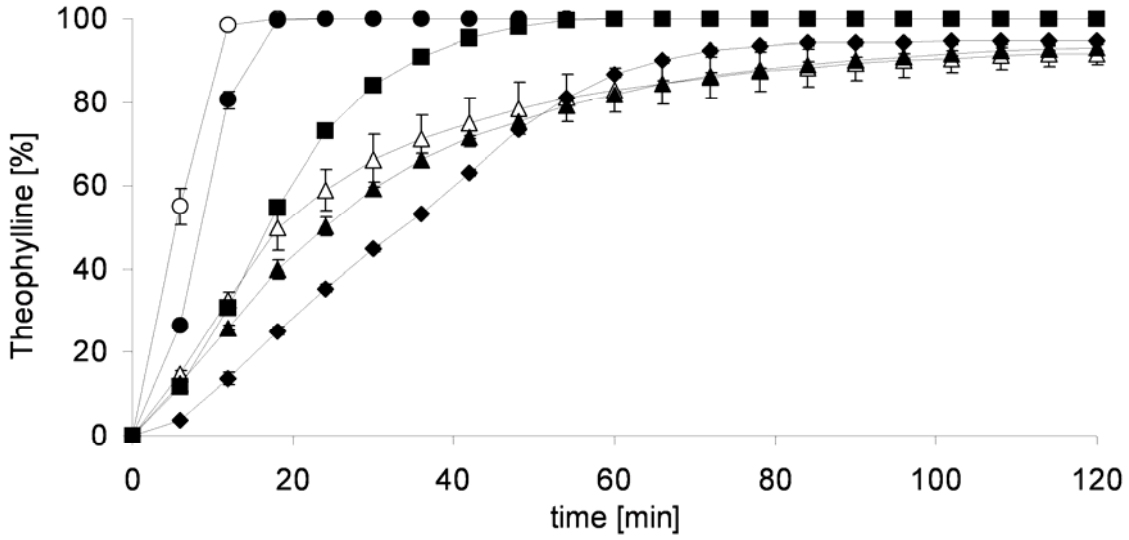

Fig. 7: Drug release from shellac-coated pellets with subcoat (CL: 1mg/cm^2) at pH 7.4 (means ± SD; n=3)
○ no subcoat, ● blank subcoat (PVP)
■ citric acid (10 %); ◆ calcium chloride (10 %)
△ Eudragit® E (10 %); ▲ Eudragit® E/citric acid (10 %/5 %)

In Fig. 7 the drug release profiles at pH 7.4 are displayed for the investigated formulations. At this pH the effect of the subcoats is found to be significantly less pronounced. As pH 7.4 is above the dissolution pH of shellac a different release mechanism is observed. In contrast to pH 6.8 the drug is not released after swelling of the coating layer by slow drug diffusion but by dissolution of the coating layer with subsequent fast drug liberation. Hence, the individual influence of the different modulating substances has changed. The effect of citric acid, which shows the greatest impact on drug release at pH 6.8, is almost negligible at pH 7.4. The dissolution medium rapidly dissolves the shellac coating leading to neutralization of the citric acid in the subcoat. This effect is also observed with the Eudragit® E formulations containing citric acid. The influence of the acid is barely visible in the initial phase of drug release. Once

the dissolution medium reaches the pellet core, the acid is neutralized and the release profile approaches that of the Eudragit® E subcoat formulation without acid additive. In comparison to citric acid, the dissolution medium adversely affects drug release from formulations containing Eudragit® E. At pH 7.4 the polymer is insoluble providing a diffusion barrier which prolongs drug release. This effect is also observed for the calcium chloride formulation. The calcium ions interact with the dissociated shellac under formation of insoluble calcium shellac. In contrast to citric acid this precipitating effect of calcium ions is non reversible under the dissolution testing conditions and leads, as observed with Eudragit® E, to the formation of a diffusion barrier that prolongs drug release. The presence of this barrier could be confirmed by visual examination of the pellet samples after dissolution testing. Pellets of formulations with calcium chloride and Eudragit® E subcoats had a jelly like shell consisting of the respective precipitate.

6.4. Conclusion

The application of modifying subcoats consisting of citric acid, calcium chloride or Eudragit® E is an effective means to obtain sustained drug release from shellac-coated pellets. Whereas the effect of calcium chloride is a result of ionic interactions with shellac the effect of citric acid is a reduction of the degree of dissociation of shellac. The influence of Eudragit® E can be explained by the solubility characteristics of this basic polymer. The choice of a suitable substance and the adjustment of its concentration in the subcoat allow tailor made sustained release profiles.

Except for Eudragit® E, all materials used in the investigated pellet formulations are approved for application in food products. Hence, the combination of citric acid or calcium chloride containing subcoats with an outer shellac coating could be of interest for application in sustained release vitamin formulations or dietary supplements.

6.5. References

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Eur. J. Pharm. Biopharm. 68: 201-206 (2008)

7. Appendix

Curriculum vitae

Personal data:

Name:	Yassin Farag
Date of birth:	August 14, 1979
Place of birth:	Hamburg
Marital status:	married

Job History:	since 01/2007	Ph.D. student, Pharmaceutical Technology, University of Hamburg; supervisor: Prof. Leopold
	04/2005-09/2006	Ph.D. student, Pharmaceutical Biology, University of Hamburg; supervisor: Prof. Heisig
	06/2004-12/2006	Pharmacist in various pharmacies in Hamburg
Job Specialization:	since 04/2006	Training as Pharmaceutical specialist for Pharmaceutical Technology
Education:	06/2004	Pharmacist Licensure
	05/2003-04/2004	Internship:
	05/2003-10/2003	AstraZeneca GmbH, Wedel
	11/2003-04/2004	Pharmacy: Eimsbütteler Apotheke, Hamburg
	04/1999-04/2003	Pharmaceutical studies, University of Hamburg
School:	06/1998	A-level diploma, Gymnasium Schwarzenbek

Publication List

Publications as first author:

Farag, Y., Leopold, C.S.
Physicochemical Properties of Various Shellac Types.
Dissolution Technol. 16: 33-39 (2009)

Farag, Y., Leopold, C.S.
Investigation of Drug Release from Pellets Coated with Different Shellac Types.
Drug Dev. Ind. Pharm., in press (2010)

Farag, Y., Leopold, C.S.
Influence of the Inlet Air Temperature in a Fluid Bed Coating Process on Drug Release from Shellac-Coated Pellets.
Drug Dev. Ind. Pharm., in press (2010)

Farag, Y., Leopold, C.S.
Mimicking the Aging Process of Shellac by Thermal Treatment.
AAPS PharmSciTech., submitted (2010)

Farag, Y., Leopold, C.S.
Development of Shellac-Coated Sustained Release Pellet Formulations.
Eur. J. Pharm. Sci., submitted (2010)

Conference contributions – oral presentations:

Farag, Y., Leopold, C.S.
Influence of the Coating Temperature on Drug Release from Shellac-Coated Pellets.
CRS Annual Meeting and Exposition, Copenhagen, Denmark (2009)

Conference contributions – oral presentations:	Farag, Y., Leopold, C.S. Investigation of the Dissolution Properties of Shellac by the Intrinsic Dissolution Method. Annual meeting of the DPhG, Bonn, Germany (2008)
Conference contributions – poster presentations:	Farag, Y., Leopold, C.S. Sustained Release from Shellac-Coated Pellets with Different Subcoats. CRS Annual Meeting and Exposition, Portland, USA (2010) Farag, Y., Leopold, C.S. Modification of Drug Release from Shellac-Coated Pellets by Ionic Interactions. 7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Valletta, Malta (2010) Farag, Y., Leopold, C.S. Comparison of Physicochemical and Coating Properties of Different Shellac Types. AAPS Annual Meeting and Exposition, Los Angeles, USA (2009) Farag, Y., Leopold, C.S. Simulation of the Aging Process of Shellac by Thermal Treatment. Annual Meeting of the DPhG, Jena, Germany (2009) Farag, Y., Leopold, C.S. New Insights into the Properties of Shellac. CRS Annual Meeting and Expositition, New York City, USA (2008)

Hazardous materials

Substance	Supplier	Danger symbol	Code letter	Risk phrases	Security phrases
Acetic acid	Carl Roth, Karlsruhe, Germany		C	10-35	23-26-45
Benzoic acid	Carl Roth, Karlsruhe, Germany		Xn	22-36	24
Calcium choride	Carl Roth, Karlsruhe, Germany		Xi	36	22-24
Citric acid	Carl Roth, Karlsruhe, Germany		Xi	36	26
Diethylether	Carl Roth, Karlsruhe, Germany		F+, Xn	12-19-22 66-67	9-16 29-33
Ethanol	Carl Roth, Karlsruhe, Germany		F	11	7-16
Eudragit® E	Evonik, Darmstadt, Germany		N	52-53	61
Eudragit® L	Evonik, Darmstadt, Germany		Xn	23	23-36
Hydrochloric acid	Carl Roth, Karlsruhe, Germany		C	34-37	26-45
Phenolphthalein	Carl Roth, Karlsruhe, Germany		T	45-62-68	53-45
Potassium carbonate	Carl Roth, Karlsruhe, Germany		Xi	36-37-38	22-26
Potassium hydroxide	Carl Roth, Karlsruhe, Germany		C	22-35	26-45 36/37/39
Salicylic acid	Carl Roth, Karlsruhe, Germany		Xn	22-45	22-24 26-39
Sodium carbonate	Carl Roth, Karlsruhe, Germany		Xi	36	22-26
Sodium hydroxide	Carl Roth, Karlsruhe, Germany		C	35	26-45 37/39
Theophylline	Temmler, Ireland		Xn	22	

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Hamburg, den

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Yassin Farag