Development of polymer blend coatings for tailor-made drug release from solid dosage forms

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Abstract

The coating of solid oral dosage forms with functional polymers is a common approach to achieve controlled drug release. However, the development of coating formulations with the required properties for the release of drugs from a solid core is often difficult. A particularly complex challenge is to achieve pH-independent release of a pH-dependent soluble drugs such as weak acids or bases from a coated dosage form. In this regard, polymer blend coatings have been proven suitable for a tailor-made drug release of weak basic drugs. However, to date no polymer coating or polymer blend coating for the pH-independent release of weakly acidic drugs is available.

The aim of this thesis was to develop a coating suitable for pH-independent release of weakly acidic drugs from coated solid dosage forms. The investigations focused on blends of cationic ammonium methacrylate copolymers and methacrylic acid - ethyl acrylate copolymer, also known under their trade names Eudragit® RL (RL) and Eudragit® L-55 (L55). Furthermore, physicochemical alterations in RL/L55 copolymer films during swelling was investigated with various analytical techniques. Finally, the in vivo release behavior of an optimized RL/L55 blend coated dosage form containing a weakly acidic drug was simulated in drug release experiments.

Initially, the suitability of RL/L55 blend coatings for pH-independent release of weakly acidic drugs from solid oral dosage forms was investigated. Theophylline pellets were coated with RL/L55 blends in various blend ratios; the pellets were coated from either organic solution or aqueous dispersion of the copolymer blends. The pH-independent soluble theophylline was chosen as a model drug to identify changes in the drug permeability of the coating in dependence on the pH of the release medium. For pellets coated with organic polymer solutions, drug release experiments in various media revealed a strong dependency of the theophylline release rate from RL/L55 coated pellets on the pH value of the release medium. Furthermore, the release rates depended on the RL/L55 blend ratios of the coating and were generally higher in acidic media than in basic/neutral media. Such a release behavior is a necessary prerequisite for a pH-independent release of weakly acidic drugs.

The release behavior of the investigated theophylline pellets depended on whether the coat-

ing was applied from organic polymer solution or aqueous dispersion. The aim of a further study was to identify the reason for the dependency of the release behavior of RL/L55 coated pellets on the coating formulation. The investigation focused on the film forming properties, the film homogeneity, and the solid state interactions between the copolymers within the films. In contrast to copolymer films from organic solution, copolymer films from aqueous dispersion were inhomogeneous on a micro scale which was demonstrated by IR spectroscopic investigations. Ionic interactions between the polymer particles during the film forming process led to these inhomogeneities resulting in the observed differences of the release behavior.

Subsequently, spectroscopic experiments on swollen RL/L55 blend films were performed. It was demonstrated, that the copolymers form interpolyelectrolyte complexes in neutral/basic swelling media. In acidic media the formation of those complexes was not observed. It is assumed that these ionic interactions are the reason for the decreased permeability of RL/L55 coatings in neutral/basic media compared to the permeability in acidic media.

Finally, mini tablets containing weakly acidic drugs were prepared and coated with RL/L55 blends. The RL/L55 blend ratio as well as the coating thickness were optimized over the course of the study in order to achieve a pH-independent drug release. A pH-independent drug release was demonstrated in compendial release media as well as in media simulating physiological conditions of the gastrointestinal tract. It was concluded that coatings of RL/L55 blends show a high potential for application in coated oral drug delivery systems with a special focus on pH-independent release of weakly acidic drugs.

Zusammenfassung

Das Überziehen von festen Arzneiformen zur peroralen Anwendung mit Polymeren ist ein häufig verfolgter Ansatz, um die Wirkstofffreisetzung zu kontrollieren. Jedoch erweist sich die Formulierung eines Überzugs mit den erforderlichen Eigenschaften häufig als schwierig. Eine besondere Herausforderung in diesem Zusammenhang ist die pH-unabhängige Freisetzung von Wirkstoffen mit pH-abhängiger Löslichkeit. So kann die Freisetzung von schwach basischen Wirkstoffen mit Hilfe von Polymermischüberzügen pH-unabhängig gestaltet werden. Für die pH-unabhängige Freisetzung von schwach sauren Wirkstoffen stehen jedoch bisher keine geeigneten Überzüge für feste perorale Arzneiformen zur Verfügung.

Das Ziel der vorliegenden Arbeit war die Entwicklung einer geeigneten Überzugsormulierung für die pH-unabhängige Freisetzung von schwach sauren Arzneistoffen aus festen überzogenen Arzneiformen. Untersucht wurden Mischungen aus kationischem Methacrylat Copolymer und Methacrylsäure - Ethylacrylat Copolymer, auch bekannt unter ihren Markennamen Eudragit® RL (RL) und Eudragit® L-55 (L55). Darüber hinaus wurden die physikochemischen Veränderungen während der Quellung von RL/L55 Mischfilmen in verschiedenen Medien untersucht. Abschließend wurden überzogene Arzneiformen entwickelt, die eine pH-unabhängige Freisetzung von schwach sauren Wirkstoffen zeigten, sowohl in herkömmlichen als auch in physiologischen Freisetzungsmedien.

Zunächst wurde die Eignung von RL/L55 Mischüberzügen für die pH-unabhängige Freisetzung von schwach sauren Wirkstoffen untersucht. Hierfür wurden Theophyllinpellets mit RL/L55-Mischungen in verschiedenen Mischungsverhältnissen überzogen, wobei die Polymermischungen entweder als organische Lösung oder als wässrige Dispersion aufgetragen wurden. Theophyllin ist ein weitgehend pH-unabhängig löslicher Wirkstoff, der als Modellarzneistoff ausgewählt wurde, um Permeabilitätsveränderungen des Überzuges in Abhängigkeit vom Freisetzungsmedium feststellen zu können. Wirkstofffreisetzungsuntersuchungen der überzogenen Theophyllinpellets zeigten eine starke Abhängigkeit der Freisetzungsrate vom pH-Wert des Freisetzungsmediums, allerdings nur für Überzüge, die aus organischer Lösung hergestellt wurden. Theophyllinpellets mit RL/L55-Mischüberzügen

aus organischer Lösung zeigten im Allgemeinen eine höhere Freisetzungsrate in salzsauren Medien als in basisch/neutralen Medien. Die Wirkstoffpermeabilität der Überzüge veränderte sich also in einer Weise, die für die pH-unabhängige Freisetzung von schwach sauren Wirkstoffen notwendig ist.

Das Freisetzungsverhalten der überzogenen Theophyllinpellets war davon abhängig, ob der Überzug aus organischer Lösung oder wässriger Dispersion aufgebracht wurde. Die Ursache für diese Unterschiede war Gegenstand der anschließenden Untersuchung. Mittels IR-Spektroskopie konnte gezeigt werden, dass freie RL/L55-Filme, hergestellt aus wässriger Dispersion, auf mikroskopischer Ebene nicht homogen waren. Im Gegensatz dazu waren freie RL/L55-Filme, hergestellt aus organischer Lösung, homogen. Dieser Unterschied in der Homogenität ist demnach auch für die Unterschiede in der Freisetzungsrate der entsprechend überzogenen Theophyllinpellets verantwortlich.

In einer weiteren Studie wurden die physikochemischen Veränderungen in RL/L55 Mischfilmen während des Quellungsprozesses untersucht. Die Untersuchungen zeigten, dass es während der Quellung in basischen/neutralen Medien zur Ausbildung von Interpolyelektrolytkomplexen kommt. Während der Quellung in sauren Medien kommt es nicht zur Ausbildung solcher Komplexe. Es muss davon ausgegangen werden, dass diese ionischen Wechselwirkungen für die niedrigere Freisetzungsrate in basisch/neutralen Medien verantwortlich sind.

Abschließend wurden Minitabletten mit schwach sauren Wirkstoffen hergestellt und mit RL/L55-Mischungen überzogen. Die Überzüge wurden durch Veränderung des Mischungsverhältnisses und der Schichtdicke hinsichtlich einer pH-unabhängigen Freisetzung optimiert. Der Erfolg der Optimierung konnte nicht nur anhand der Freisetzungsmedien des Arzneibuches gezeigt werden, sondern auch in Medien, welche die physiologischen Bedingungen im Gastrointestinaltrakt simulieren. Diese Ergebnisse unterstreichen die Eignung von RL/L55-Mischüberzügen für den Einsatz zur kontrollierten Freisetzung von schwach sauren Wirkstoffen aus festen peroralen Arzneiformen.

Contents

1 Introduction

1.1 Coated dosage forms

Coated dosage forms play a major role as oral drug formulations in the pharmaceutical industry. By definition, they consist of a solid core, for example a tablet or pellet, which is covered with a smooth and homogeneous film. In the 19th century the history of pharmaceutical coatings began with sugar coatings, which were applied to mask the unpleasant, mostly bitter taste of drugs [1, 2]. Today, sugar coatings have mostly been replaced by polymer coatings due to their lower processing costs and large variety of applications [3].

Coating of pharmaceutical solids is a frequently used approach to overcome various problems that may occur with solid dosage forms. The above mentioned masking of unpleasant taste or odor is of great interest, especially for dosage forms used in pediatric therapy [4, 5]. Furthermore, solid dosage forms are often colored with coatings that contain pigments or dyes to improve the patients compliance and to facilitate product differentiation. Colored coatings also have a protective function against light which is of particular interest for formulations that contain photosensitive substances [6, 7]. Coatings are often applied for their decorative aspects to satisfy customer expectations. Moreover, film coatings can function as a barrier against moisture and/or oxygen and thus provide an increased storage stability for sensitive formulations [8, 9]. Large tablets and capsules are often coated just to improve the oral intake. Such thin polymer coatings that are not designed to modify drug release are defined as film coatings.

A more sophisticated field of application of polymer coatings is the controlled release of drug from the core. Polymer coatings may be used to target specific regions in the gastrointestinal (GI) tract. So-called enteric coatings resist the gastric acid and thus delay drug

release until the dosage form reaches the small intestine. Enteric coatings are usually applied to protect the stomach from drugs that might cause irritations of the stomach mucosa or to protect drugs from the acidic gastric environment [10–12]. Drug release may be further delayed for the local treatment of colonic disorders, for example ulcerative colitis [13–15].

Another application for coated solid dosage forms that is of great relevance is the prolonged or sustained drug release. Embedding of drugs with a short elimination half-life in sustained release formulations is mostly performed to reduce the daily dosing frequency, preferably to a once daily administration, and thus to improve patient compliance [16]. However, these goals cannot be met with drugs which require therapeutic doses that exceed the acceptable mass for a single application. Further goals of sustained release formulations may be the prevention of high local drug concentrations in the GI tract that might cause irritations and the avoidance of high blood level peaks of drugs with a low therapeutic index.

1.2 Coating process

Coated dosage forms are usually produced by spraying a liquid consisting of dissolved or dispersed coating material onto cores. During evaporation of the liquid the coating material forms a film on the cores. Furthermore, coating techniques are available that apply coating materials in powder form or in a molten state to the cores and thus do not require solvents at all. These processes have been described elsewhere [2]. In the following sections, coating processes involving polymer solutions and dispersions are described in detail.

The most simple process to produce coated dosage forms is to spray a solution of the coating material onto the cores. Under suitable conditions, the solvent evaporates while the coating material remains on the core. For water soluble polymers this is an adequate choice. Furthermore, it is possible to spray organic polymers solution onto the cores. As solvents ethanol, isopropanol, acetone or mixtures thereof may be used. Even though this is a straight forward approach, film coating processes based on organic solvents involve several disadvantages related to the solvents. Organic solvents are toxic and flammable and may therefore create health and safety hazards. Due to environmental regulations organic solvents have to be recovered from the exhaust air which can be a costly process.

Furthermore, limits, what the amount of residual organic solvent in the final product are concerned, have to be met.

Due to the described disadvantages, organic polymer solutions for coating purposes have in the past been replaced by aqueous polymer dispersions to a large extent [17, 18]. These dispersions consist of fine polymer particles which are dispersed in water. Such polymer dispersions are often referred to as latex or pseudolatex systems, depending on the production technique. To obtain a stable dispersion and avoid sedimentation, the particles are usually less than 1 µm in diameter and thus underlay the Brownian molecular motion [19]. To avoid particle growth and aggregations, aqueous coating dispersions often contain emulsifiers and/or peptizisors. However, the higher amount of energy that is necessary to evaporate water compared to organic solvents lead to longer drying times and thus prolonged process times. The longer drying times may be compensated by increasing the amount of solid coating material in the coating liquid. However, the solid content in the coating liquid may only be increased to a certain amount as it is accompanied by an undesired increase of viscosity. Furthermore, aqueous dispersions may show coagulations that might block the spraying nozzle, especially if the pH is changed, the temperature is increased, or high shear forces are applied.

1.2.1 Film formation

The film formation process from polymer solutions is rather simple. After a solution of the coating material is sprayed onto a core, the solvent starts to evaporate. The solution transforms into an intermediate gel-like state. Under ongoing solvent evaporation, the polymer molecules approach each other and finally form a continuous film [20]. A schematic representation of the film formation process from polymer solutions is shown in Fig. 1.

The film formation of aqueous polymer dispersions is significantly different from the film formation of polymer solutions [21–23]. After the polymer dispersion is sprayed onto the core, the water starts to evaporate. As a result of the reducing water volume, the polymer particles approach each other and form a tightly-packed arrangement with water filled voids. If the polymer particles are of sufficiently low viscosity, they start to deform under capillary pressure and interfacial tension. Finally, the particles coalesce and form a homogeneous

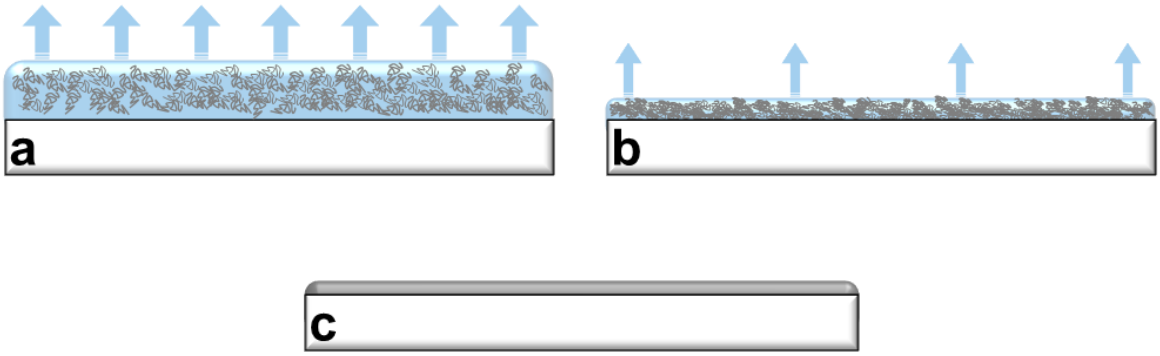


Fig. 1: Film formation from polymer solutions. a) Solvent evaporation; b) Intermediate gel-like state; c) Homogeneous polymer film

film. The viscosity and deformability of the particles depends on the mechanical properties of the polymer, on the additives that may plasticize the polymer, and on the temperature of the particles. The temperature at which polymer particles coalesce is called the Minimum Film Forming Temperature (MFFT). The film formation process from aqueous polymer dispersions is displayed in Fig. 2.

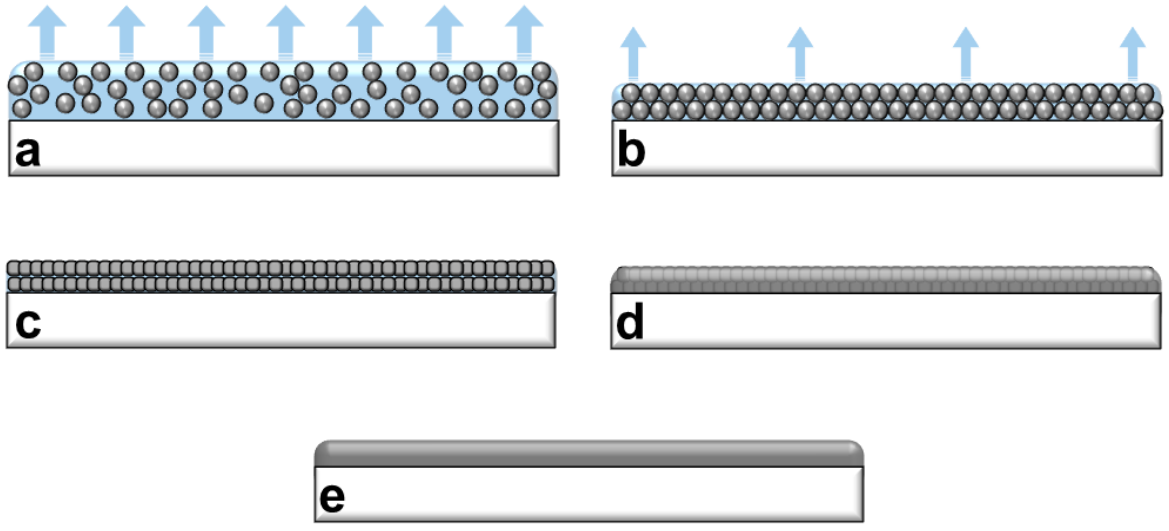


Fig. 2: Film formation from aqueous polymer dispersions. a) Water evaporation; b) Formation of tightly-packed polymer particles; c) Deformation of polymer particles; d) Coalescence of polymer particles (above MFFT); e) Homogeneous film after storage above the glass transition temperature

1.3 Physiological conditions in the gastrointestinal tract

The GI tract is a very complex and effective system to extract nutrients from a versatile diet. For an optimal effectiveness, the gastrointestinal tract is separated in functional compartments, each with specific tasks. An overview of the GI tract is given in Fig. 3.

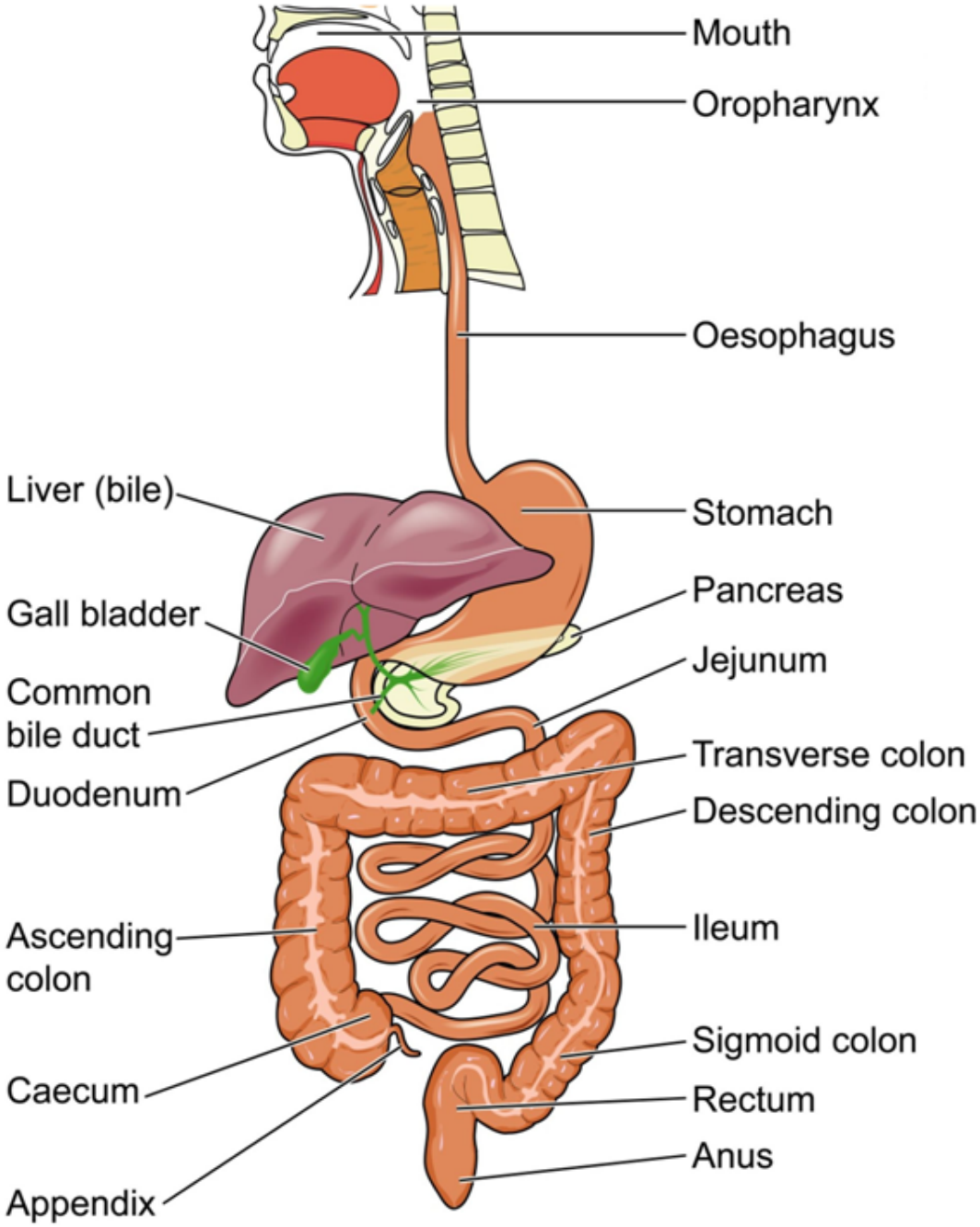


Fig. 3: Anatomy of the human GI tract.

In each specialized compartment, the processing of the gastrointestinal content is performed differently in terms of mechanical forces, enzymatic processing, volume of digestive

fluids and their composition [24]. Furthermore, the various tasks require different time periods resulting in different transit times of the gastrointestinal content through the functional compartments. The release behavior of orally administered coated dosage forms as well as the absorption of the released drugs are strongly affected by the properties of the surrounding digestive fluids. The factors relevant for drug release are of physical and chemical nature. For example, mechanical stress, temperature, buffer capacity, osmolarity, as well as the pH may influence drug release. Among these factors, the pH value is of special interest, as a high number of drugs and various excipients are weakly basic or acidic and therefore pH-dependent soluble. Thus, the drug release behavior of many formulations depends on the pH value of the surrounding digestive fluids. The development of controlled release dosage forms requires a detailed knowledge of the physicochemical conditions in the GI tract.

1.3.1 Oral cavity and esophagus

The transit through the GI tract begins in the oral cavity followed by the esophagus. The function of this compartment is primarily the chewing and grinding of food and the transportation to the stomach. Coated dosage forms are usually not chewed leading to a rather short residence time in the oral cavity and therefore a negligible influence on drug release. However, a prerequisite for the fast transit is that the dosage form is administered with a sufficient volume of fluid [25–28].

1.3.2 Stomach

The stomach plays an important role in the mechanical digestion of food. Furthermore, the chemical and enzymatic digestion of the ingested food starts in the stomach, mainly caused by the enzyme pepsin. Pepsin is a protease which has its maximum activity at pH 2.0 and is inactive at pH values above 6.5 [29]. The pH value in the stomach is regulated by the production of hydrochloric acid. The resulting pH values are usually low enough to provide a good activity of pepsin and to reduce the amount of bacteria in the stomach content. However, the gastric pH is highly variable and may therefore cause an intra- and intersubject

variability of drug release from solid dosage forms. Among several factors influencing the stomach pH the ingestion of food is the most predominant. The pH value in the fasted state is usually between pH 1 and 3 [30–32]. Typical stomach pH values after a meal range between pH 4.5 and 5.5 but can also raise ut to pH 7 and higher [31, 33].

The second stomach-related parameter influencing drug release is the transit time of a solid dosage form through the stomach. It mainly depends on the size of the dosage form and whether the stomach is fasted or fed. As a result, transit times vary between a few minutes and several hours [34–36].

1.3.3 Small intestine

The chyme is passed on from the stomach to the small intestine which absorbs the majority of the available nutrients, water, and salts. It is divided in three subsections: duodenum, jejunum, and ileum. The duodenum is the first short section of the small intestine. It contains Brunner's glands which secrete hydrogen carbonate to neutralize the gastric acid. Furthermore, the pancreas and the bile bladder secrete digestive enzymes, hydrogen carbonate, and gall salts into the duodenum to emulsify fats, increase the pH value of the chyme and initiate further digestive processes. Jejunum and ileum are the main compartments of absorption. Both sections contain villi to increase the surface area which is available for absorption. Most orally administered drugs are predominantly absorbed in the small intestine.

In the first section of the small intestine a fast pH increase can be observed resulting from the duodenal and pancreatic secretion of hydrogen carbonate. Towards the ileum the pH value increases further. In the fasted state, the average pH value in the duodenum is about pH 6 whereas in the jejunum and ileum slightly higher pH values up to pH 7 or 8 are reached [32, 37]. The pH value in the fed state depends on the buffer capacity of the ingested food [31, 38].

The small intestinal transit time is more constant than that of the stomach with typical transit times between 3 h and 4 h [28, 39, 40]. Nevertheless, transit times that significantly differ from these values are not unusual.

1.3.4 Large intestine

The main functions of the large intestine is the formation of a solid stool and the defecation of feces. It is defined as the combination of the cecum, colon, rectum, and anus. The large intestine is characterized by a large number of bacteria which are missing in the stomach and small intestine. Bacteria inhabiting the colon enzymatically digest the intestinal content. This fermentation process makes certain nutrients accessible for absorption. Within this context it has to be mentioned, that the vitamins K and B_7 are synthesized by colonic bacteria and are absorbed in the colon [41, 42]. Villi are missing in the colon, therefore the surface of the colon is small compared to that of the small intestine. Most drugs are not absorbed in the colon. Nevertheless, for some drugs such as theophylline and metoprolol absorption in the colon has been reported [43, 44]. Because of the poor drug absorption in the colon, some diseases as ulcerative colitis may be treated locally with oral solid dosage forms.

The pH value in the large intestine can be characterized as highly variable, continuous measurements of the pH during the large intestinal passage are challenging because of the low volume of present fluids. Directly after the small intestinal passage the pH value decreases rapidly. Zarate et al. [45] observed a pH drop from 7.6 to 6.1 in the initial part of the ascending colon of several human subjects. This decrease of the pH results from extensive bacterial degradation of polysaccharides and oligosaccharides to short-chain fatty acids [14]. Subsequently, the pH value slowly increases up to a baseline pH between 7 and 8 [30, 32]. The exact value of the pH drop and the time period until the baseline pH is reached varies between subjects and depends on various factors, e. g. the consumed diet [46].

The transit time through the large intestine varies between a few hours and up to 3 days. Furthermore, the transport of intestinal content through the large intestine is not straight forward but may include backward movements [47, 48].

1.4 Drug release test methods and media mimicking the gastrointestinal passage

Standard drug release tests monographed in the Pharmacopeias are primarily designed for quality control purposes. Drug release tests are a requirement for the confirmation of a low batch-to-batch variability of drug formulations. For oral coated dosage forms simple release media such as hydrochloric acid or phosphate buffers of specified pH at 37 °C in apparatus 1 or 2 (USP) are sufficient for quality assessments. However, drug release test conditions with standard dissolution apparatuses and the mentioned release media differ significantly from the physiological conditions in the GI tract. These differences may cause deviations of the in vitro drug release from the in vivo behavior [49–52]. Therefore, the predictive power for drug release in the human GI tract of those tests is very low.

For the development of oral solid dosage forms a highly predictive in vitro drug release test is desired. A precise prediction of the in vivo drug release is a prerequisite for reliable in vivo/in vitro correlations. Thus, a high predictive power of drug release studies in the development of solid oral dosage forms may help minimizing costs and risks of clinical studies [47].

Drug release from solid oral dosage forms in the GI tract may only be reliably predicted by mimicking the gastrointestinal environment. The physicochemical factors which may influence drug release from coated dosage forms are temperature, mechanical forces acting upon the dosage form, the composition of the surrounding medium and its pH [53]. Each of these factors should be considered in drug release tests. However, the physicochemical conditions differ significantly between the sections of the GI tract. Therefore, physiological drug release tests are often designed to mimic a specific section of the GI tract.

Over the last decades several attempts have been made to increase the predictive power of drug release tests by mimicking the gastrointestinal environment. In order to do so, the apparatuses as well as the release media were optimized in several ways to address this issue. More sophisticated apparatuses were developed. In the early 1990s, the US Pharmacopeia introduced the dissolution apparatus 3 and 4. Apparatus 3, also called the reciprocating cylinder apparatus, offers the possibility to alter the release medium during

the dissolution test. In this manner, GI pH gradients and the influence of food components may be accurately simulated. Furthermore, the proposed volume of the release medium in this apparatus (200 - 250 ml) is closer to the actual volume of the luminal content in the GI tract than in apparatus 1 and 2 (900 - 1000 ml). The smaller volume of the release medium is a substantial improvement as it allows the simulation of non-sink conditions that may occur in the GI tract.

In cases where sink conditions are needed (drug concentration $\leq$ 10 % solubility), dissolution apparatus 4 may be used. This apparatus is a flow-through cell which may be operated as an open system to generate sink conditions [54]. Furthermore, it also offers the possibility to modify the medium during the drug release test.

Moreover, attempts have been made to design experimental methods which simulate the mechanical forces generated by the GI tract [55, 56]. Of special interest in this regard is the stomach, the organ which is responsible for further mechanical mixing and homogenizing the ingested food after passing the oral cavity. Most recently, a drug release device for the simulation of physiological forces in the GI tract has been introduced and successfully used for the investigation of drug release from sustained release formulations [57, 58]. The device is operated within a dissolution apparatus 2 and is able to apply biorelevant pressure patterns on a dosage form with a periodically inflating and deflating balloon. A representation of this device is displayed in Fig. 4.

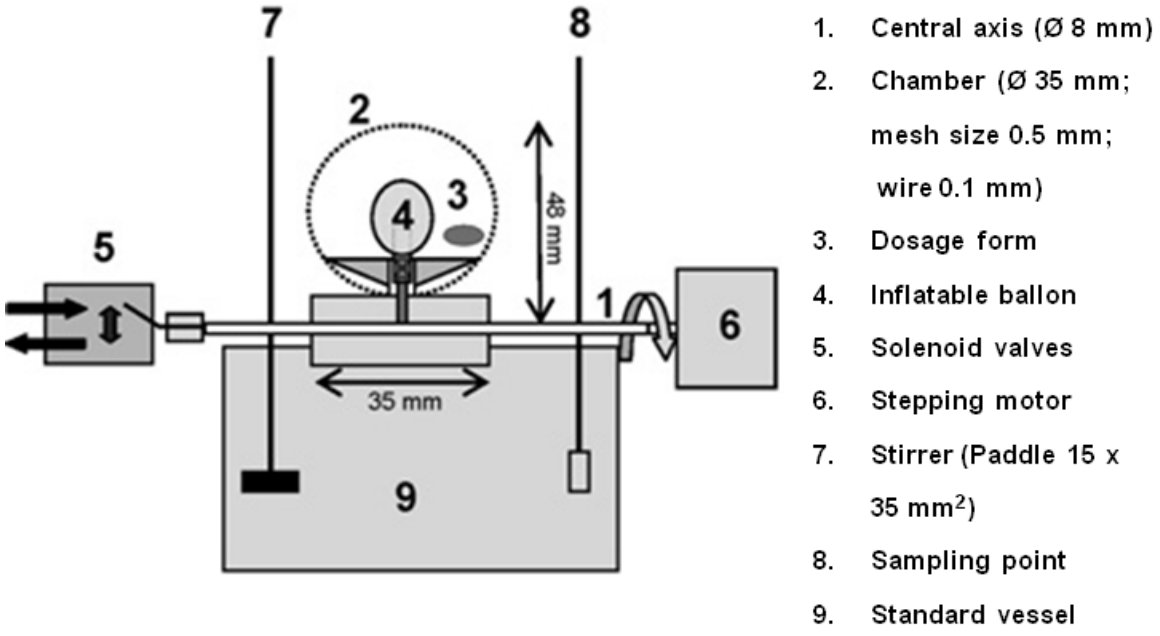


Fig. 4: Schematic representation of the stress test device (reprinted with permission from [58]).

The release media were modified in order to achieve more physiological conditions during drug release tests. Therefore, the Pharmacopeias recommend release media of different pH such as hydrochloric acid 0.1 mol l^{-1}, acetate buffer pH 4.5, and phosphate buffer pH 6.8. Subsequently, further improvements were made by addition of salts and enzymes into the release media, resulting in the compendial monographs “Simulated Gastric Fluid” (SGF) and “Simulated Intestinal Fluid” (SIF). Nevertheless, these compendial release media only considered a few aspects of the physiological conditions in the GI tract; prandial conditions are not considered at all.

Several studies dealt with a further adjustment to physiological conditions by a modification of the osmolarity, buffer capacity, surface tension, and a simulation of the presence of food which led to the so-called biorelevant media [59–62]. Individual media for the simulation of the gastric and the small intestinal contents in the different prandial states were designed. The composition of various media used to simulate the gastrointestinal fluids in the fasted state are displayed in Table 1, where the compendial media SGF and SIF as well as the biorelevant media “Fasted State Simulated Gastric Fluid” (FaSSGF) and “Fasted State Simulated Intestinal Fluid” (FaSSIF) are listed together with the physiological hydrogen carbonate buffer called Hanks buffer.

Other authors suggested less complex release media containing synthetic emulsifiers instead of bile salts [63, 64]. To simulate food effects in the stomach or the small intestine several buffers with high buffer capacity and osmolarity have been developed. The carbohydrate : fat : protein ratio has been often mimicked with whole milk or enteral nutrition products. More detailed information on media simulating the fed state is given elsewhere [65–67].

The hydrogen carbonate buffer system is the predominant buffer in the intestinal fluids. Nevertheless, none of the so-called biorelevant release media contain hydrogen carbonate buffers but instead phosphate, maleate, or acetate buffers [65]. This can be explained by the problems associated with hydrogen carbonate buffers. Hydrogen carbonate is generated by the dissociation of carbonic acid according to Eq. 1.

$$CO_{2\,(gas)} \longleftrightarrow CO_{2\,(sol)} + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^- \quad (1)$$

Table 1: Composition of various release media.

Component	**SGF**	**FaSSGF**	**SIF**	**FaSSIF**	**Hanks buffer**
CaCl ($mmol\,l^{-1}$)	-	-	-	-	0.36
HCl ($mmol\,l^{-1}$)	71.00	25.10	-	-	-
Lecithin ($mmol\,l^{-1}$)	-	0.02	-	0.75	-
$MgSO_4$ ($mmol\,l^{-1}$)	-	-	-	-	0.81
KH_2PO_4 ($mmol\,l^{-1}$)	-	-	49.97	-	0.44
NaH_2PO_4 ($mmol\,l^{-1}$)	-	-	-	28.36	0.30
Pepsin ($mg\,ml^{-1}$)	3.20	0.10	-	-	-
Pancreatin ($mg\,ml^{-1}$)	-	-	10.0	-	-
KCl ($mmol\,l^{-1}$)	-	-	-	-	5.37
NaCl ($mmol\,l^{-1}$)	34.20	34.20	-	105.85	136.89
$NaHCO_3$ ($mmol\,l^{-1}$)	-	-	-	-	4.17
NaOH ($mmol\,l^{-1}$)	-	-	22.4	8.70	-
Sodium taurocholate ($mmol\,l^{-1}$)	-	0.08	-	3.00	-
pH	1.2	1.6	6.8	6.5	6.8
Buffer capacity ($mmol\,l^{-1}$)	-	-	23.0	10.0	3.1

Carbonic acid is unstable and decomposes into CO_2 and water. CO_2 may leave the solution in the gaseous state accompanied by a pH increases. At the same time, gaseous CO_2 from the surrounding air redissolves in the buffer and consequently the pH value decreases again. Which process dominates primarily depends on the CO_2 partial pressure. For drug release tests, a precisely controlled pH value is essential. Thus, the loss of CO_2 must be prevented if using hydrogen carbonate buffers as release medium, which is hardly feasible under standard drug release test conditions. Another option is the replacement of the degased CO_2 by introducing equivalent volumes of CO_2 into the release medium. Recently, devices have been designed that measure the actual pH and add CO_2 in sufficient amounts to maintain a preset pH value [68, 69]. Unfortunately, the use of bile salts and other emulsifiers is almost impossible with CO_2 feeding devices because the introduction of gas into a medium with surface-active agents may lead to foaming [70].

However, carbonate buffers with physiological composition such as the Hanks buffer (Table 1) have proven to be more discriminative than compendial and biorelevant buffers in drug release tests involving ionizable drugs or pH sensitive drug formulations [71, 72]. Furthermore, hydrogen carbonate buffers offer the possibility to apply pH gradients equivalent to physiological pH gradients in the GI tract. The concept of dynamic pH regulation of hydrogen carbonate buffers is implemented in the most recently developed pHysio-grad® device (Physiolution, Germany) [73]. The device provides acidification by introducing CO_2 and alkalisation by purging with a inert gas (e. g. N_2). The application of physiological pH gradients is of special interest for formulations containing drugs and/or excipients with pH-dependent solubility. A schematic presentation of the pHysio-grad® device is given in Fig. 5.

A special challenge is the simulation of the physiological conditions in colon due to its low amount of fluid and its versatile composition regarding bacteria and enzymes. Therefore, to achieve a suitable enzymatic composition of the release medium, colonic bacteria or enzymes are added. Closer information on this topic is given elsewhere [74–76].

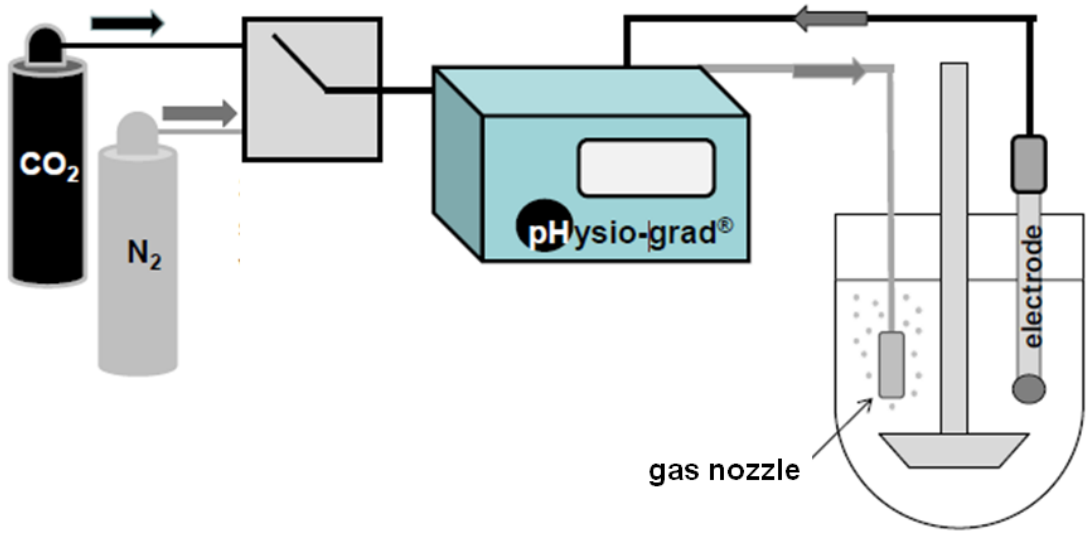


Fig. 5: Schematic presentation of the pHysio-grad® device.

1.5 Coating materials

Today, a variety of coating polymers of natural, semisynthetic, and synthetic origin are available on at the market and often used for the manufacture of solid dosage forms thereby widely replacing the classical monomeric and oligomeric coating materials such as waxes, fats, and sugar.

A prominent example for natural a coating polymer is shellac. It is the purified product of natural resin lac which is the hardened secretion of the insect Karria Lacca [77]. The composition is complex and underlies batch-to-batch variability which is typical for natural products. However, characteristic components of shellac are esters and polyesters of polyhydroxy acids [78]. Due to the free carboxy groups, shellac may be used as an enteric coating. Furthermore, the possible use as sustained release coating has been postulated [79, 80]. Further examples for coatings of natural origin are Zein, a protein extracted from corn, and chitosan, a polysaccharide of crustaceans [81, 82].

The group of semisynthetic coating polymers is dominated by cellulose derivatives. The poor water solubility of cellulose may be altered by esterification and/or etherification of the hydroxyl groups of the repeating glucose units. In a similar way, the film forming properties may be improved. Derivatives for immediate release with good water solubility may be gen-

erated by converting the hydroxyl groups to hydroxypropyl or hydroxyethyl ethers resulting in hydroxypropyl cellulose (HPC) or hydroxyethyl cellulose (HEC) [83–85]. Furthermore, the frequently used coating polymer hypromellose (HPMC) may be synthesized by introducing hydroxypropyl and methyl groups to the cellulose molecule. At molecular weight between 120,000 and 150,000 g mol^{-1}, the polymer is characterized by a good water solubility and excellent film forming properties.

Ethyl cellulose (EC) is an important sustained release coating polymer. Unfortunately, EC forms very brittle coatings and thus has to be processed with high amounts of plasticizer [86, 87]. For most applications, the drug permeability of EC coatings is too low and pore formers need to be added to the coating formulation [88–90]. Furthermore, various studies found an unintended pH dependency of the drug release rate from EC-coated solid dosage forms [86, 88, 91].

To obtain cellulose derivatives with a desired pH-dependent solubility, free carboxyl groups may be introduced. A prominent example is hydroxypropyl methylcellulose acetate succinate (HPMC-AS) [92, 93].

Synthetic coating polymers are widely used for pharmaceutical coatings. An advantage of synthetic coating polymers over the natural and semisynthetic coating polymers is a higher batch-to-batch uniformity. Synthetic coating polymers cover all pharmaceutical coating applications and can be categorized according to their chemical structure.

Derivatives of polyvinyl derivatives are frequently used as immediate release and/or sustained release coatings. For example, Kollicoat® IR is a polyvinyl alcohol - polyethylene glycol graft copolymer for immediate release coatings with high flexibility and low viscosity in aqueous solution [94]. Polyvinylpyrrolidone is another example for a fast dissolving immediate release coating that is often used because of its high gloss [95]. A further coating polymer from the group of polyvinyl derivatives is polyvinyl acetate used for sustained release coatings. Due to the low MFFT of this polymer, plasticizers are not necessary [96]. Even though the polymer has been subject to several studies in the last decade, the release mechanism of solid dosage forms coated with polyvinyl acetate has not yet been completely understood [96, 97]. Most likely, drug release is driven by osmotic pressure and drug diffusion through the swollen polymer film [98, 99].

One of the most commonly used and most versatile group of synthetic coating polymers is the group of polymethacrylate copolymers which is described in more detail in the next chapter.

1.5.1 Polymethacrylate copolymers

The history of polymethacrylate copolymers for pharmaceutical coatings began with the introduction of the polymethyl methacrylate (Plexiglas®) to the marked in the 1930s. Plexiglas® is a transparent and lightweight thermoplastic polymer with a broad variety of application. Plexiglas® panes are practically unbreakable, insoluble and nearly unswellable in water which qualified the polymer for several technical applications. Additionally, the excellent biocompatibility of this polymer allowed its medical application as contact lenses and in dental prostheses [100]. Polymethyl methacrylate can be synthesized by radical polymerization of methyl methacrylate. The respective chemical structure is displayed in Fig. 6.

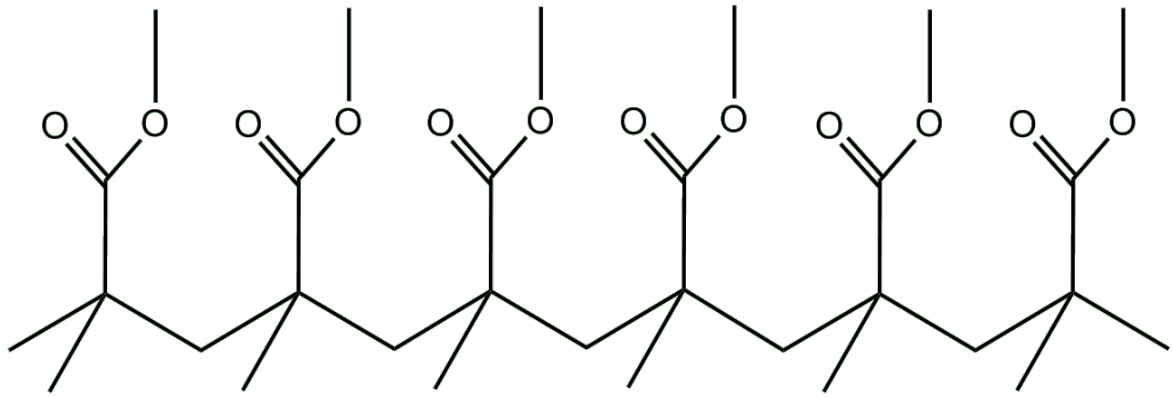
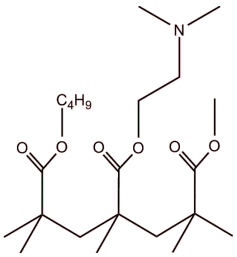
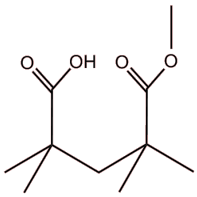
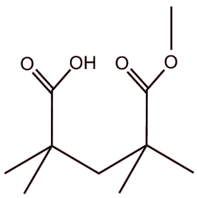
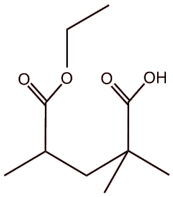
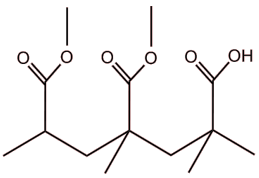


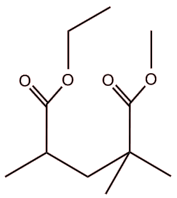
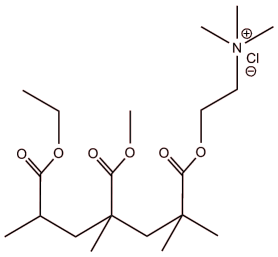
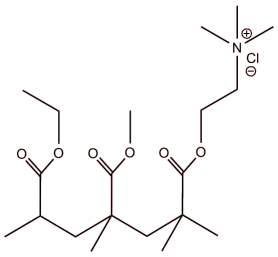
Fig. 6: Polymethyl methacrylate (Plexiglas®)

The polymethyl methacrylate (PMMA) structure may be modified to alter the solubility, flexibility, and permeability of the polymer to meet the requirements for coating films of solid oral dosage forms. The methyl groups may be removed resulting in free carboxyl groups generating a pH-dependent solubility. This concept was realized with the first coating polymers with a PMMA structure for solid oral dosage forms, Eudragit® L and Eudragit® S, that were available in the market in the 1950s. A further option for modification of the PMMA copolymer properties is the substitution of the esterified methyl groups with other groups. Other functional groups may be introduced to influence the solubility and/or permeability of the resulting film. To obtain a higher flexibility, some methacrylate groups may be substi-

tuted by acrylate groups. Since the 1950s several polymer types with the PMMA structure have been developed using the mentioned chemical modifications. An overview of the currently commercially available PMMA derivatives for the coating of oral solid dosage forms is given in Table 2.

Table 2: Overview of the polymethacrylate copolymers for pharmaceutical coatings.

Trade name	IUPAC name	Function	Structure
Eudragit® E	Poly(butyl methacrylate -co- (2-dimethylaminoeethyl) methacrylate -co- methyl methacrylate) 1:2:1	Immediate release, soluble < pH 5.0	
Eudragit® L	Poly(methacylic acid -co- methyl methacrylate) 1:1	Enteric coating, soluble > pH 6.0	
Eudragit® S	Poly(methacylic acid -co- methyl methacrylate) 1:2	Enteric coating / colon targeting, soluble > pH 7.0	
Eudragit® L-55, Kollicoat® MAE	Poly(methacrylic acid -co- ethyl acrylate) 1:1	Enteric coating, soluble > pH 5.5	
Eudragit® FS	Poly(methyl acrylate -co- methyl methacrylate -co- methacrylic acid) 7:3:1	Colon targeting, soluble > pH 7.0	

Trade name	IUPAC name	Function	Structure
Eudragit® NE, Kollicoat® EMM	Poly(ethyl acrylate -co- methyl methacrylate) 2:1	Sustained release, insoluble	
Eudragit® RL	Poly(ethyl acrylate -co- methyl methacrylate -co- trimethylammonioethyl methacrylate chloride) 1:2:0.2	Sustained release, (immediate release), insoluble	
Eudragit® RS	Poly(ethyl acrylate -co- methyl methacrylate -co- trimethylammonioethyl methacrylate chloride) 1:2:0.1	Sustained release, insoluble	

1.5.1.1 Copolymers with PMMA structure for immediate release coatings

The so-called Eudragit® E is functionalized with a dimethylamino group. Based on its basic nature, the amino groups are mostly protonated in the physiological pH range and thus the polymer is positively charged at least to some extent after swelling in the digestive fluids. Eudragit® E coatings are permeable at pH above 5 and soluble at pH below 5. These are suitable properties for immediate release coatings and coatings for taste masking. Eudragit® RL is predominantly used for sustained release coatings. However, thin coatings of this polymer are also used for immediate release coatings because of the high swellability of the polymer. Eudragit® RL is described in more detail in section 1.5.1.3.

1.5.1.2 Copolymers with PMMA structure for delayed release coatings

As mentioned above, the copolymers Eudragit® L and S were the first coating polymers with PMMA structure on the marketed. The two copolymers only differ by the ratio of free carboxyl groups to esterified carboxyl groups. In Eudragit® L statistically every second monomer carries a free carboxy group whereas in Eudragit® S it is only every third. Consequently, Eudragit® S dissolves at higher pH values. The copolymers may be blended to adjust the pH value at which the resulting coating dissolves. However, these copolymers are extremely brittle and cannot be sprayed onto cores without plasticization. Furthermore, the dissolution pH of the polymers is too high for fast dissolution of the coating immediately after passage of the stomach. For enteric coatings a fast dissolution in the small intestine and high polymer flexibility are desirable. Therefore, the copolymer poly(methacrylic acid-co-ethyl acrylate) was developed, better known under the trade names Eudragit® L-55 and Kollicoat® MAE. This polymer already dissolves at a pH value of 5.5, which is more suitable for the application as enteric coating polymer. However, recent investigations on Eudragit® L-55 (L55) coated dosage forms showed a delayed dissolution of 66 $\pm$ 22 min after gastric emptying [101]. The delay can be significantly reduced by applying an inner layer of partially neutralized L55 and an outer layer of standard L55 onto the solid dosage form with the same total coating thickness [101, 102].

Eudragit® FS was developed as a highly flexible material for colon targeting. The copolymer dissolves above pH 7, a pH value that is primarily found in the colon. However, as mentioned above the pH value of the colon is highly variable. Furthermore, a pH of 7 may also be present in the distal small intestine. Thus, the dissolution of an Eudragit® FS coating in the colon is hardly reproducible as dissolution might happen either prior to colon arrival or the dosage form might pass the colon intact. In a study of Ibekwe et al. [103] the in vivo performance of Eudragit® FS coatings was tested. Out of 16 administered Eudragit® FS coated tablets 14 disintegrated at the ileo-caecal junction and the ascending colon, one tablet disintegrated prematurely and one tablet passed the GI tract intact. The performance was superior to Eudragit® S coatings. However, it appears that colon targeting with pH dependent soluble polymers have immanent constrains with regard to reproducibility of drug release due to intra and inter subject variations of the pH values in the intestinal fluids.

1.5.1.3 Copolymers with PMMA structure for sustained release coatings

Poly(ethyl acrylate-co-methyl methacrylate), referred to as Eudragit® NE or Kollicoat® EMM, is a copolymer for sustained release coatings. It is a neutral ester and contains no functional groups. Thus, its chemical structure is very similar to PMMA as displayed in Table 2. However, the small differences between the chemical structure of the two polymers have a significant influence on the mechanical properties. In contrast to PMMA, poly(ethyl acrylate-co-methyl methacrylate) shows a high flexibility manifesting itself in an Elongation at break value of 600 % and a T_g of –8 °C [100]. The copolymer may for example be used for sustained release coating of pellets or granules that are intended for multiple unit tablets. The highly flexible NE coating remains intact during the compacting step. Thus, after tablet disintegration drug release rates from the coated pellets remain unchanged.

Coating copolymers with PMMA structure containing quaternary ammonium groups (QAGs) play a special role among the sustained release coating polymers due to their cationic character. QAGs contain a positively charged nitrogen atom and a chloride as counter anion. Eudragit® RS (RS) and Eudragit® RL (RL) contain approx. 5 % and 10 % (w/w) monomers with QAGs, respectively, and are miscible at any ratio. In the Ph. Eur. they are referred to as ammonium methacrylate copolymer type A and B. The cationic groups cause a hydrophilic character of the polymers and increase the drug permeability of the resulting copolymer film. The density of QAGs may be varied by mixing RL and RS. This is common practice to adjust the permeability of ammonium methacrylate coatings. Furthermore, the density of QAGs is reduced by excipients added to the film such as plasticizers or anti-sticking agents [9].

Drug release from ammonium methacrylate copolymer-coated solid dosage forms is independent of the pH value of the surrounding medium [104]. The swelling of free ammonium methacrylate copolymer films is affected by the composition of the swelling medium but cannot be correlated to the release rate of the respective coated pellets [105]. The release mechanism of RL/RS-coated dosage forms is mainly driven by ion exchange [104–106]. When a RL/RS coating is exposed to gastrointestinal fluids or artificial release media, the chloride ions are exchanged by anions from the surrounding fluid [107]. Additionally, the exchange of chloride ions by dissolved anions from within the dosage form such as anionic

drugs or excipients has also been observed [108–111]. The ion exchange of the coating with the surrounding medium induces an increased water flux. Therefore, dissolved drug molecules may diffuse faster into the release medium. Thus, a higher water flux is accompanied by a higher drug release rate. The extent of the water flux is determined by the attraction of the exchanged ions to the QAGs i. e. anions with low affinity to QAGs induce a high water flux and vice versa. Examples for anions with a low attraction are acetate and monosuccinate; anions with high attraction are nitrate and chloride [100, 112]. In general, di- and multivalent ions are highly attracted to QAGs as they provide multiple possibilities for ionic interactions. Multivalent ions may crosslink QAGs leading to a significantly reduced the water flux through ammonium methacrylate coatings, an event known as “sealing effect”.

Not only the type of anions available for exchange but also the anion concentration determines the permeability of a ammonium methacrylate copolymer coating. An increasing ion concentration leads to a higher permeability of ammonium methacrylate copolymer films until a maximum is reached [112]. Concentrations that exceed a certain level are accompanied by a decreased ion activity. Thus, the effective amount of ions that is available for ion exchange is also decreased. A special case is the presence of chloride ions together with other anions. If the chloride exchange of QAGs with an other anion (X^-) present in the surrounding medium is regarded as a chemical balance, an equation describing this balance may be formulated as follows:

$$Cl^-_{(QAG)} + X^-_{(unbound)} \longleftrightarrow Cl^-_{(unbound)} + X^-_{(QAG)} \quad (2)$$

It is obvious from this equation, that an increase of the amount of chloride ions increases the amount of bound Cl^-. Thus, the drug release rate from ammonium methacrylate-coated pellets will be decreased if the chloride concentration in the release medium is increased. Chloride is an omnipresent anion in the gastrointestinal fluids. However, its concentration varies between the different gastrointestinal sections. This may influence the in vivo drug release from RL and RS-coated dosage forms. Thus, this sensitivity for anions and especially for chloride should be considered in drug release tests.

The release mechanism of ammonium methacrylate-coated dosage forms is significantly different from the drug release mechanism of dosage forms coated with other sustained release coatings. Nevertheless, the release rate of ammonium methacrylate-coated dosage forms may be adjusted by common measures. For example, pore formers such as HPMC may be added to introduce an additional diffusion pathway for dissolved drug molecules[113]. Furthermore, insoluble particles which are included into the coatings such as the anti sticking agent talc or coloring pigments may influence the drug permeability in dependence on their particle size [9].

1.5.2 Polymer blends for coatings of solid dosage forms

There are various possibilities to adjust the drug release rate of coated solid dosage forms, the mechanical properties of the coatings , and their film forming properties. To optimize the properties of a functional coating, the coating formulation (organic solution vs. aqueous dispersion), the amount of used plastizicer, the coating thickness, and process parameters such as temperature and humidity may be adjusted. However, the variation of these factors is subject to certain limitations. For example, excessive high amounts of plastizicer lead to sticking of the coating. Thick coatings lead to increased process times and thus to higher production costs, whereas very low coating thicknesses may lead to incomplete films.

A common approach to overcome these restrictions is to blend coating polymers to obtain better properties of the resulting coating. In this manner, the drug release behavior, the mechanical properties, and the film forming properties of a coating may be adjusted. However, polymers are often immiscible or show other incompatibilities. In the case of immiscible or partly miscible polymers, phase separation occurs affecting the permeability and mechanical strength of the resulting polymer coating [90, 114, 115].

For polymer blends the coating formulation (organic solutions vs. aqueous dispersion) is of high importance. Some incompatibilities only occur in aqueous dispersions. For example, blends of oppositely charged polymers may flocculate or precipitate while in organic solutions the same polymers may be compatible. Another example is the flocculation of EC dispersions if HPMC is added [116]. This incompatibility occurs if a critical HPMC concentration is exceeded and depends on the molecular weight of the used HPMC grade. A

further difference between polymer films obtained from aqueous dispersion and those obtained from polymer solution is the degree of polymer chain interpenetration which arises from the different film formation processes. The film formation process of dissolved polymer blends is represented in Fig. 7.

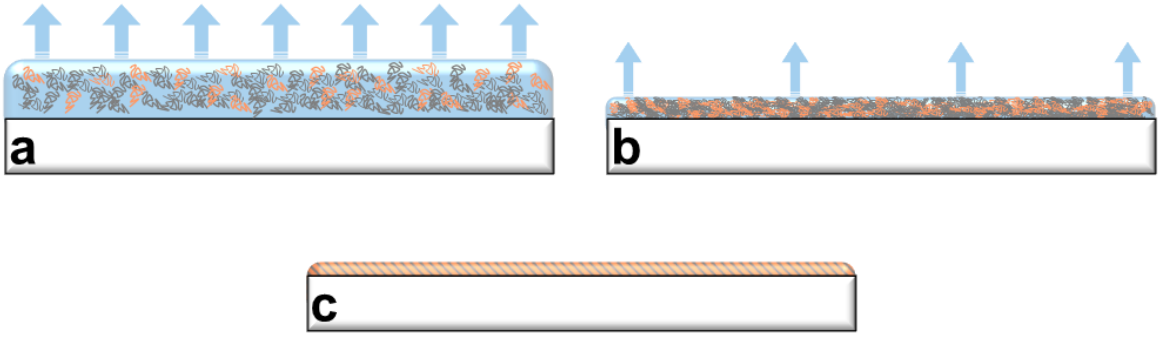


Fig. 7: Film formation from a polymer solution containing two different polymers. a) Solvent evaporation; b) Intermediate gel-like state; c) Homogeneous polymer blend film. (Modified from [117].)

In blends of miscible polymers, the polymer chains are homogeneously distributed within the polymer film. Film formation from blends of aqueous dispersions follows a different mechanism which is represented in Fig. 8.

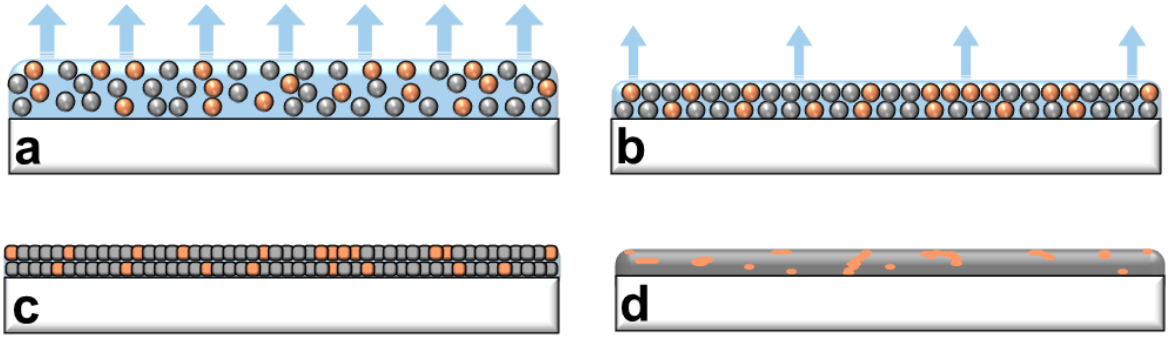


Fig. 8: Film formation from aqueous dispersion containing two different polymers. a) Water evaporation; b) Formation of tight-packed arrangements; c) Deformation of polymer particles; d) Coalescence of polymer particles above the glass transition temperature (Modified from [117])

Typical particle sizes of dispersed polymer particles in aqueous dispersions are between 100 nm and 300 nm [19]. After coalescence of the polymer particles, the polymer is immobilized. Thus, in the case of polymer blends the interpenetration of the polymers is low and the films are inhomogeneous on a micro scale. The size of domains in which one of the polymers dominates depends on the size of the dispersed particles. The different degree

of polymer interpenetration resulting from the selected type of film formulation affects film blend in terms of mechanical strength and drug permeability [117, 118].

Usually, polymer blends for controlled release coatings contain at least one sustained release polymer. In the following subsection, several polymer blends which are commonly used as coatings for solid oral dosage forms are presented.

1.5.2.1 Blends of sustained release polymers

Coating polymers which are insoluble in the GI tract are often blended to adjust the drug permeability. As mentioned above, aqueous dispersions of RL and RS as well as organic solutions of the two polymers may be blended in any ratio for the adjustment of the coating permeability [119]. Thus, three different drug delivery systems have been marketed by Evonik based on the mixture of RL and RS: Eudrapulse®, Eudramode®, and Eudracol®.

The Eudrapulse® system is composed of a core which contains salts of organic acids and is coated with an RL/RS blend. After water uptake, the salts of the organic acids electrostatically interact with the QAGs of the blend coating and generate osmotic pressure. Simultaneously, the organic acids act as a plasticizer within the coating. The result is a sigmoidal drug release profile [109]. The system was further developed by separating the core and the RL/RS coating by an NE layer, resulting in the Eudramode® drug delivery system. The NE layer controls the diffusion of the salts of the organic acids into the RL/RS coating and thus offers an additional possibility to control drug release towards the desired drug release profile [120, 121]. The drug delivery system Eudracol® combines the concepts of sustained release and colon targeting. The drug containing core is coated with an RL/RS sublayer and an outer layer of Eudragit® FS [122–124]. The outer layer is soluble at pH values above pH 7 and is intended to be intact until arrival in the colon. Subsequently, the RL/RS coating provides sustained release in the colon.

Drug release from coated dosage forms may also be controlled by the addition of Eudragit® NE (NE) to polyvinyl acetate [125]. The cracking of coatings resulting from the osmotic pressure within a coated pellet after water uptake is an important drug release mechanism for polyvinyl acetate-containing coatings. The flexibility of the coating is significantly increased by the addition of NE accompanied by a reduced cracking of the coatings.

A high polymer flexibility is especially necessary for solid oral dosage forms that show a high degree of swelling upon contact with GI fluids. For example, a strategy for gastric retention is to develop dosage forms that swell in gastric fluid up to a size that cannot pass the pylorus. Blends of NE and RL have been shown to be suitable for this strategy [126, 127].

1.5.2.2 Blends of sustained release and immediate release polymers

The sustained release polymer EC combined with the water soluble HPMC is one of the mostly used polymer combination for controlled release coatings. HPMC swells and potentially leaches out of the coating if in contact with aqueous media. Thus, it acts as pore former and increases the release rate [128]. However, as with many other polymers HPMC cannot be considered as a “true pore former” [90]. In contrast to small molecules, polymers neither completely leach out of the coating nor form pores in a classical sense. Moreover, HPMC forms highly hydrated domains within the coating through which drugs may diffuse out of the solid dosage form.

Even though EC and HPMC are often used in combination in functional coatings, they show a limited miscibility. Often, phase separation occurs within these coatings [83, 114, 129]. This may cause problems during long term storage. Therefore, it has been recommended to use other pore forming polymers such as polyethylene glycol, polyvinyl pyrrolidone, or poly(vinyl alcohol) - poly(ethylene glycol) graft polymers [130].

Similar to EC/HPMC blends, it is possible to increase the drug release rate from dosage forms coated with RS by addition of HPMC as pore former [113]. Another approach is to influence the film formation from aqueous RS dispersions by addition of HEC. As a consequence, the storage stability of theophylline pellets coated with an RS/HEC blend (blend ratio of 9:1) could be significantly increased [84]. Because HEC and RS are immiscible, HEC forms a separate phase around the RS particles. Thus, further coalescence of RS particles in the solid coating is hindered. The drug release from RS/HEC blend-coated theophylline pellets and the water vapor permeability of free RS/HEC films remained constant for at least one month [84].

1.5.2.3 Blends of sustained release and delayed release polymers

The combination of polymers for sustained release with polymers for delayed release is not commonly used for pharmaceutical coatings. However, the combination may be used to provide a higher polymer flexibility for enteric coatings which are usually very brittle. This is of special interest for enteric-coated pellets intended for multiple unit tablets. For instance, the addition of NE to Eudragit® L coatings reduced the amount of pellets damaged by compaction significantly [131]. In a similar manner, Dashevsky et al. [132] increased the mechanical stability of L55 coatings by addition of NE resulting in less pronounced cracking of coatings upon compaction.

The patented Colal® coating system for colon targeting consists of a blend of EC and amylose which is susceptible to bacterial degradation [133, 134]. Once a solid dosage form coated with Colal® arrives in the colon, the amylose is enzymatically decomposed by colonic bacteria and the coating disintegrates.

Blends of sustained release polymers with polymers for delayed release are suitable for coatings that provide a pH-dependent drug permeability. For example, the weakly basic drug verapamil HCl is highly soluble in the acidic environment of the stomach and has a much lower solubility in the neutral/basic environment of the small and large intestine [135]. Thus, the release of verapamil HCl from coated dosage forms is higher in the stomach than in the intestine. Therefore it is challenging to develop sustained release dosage forms for weakly basic drugs. This problem may be overcome with coatings that are less permeable in acidic media than in neutral/basic media. Dashevsky et al. [136] coated verapamil HCL-containing cores with blends of the aqueous dispersions of polyvinyl acetate and L55 . In neutral/basic media the L55 polymer leached out of the film and acted as a pore former. Thus, the coating became more permeable in media representing the small and large intestine. Munday [137] followed a similar approach by applying a blend coating of RS and HPMC-AS onto verapamil HCl-containing cores. However, for a pH-independent release of verapamil HCl the addition of fumaric acid to the core was necessary to adjust the pH value within the dosage form. Wu and McGinity [138] observed an increased permeability of RS/L55 blend coatings (from aqueous dispersion) in basic media compared to plain RS coatings. Furthermore, the blend coatings showed a higher storage stability.

Overall, blends of sustained release polymers with polymers for delayed release lead to pH sensitive coatings which may be suitable for constant delivery of weak bases. However, coatings that are suitable for constant delivery of weak acids from solid dosage forms are not yet available. The only approach to encounter this problem is the addition of pH-adjusting excipients to the core [139, 140].

1.5.3 Interpolyelectrolyte complexes for functional coatings

The interactions between the coating polymers in film blends are almost exclusively based on van der Waals forces or hydrogen bonds. However, in blends of oppositely charged polymers ionic interactions may occur, resulting in interpolyelectrolyte complexes (IPECs). Using these ionic complexes is a straight forward approach to develop pharmaceutical formulations with new properties while using well known excipients [141, 142]. Furthermore, IPECs are very versatile and their properties may easily be adapted for specific applications by varying the blend ratio of the polymers. If pH-dependent ionic excipients such as polycarboxylic acids are applied, the pH value during the IPEC formation may be used to obtain the desired properties with regard to drug release, swelling behavior, and polymer flexibility.

The formation of IPECs in a liquid phase is usually accompanied by precipitation or flocculation. Thus, the application as coating material is difficult. Consequently, most studies dealing with ionic complexes of coating polymers have been carried out with matrix tablets [142]. Combinations of chitosan with anionic polymers such as pectin, sodium alginate, carbopol, and κ-carrageenan have been used for matrix tablet formulations for controlled drug release [143–145]. Furthermore, investigations with combinations of Eudragit® E and anionic coating polymers led to very interesting results. Prado et al. [146] achieved a controlled release of ibuprofen from matrix tablets consisting of IPECs of Eudragit® E and κ-carrageenan and adjusted the release pattern by modifying the polymer blend ratio. Ionic complexes between Eudragit® E and Eudragit® L or L55, respectively, showed a pH-dependent swelling behavior which was explained by the pH-dependent degree of ionization of the polymethacrylic acid in the two enteric polymers [147–150]. Other authors suggested the use of Eudragit® E/Eudragit® L salts in matrix tablet formulations instead of

the respective IPEC. The ionic complex is thus formed during swelling of the tablets which leads to an almost constant drug release from the matrix tablets [151, 152].

As a consequence of the difficulties which occur during preparation of IPEC containing coating formulations, only a few studies were conducted with coatings or free films containing IPECs. Sauer and McGinity [153] applied a dry powder coating approach to coat theophylline tablets with blends of Eudragit® E and L55. However, the study showed that the interdiffusion of the polymers was insufficient to develop considerable ionic interactions. Another option to prepare interpolyelectrolyte coating formulations is to adjust the aqueous polymer dispersions/solutions to the same pH and mix them carefully. In this manner, free film blends of RL and sodium alginate were cast from aqueous dispersion [154]. The film blends showed ionic interactions and a pH-dependent swelling behavior. Furthermore, differences between the drug permeability of the free film blends at various pH values were determined. The pH-dependent degree of ionization of sodium alginate was assumed to influence the pore formation of the film blends and thus their drug permeability. Interestingly, the influence of ionized sodium alginate in RL films on the ion exchange with the release media was not taken into account.

To avoid the precipitation of the polymers, in some cases mixtures of their organic solutions may be used. For example, the copolymers RS and HPMC-AS are both soluble in organic solvents and were coated onto verapamil HCl pellets [137]. It was assumed that ionic interactions between the polymers influenced the release of verapamil HCl from the coated pellets. However, the ionic interactions were not further investigated.

A case of unintended ionic interactions between coating polymers was reported for the double layer coating of the Eudracol® drug delivery system [155]. After dissolution of FS at pH values above 7, the carboxylate groups interacted with the QAGs of the RL/RS coating. This interaction resulted in a decreased release rate compared to the respective formulation without FS coating.

As mentioned above, the release mechanism of RL/RS-coated dosage forms is mainly driven by ion exchange. In this regard, ionic interactions with anionic polymers are of particular interest as these interactions directly influence the drug release mechanism. The influence of drug release from RL/RS-coated dosage forms by anionic monomeric

excipients is a well known concept. Drug release may be altered by adding lactate or salicylate to the coating or by adding salts of organic acids to the core (Eudrapulse®, Eudramode®) [110, 121, 156, 157]. However, monomeric anions leak out of the coating or diffuse out of the core during the drug release process. This is not necessarily the case with anionic polymers. Thus, the application of coatings containing IPECs of RL/RS and an anionic polymer is a promising approach. Due to their good miscibility with RL/RS, acidic polymethacrylate copolymers are the first choice as anionic components. Furthermore, the pH sensitivity of these polymethacrylate copolymers may cause a pH-dependence of the drug permeability of the coating.

Several studies have dealt with blend coatings of RL/RS and an acidic polymethacrylate copolymer [13, 138, 158–161]. However, these studies were not designed to take advantage of ionic interactions between the polymers. In most of the studies, interactions were not even possible due to the lack of polymer/polymer interdiffusion. In other studies, the amount of enteric polymer in the blend coating was so high that the coating dissolved completely upon ionization of the enteric polymer.

1.6 Objectives of the study

Over the last decades numerous studies have been performed to investigate polymer coatings and polymer blend coatings for solid oral dosage forms and countless solid oral dosage forms have been developed based on the results. Despite the enormous scientific effort which have been made, some goals for the formulation of solid oral dosage forms are not yet achievable with polymer coatings. One example is the pH-independent delivery of acidic drugs from coated oral dosage forms.

The objective of this study was the development of a coating suitable for a pH-independent drug release of acidic drugs from a coated oral dosage form. The approach to achieve this goal was to use combinations of countercharged coating polymers with polymethacrylate structure. The resulting ionic interactions between the copolymers were expected to induce a pH-dependent permeability of the blend coating which counteracts the pH-dependent solubility of acidic drugs.

Further goals were to gain a sound understanding of the mechanism of drug release from the developed coated dosage form and a confirmation of the pH-independent release of acidic drugs under simulated gastrointestinal conditions.

2 Materials & methods

2.1 Materials

The coating copolymers Eudragit® RL PO, Eudragit® RL 30 D, Eudragit® L 100-55 and Eudragit® L 30 D-55 and the glidant and Aerosil® 200 were donations from Evonik (Germany). Talc ($d_{50.0\,\%}$ = 7.5 µm) was obtained by Riedel-de Haën and Caelo ($d_{50.0\,\%}$ = 18.6 µm) (Germany), triethylcitrate by Fluka (Switzerland); acetone and isopropanol by Biesterfeld Spezialchemie (Germany). Theophylline pellets containing 96.5 % theophylline were a gift from Temmler (Ireland). Ketoprofen was obtained from Kreussler Pharma (Germany), naproxen from Roche (Switzerland), and theophylline from Caelo (Germany). Prosolv® SMCC 90 was donated by JRS Pharma (Germany), Avicel® PH-200 from FMC BioPolymer (Ireland), and Kollicoat® IR Red from BASF (Germany). Hydrochloric acid, sodium hydroxide, TRIS (Trometamol), citric acid, trisodium phosphate, and sodium acetate were all purchased from Carl Roth (Germany). Calcium chloride and magnesium sulfate heptahydrate were obtained from Merck (Germany). Sodium chloride and sodium hydrogen phosphate were provided by Grüssing (Germany). Sodium hydrogen carbonate and magnesium stearate were obtained from Fagron, Germany. All chemicals were of analytical grade and used as received. Carbon dioxide from Linde AG (Germany) and compressed air were of technical grade.

2.2 Methods

2.2.1 Methods of "Drug release from Eudragit® RL/L55 copolymer blend-coated theophylline pellets"[1]

2.2.1.1 Preparation of coating suspensions

The aqueous dispersions Eudragit® RL 30 D (RLD) and Eudragit® L 30 D-55 (L55D) were mixed in weight ratios (RLD:L55D) of 1:0, 4:1, and 8:1, corresponding to RL fractions of 100.0 %, 80.0 %, and 88.9 % (w/w). The dispersions were adjusted to the same pH value (4.0) and the L55D was added drop wise to the RLD to avoid aggregation. Moreover, Eudragit® RL PO (RL) and Eudragit® L 100-55 (L55) powders were dissolved separately in an organic solvent (acetone 57 %, isopropanol 38 %, water 5 % (w/w)) and mixed in the weight ratios (RL:L55) of 1:0, 4:1, 8:1, 12:1, and 16:1. These weight ratios correspond to RL fractions of 100.0 %, 80.0 %, 88.9 %, 92.3 %, and 94.1 % (w/w). In the 4:1, 8:1, 12:1 and 16:1 (w/w) blends, the molar ratios of the functional groups (QAG/COOH) are approximately 0.4:1, 0.9:1, 1.3:1, 1.8:1.

Talc and triethyl citrate were homogenized in the organic solvent and purified water, respectively, with an Ultra Turrax® (IKA,Germany). These suspensions were added to the dispersions and solutions, respectively, resulting in 10.0 % copolymer, 5.0 % talc, and 1.0 % triethyl citrate content (w/w). For studies on the influence of the coating level and the influence of pH values of phosphate buffers, respectively, talc with a medium particle size of 7.5 µm was used to adjust the permeability of the resulting film coating. For all other coatings talc of a medium particle size of 18.6 µm was used.

2.2.1.2 Film coating of theophylline pellets

Theophylline pellets were sieved and the fraction of 0.8 - 1.0 mm was coated in a Solidlab 1 (fluid bed configuration, Bosch, Germany). The coating parameters of the fluid bed coating process are displayed in Table 3. Coating levels of 2.5 %, 5.0 %, and 10.0 % defined as weight gain referring to the copolymer mass were applied on the theophylline pellets. The

[1] This chapter has been published as shown in Section 5.2

coated pellets were postdried in an oven for 24 h at 40 °C.

Table 3: Process parameters used for fluid bed coating of mini tablets.

Process parameter	Setting
Inlet air flow rate	40 - 42 $m^3\,h^{-1}$
Inlet air temperature	40 °C
Atomizing air pressure	1.0 bar
Microclimate	0.4 bar
Feeding rate	2 - 4 $g\,min^{-1}$
Mass per batch	400 g
Nozzle diameter	0.8 mm

2.2.1.3 Dissolution testing

Dissolution tests were performed with a paddle apparatus (Distek Premiere 5100, Distek, USA) at 100 rpm and 37.0 °C. Hydrochloric acid pH 1.2, phosphate buffer pH 5.8, 6.8, and 7.6 at 0.05 mol l^{-1} (USP) were chosen as release media. The pH values of these media are similar to the pH of Simulated Gastric Fluid (pH 1.2, Ph. Eur.), Simulated Intestinal Fluid (pH 6.8, Ph. Eur.) and media for the simulation of colonic fluids (pH 5.8 and 7.6 [162]). Additional release media were acetate buffer pH 6.8 and 4.7 at 0.05 mol l^{-1}, TRIS buffer pH 6.8 at 0.05 mol l^{-1}, citrate buffer pH 6.8 at 0.05 mol l^{-1}, sodium chloride solution pH 3.0 and 4.0 at 0.05 mol l^{-1} (adjusted with hydrochloric acid) as well as sodium chloride solutions pH 4.0 at concentrations of 0.10 mol l^{-1}, 0.20 mol l^{-1}, and 0.50 mol l^{-1}. Dissolution testing for delayed release solid dosage forms according to Ph. Eur. (Method B) was performed, except for a reduction of the acidic stage to 60 min. All release profiles were recorded online with a UV spectrometer (Agilent 8453, Agilent, USA) equipped with 1.0 cm flow through quartz cells at 272 nm.

2.2.1.4 Statistical analysis

For statistical analysis the software Design Expert (version 8.0.7.1, Stat-Ease, USA) was used. Two factor historical designs were performed for dissolution tests. As factors, the

percentage of the RL fraction in the coating and either the coating level expressed as percentage of copolymer weight gain or the pH value of the dissolution medium were used. Responses were the time point of 10 % drug release ($t_{10\%}$), the slope of the linear release phase, and the shape parameter β, calculated from the Weibull equation (Eq. 3)

$$M_t = M_\infty \cdot \left[1 - exp\left(\frac{t - t_0}{\tau_d}\right)^\beta\right] \tag{3}$$

where M_t is the drug release at time point t, M_∞ is the drug released at infinite time, t_0 is the lag time and τ_d is the time point of 63.2 % drug released. The Weibull equation has been successfully used in modeling sigmoidal-shaped dissolution curves [163, 164]. The significance of the calculated models were tested with analysis of variance (ANOVA), results were considered significant if the calculated P value was lower than 0.05.

2.2.2 Methods of "Investigation on solid state interactions and homogeneity of free Eudragit®RL/L55 copolymer blend films from aqueous dispersion and organic solution"[2]

2.2.2.1 Acidimetric titration

The acidic properties of L55D were determined by back-titration. 2.0 g of L55D were dissolved in 40 ml of sodium hydroxide (0.1 mol/l) and titrated with hydrochloric acid (0.1 mol/l) using a Mettler 70 DS Titratior with potentiometric endpoint indication. Measurements were performed in triplicate. The Acid Values (Ph. Eur.) were calculated from the volume of consumed hydrochloric acid at the equivalence point, pK_a values were determined as the pH values at the semi equivalence point.

2.2.2.2 Preparation of physical mixtures of the copolymers

Physical mixtures (PM) were prepared in an agate mortar by gentle mixing of RL and L55 with an agate pestle for at least 5 min. Weight ratios were (RL:L55) 1:4, 1:1 2:1, 4:1, and 8:1, corresponding to RL fractions of 20.0 %, 50.0 %, 66.6 %, 80.0 %, and 88.9 %.

2.2.2.3 Preparation of free copolymer films

The aqueous dispersions RLD and L55D were diluted with water resulting in a solid content of 10.0 % and adjusted to pH 4.0 using a sodium hydroxide solution (1.0 mol l^{-1}). The dispersions were mixed in weight ratios (RLD:L55D) of 1:0, 1:1, 2:1, 4:1, 8:1, and 0:1. L55D was added dropwise to RLD to avoid aggregation. In the same manner, RLD and L55D dispersions were adjusted to pH 5.0 and mixed in the same weight ratios.

RL and L55 powders were dissolved separately in an organic solvent (acetone 57 %, isopropanol 38 %, water 5 % (w/w)) and mixed in the weight ratios (RL:L55) of 1:0, 1:1, 2:1, 4:1, 8:1, and 0:1, corresponding to RL fractions of 100.0 %, 50.0 %, 66.6 %, 80.0 %, 88.9 %, and 0.0 % (w/w).

A predefined mass of all prepared blends was cast into individual Teflon® molds and stored in an oven at 40 °C for 24 h at 0 % RH. This drying process corresponds to standard

[2]This chapter has been published as shown in Section 5.2

post drying conditions used for coated solid dosage forms in the pharmaceutical industry and ensure a minimum and constant residual solvent content in the copolymer films. To remove the organic solvent/water completely, higher temperatures and/or lower pressure would be required which may significantly affect the copolymer film structure and potentially the copolymer interactions. Therefore constant drying conditions were chosen to ensure low variability of residual solvent between the different copolymer films. After drying, the films were cut into squares of 20 $\times$ 20 mm and subsequently stored in a glass container at 0 % RH.

2.2.2.4 Thermoanalysis

Differential Scanning Calorimetry (DSC) was performed with a DSC821 (Mettler Toledo, Switzerland). The prepared samples (8 - 12 mg) were weighed into aluminum pans with pin holes. The oven was purged with nitrogen (20 ml min^{-1}). Samples were equilibrated at 0 °C for 15 min and then heated to 120 °C. Afterwards the samples were cooled down to 0 °C and equilibrated for 15 min. The temperature was raised to a final temperature of 150 °C in a second heating run. The cooling and heating rates were 10 °C min^{-1}. DSC curves were analyzed using the STARe software v. 11.00a (Mettler Toledo, Switzerland).

Thermal Gravimetric Analysis (TGA) was performed with a Perkin Elmer Pyris 1 TGA (Perkin Elmer, USA). The initial temperature of 50.0 °C was held for 10 min and subsequently raised to 480 °C at a rate of 5 °C min^{-1} under nitrogen atmosphere at a flow rate of 20 ml min^{-1}. The initial mass of the samples was between 8 and 10 mg. Measurements were performed in triplicate. Decomposition temperatures were determined by differentiation of the thermograms and computing the resulting peak minimum.

2.2.2.5 ATR-FTIR spectroscopy

IR spectra were recorded with a Tensor 37 (Bruker, Germany) equipped with a cooled MCT detector and a Pike MIRacle ATR unit (PIKE, U.S.) with a ZnSe crystal (1.8 mm ø). The air for continuous purging of the beam path was dried and carbon dioxide was removed with a SDAT-670/420 double column air dryer (DRUMAG, Germany). A minimum of 128 scans per sample were collected at a resolution of 1 cm^{-1}. Samples were measured at least three

times; in the case of copolymer films various randomly chosen spots were measured. From all IR spectra the spectral region between 1800 and 700 cm^{-1} was selected. The remaining bands were not considered as they are strongly influenced by water and the used organic solvents. IR spectra were treated with the ATR correction algorithm of Opus software v. 7.0 (Bruker, Germany).

2.2.2.6 Chemometrics

The spectra were pretreated using the Savitzky-Golay smoothing (13 points, symmetric kernel) and the Standard Normal Variate algorithms. Principal Component Analysis (PCA) was performed with The Unscrambler software v. 10.1 (Camo, Norway).

2.2.3 Methods of "Investigation on the drug release mechanism Eudragit® RL/L55 copolymer blend-coated solid dosage forms"[3]

2.2.3.1 Preparation of free copolymer films

RL and L55 powders were dissolved separately in an organic solvent (acetone 57 %, isopropanol 38 %, water 5 % (w/w)) and mixed in the weight ratios (RL:L55) of 1:0, 4:1, 8:1, 12:1, 16:1 and 0:1, corresponding to RL fractions of 100.0 %, 80.0 %, 88.9 %, 92.3 %, 94.1 %, and 0.0 % (w/w). Furthermore, copolymer solutions of the same copolymer ratios were prepared with 1 % triethylcitrate (TEC) as plasticizer. Solutions of RL and L55 are miscible at any ratio and form copolymer films without phase separation.

A predefined mass of all prepared copolymer solutions were cast into individual Teflon® molds and dried under the conditions described in Subsection 2.2.2.3. After drying, the films were cut into squares of 20 × 20 mm or circles of 6 mm diameter and subsequently stored in a glass container at 0 % RH.

2.2.3.2 Raman spectroscopiy of swollen copolymer films

Copolymer films (6 mm diameter) of the blend ratios (RL:L55) 1:0, 4:1, 8:1 and 0:1 were placed on a microscopic slide and each film sample was wetted with 50 µL of hydrochloric acid pH 1.2 and phosphate buffer pH 6.8, respectively. After 0 min, 15 min and 30 min of copolymer swelling, the swelling medium was carefully removed with a lint-free tissue and Raman spectra were recorded using the dispersive Raman microscope Senterra (Bruker, Germany) with a LMPlanFL N 20 × objective (Olympus, Germany). The laser was operated at 532 nm with a power of 20 mW; four scans with an integration time of 4 s were co-added at a resolution of 1 cm^{-1}. All obtained spectra were manually baseline-corrected (Opus software v. 7.0; Bruker, Germany). Subsequently, the spectral regions with no relevant signals were excluded from further analysis: $>3100\,cm^{-1}$, 2800 - 1780 cm^{-1}, 1400 cm^{-1} - 900 cm^{-1}, $<560\,cm^{-1}$.

[3]This chapter has been published as shown in Section 5.2

2.2.3.3 ATR-FTIR spectroscopy of swollen copolymer films

Quadratic copolymer film samples (20 × 20 mm) of the blend ratios (RL:L55) 1:0, 4:1, 8:1, and 0:1 were investigated with ATR-FTIR. Three copolymer film samples of each blend ratio were immersed in 100 mL of the swelling media at room temperature for 0 h, 1 h, 2 h, and 3 h in an Erlenmeyer flask that was continuously agitated by a benchtop shaker. In media of pH 6.8, L55 samples were removed from the media after 3 min to avoid full dissolution of the films. After swelling, the films were transfered to Teflon® mats and dried in an oven at 40 °C and 0 % RH for 24 h.

IR spectra of the dried copolymer films were recorded as described in Subsection 2.2.2.5.

2.2.3.4 Chemometrics

Chemometrics were performed as described in Subsection 2.2.2.6

2.2.3.5 Determination of polymer erosion of copolymer films

The erosion of all prepared copolymer films was determined gravimetrically in hydrochloric acid pH 1.2 and phosphate buffer pH 6.8 . Film samples (20 × 20 mm) were accurately weighed (w_0) and afterwards immersed in continuously agitated hydrochloric acid pH 1.2 and phosphate buffer pH 6.8 at room temperature. Samples were collected after 0.5 h and 24 h, dried on a Teflon® mat in an oven for 24 h at 40 °C and afterwards accurately weighted (w_E). The polymer erosion (PE) was calculated as follows:

$$PE = \left(\frac{w_0 - w_E}{w_0} \right) \cdot 100\% \tag{4}$$

2.2.3.6 Determination of the swelling index for copolymer films

The swelling characteristics of all prepared plasticized copolymer films were determined in hydrochloric acid pH 1.2 and phosphate buffer pH 6.8 at room temperature. Film samples (20 × 20 mm) were accurately weighed (w_0), immersed in the agitated media and removed at several predetermined time points. Residuals of the media adhering to the film samples were carefully wiped off with lint-free tissue and the samples were immediately weighed

(w_t). With the determined weights a swelling index (SI) was calculated as follows [165]:

$$SI = \left(\frac{w_t - w_0}{w_0} \right) \cdot 100\% \tag{5}$$

2.2.4 Methods of "Controlled release of acidic drugs in compendial and physiological hydrogen carbonate buffer from Eudragit® RL/L55 blend-coated oral solid dosage forms"[4]

2.2.4.1 Production of mini tablets

Ketoprofen, naproxen, and theophylline were mixed with Prosolv® SMCC 90 in a Turbula® blender (T2F equipped with a 2 l container, Willy A. Bachofen, Switzerland) for 60 min at 72 rpm, respectively. Subsequently, talc and Aerosil® 200 were added and mixing was continued for 2 min. The final powder mass was 300 g and contained 10 % drug, 88.5 % Prosolv® SMCC, 1 % talc, and 0.5 % Aerosil. The powder blend was compacted with a rotary tablet press (Fette 102i, Fette Compacting, Germany) equipped with a Fill-o-Matic fill shoe and Euro-B 19-tip punches at a compression speed of 5 rpm and a medium compaction force of 2.2 kN. The mass of the obtained biconvex mini tablets was approximately 6 mg, the diameter and the band height were both 2 mm. The resulting mini tablets were tested to ensure a similar performance in the subsequent coating step and to verify an uniform drug content. The tablets were accurately weighed, subsequently the content uniformity of the mini tablets was tested by dissolving randomly selected tablets in phosphate buffer pH 6.8 and determining the content spectrophotometrically at compound specific wavelengths (n = 5; Agilent 8453, Agilent, USA). Table 4 shows the determined tablet characteristics.

In addition, placebo tablets consisting of Avicel® 200, magnesium stearate and Aerosil® PH-200 with the same dimensions were prepared.

Table 4: Tablet characteristics.

	Mass [mg]	**Drug content [%]**	**Drug mass [mg]**
Ketoprofen	6.09 ± 0.07	9.95 ± 0.12	0.61 ± 0.01
Naproxen	5.95 ± 0.05	9.80 ± 0.20	0.58 ± 0.01
Theophylline	5.86 ± 0.12	10.10 ± 0.22	0.59 ± 0.01

[4] This chapter has been published as shown in Section 5.2

2.2.4.2 Preparation of coating suspensions

The organic coating suspensions contained 10 % coating polymers, 5 % talc and 1 % triethylcitrate (w/w) and were prepared as follows: RL and L55 powders were dissolved separately in a mixture of acetone, isopropanol, and water (57 %, 38 %, 5 %; w/w). The polymer solutions were mixed, resulting in polymer weight ratios of (RL:L55) 4:1, 8:1, 11:1 and 16:1. Talc and triethylcitrate were homogenized in the organic solvent mixture using an Ultra-Turrax® (IKA, Germany) and subsequently added to the solutions of the polymer mixtures.

2.2.4.3 Coating of mini tablets

The prepared mini tablets were coated with a Solidlab 1 (fluid bed configuration, Bosch, Germany). For each batch 30 g of drug-containing tablets were coated together with 270 g placebo tablets previously colored with a thin layer of Kollicoat® IR Red to reduce the necessary amount of drug-containing tablets. The coating parameters of the fluid bed coating process are displayed in Table 5. The coating process was stopped at either 5 % or 7.5 % polymer weight gain with respect to the initial batch weight. The coated mini tablets were postdried in an oven for 24 h at 40 °C. The colored placebo tablets were sorted out and discarded after the drying process.

Table 5: Process parameters used for fluid bed coating of mini tablets.

Process parameter	Setting
Inlet air flow rate	40 - 45 $m^3\,h^{-1}$
Inlet air temperature	35 °C
Atomizing air pressure	1 - 1.2 bar
Microclimate	0.15 bar
Feeding rate	2 - 4 $g\,min^{-1}$
Mass per batch	300 g
Nozzle diameter	0.8 mm

2.2.4.4 Drug release from mini tablets

All drug release experiments were performed in a paddle apparatus (either Distek Premiere 5100, Distek, USA or ERWEKA DT7R, ERWEKA, Germany) at 100 rpm and 37 °C using 1000 ml release medium. The pH values of the used release media were either kept constant or changed gradually to achieve a defined pH sequence. Experiments at a constant pH of 6.8 were performed with phosphate buffer (USP), Hanks buffer, sodium hydrogen carbonate solution (0.038 mol l^{-1}), and Hanks buffer without sodium hydrogen carbonate. Hanks buffer is a carbonate based buffer that is used to mimic the ion composition in the intestinal tract (Table 1). To avoid the uncontrolled increase of the pH value in carbonate containing buffers, outgassed carbon dioxide was substituted by pHysio-stat® devices (Physiolution, Germany). A detailed description of these devices is given elsewhere [68].

The first applied pH sequence was in accordance with the dissolution test for "delayed release solid dosage forms" (Ph. Eur., Method B) involving a pH change from pH 1.2 to pH 6.8 after 120 min (Fig. 9, sequence 1).

The second pH sequence simulated the physicochemical conditions of the GI tract by using Hanks buffer and by applying a pH sequence adapted from Klein et al. [166]. Prior to recording release profiles, the investigated tablets were immersed in 250 ml hydrochloric acid pH 1.2 for 30 min to simulate gastric transit. Subsequently, the tablets were transferred into Hanks buffer and the pH was changed after defined periods of time as displayed in Fig. 9 (sequence 2). The pH value was controlled by introducing the required volumes of carbon dioxide and compressed air with pHysio-grad® devices (Physiolution, Germany) described by Garbacz et al. [73].

The third pH sequence was adapted from Koziolek et al. [32]. The pH sequence was set up using the average pH values measured in the small intestine of ten healthy human subjects and the average small intestinal transit time of 240 min. Prior to measurement of drug release the investigated tablets were immersed for 30 min in 250 ml hydrochloric acid pH 1.2. The amount of drug released in hydrochloric acid was not recorded online for practical reasons. Subsequently, tablets were transferred into Hanks buffer and the pH was changed every 10 min (Fig. 9, sequence 3) for 240 min and then kept constant at pH 6.5 until drug release was finished. The pH was controlled using the pHysio-grad® system

as described above. For calculation of the percentage of drug release only the release in Hanks buffer was considered.

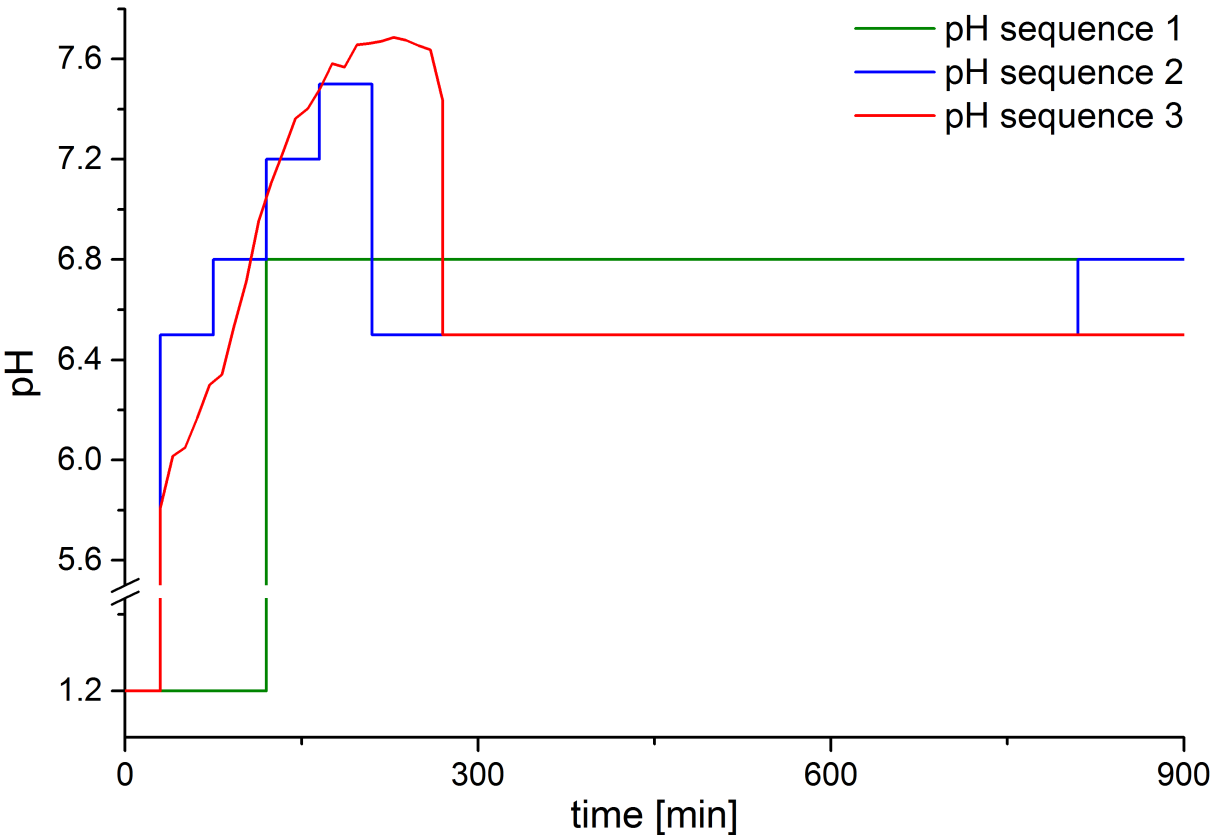


Fig. 9: Applied pH gradients for the simulation of the gastrointestinal passage.

Drug release experiments were performed with 30 - 31 coated mini tablets (total mass 200 mg, accurately weighed) corresponding to a drug mass of 18 - 19 mg in the release medium (Table 4), depending on the coating thickness. Theophylline is pH-independent soluble within the physiological pH range, whereas ketoprofen and naproxen are weak acids and are therefore less soluble in acids than in neutral basic media. However, with the exception of naproxen release in hydrochloric acid pH 1.2 (naproxen solubility (c_s) = 41 $\pm$ 5 mg), drug release experiments were carried out under sink conditions ($c \leq c_s \cdot 0.9$), because the pH-dependent solubilities of the investigated drugs are releatively high [167, 168]. The release experiment with naproxen at pH 1.2 was carried out under non-sink conditions.

All release profiles were recorded by online UV-Vis spectroscopy. Two different setups were used. The first consisted of an UV spectrometer (Agilent 8453, Agilent, USA) equipped with 1.0 cm flow-through quartz cells. Measurements were performed at suitable

wavelengths. The second setup consisted of a Cary 50 Bio spectrophotometer (Varian Inc., USA), multiplexer and optic fibers (2 m length, 10 mm light path). The absorbance was measured in differential mode at compound specific wavelengths and at 450 nm (background) in 5 min intervals (1 s per wave length). Data acquisition and processing was performed with commercial software (Varian WinUV, Varian Inc, USA).

2.2.4.5 Determination of intrinsic dissolution rates

The intrinsic dissolution rates of ketoprofen, naproxen, and theophylline were determined using a fixed disk system (Intrinsic Dissolution Apparatus, Distek, USA). The disk diameter was 0.8 cm; the drugs were compressed for 5 min at 200 MPa with a hydraulic bench top press. Subsequently, the disks were tested in a Distek Premiere 5100 (Distek, USA) paddle apparatus equipped with flat bottom dissolution vessels at 100 rpm and 37 °C in hydrochloric acid pH 1.2, phosphate buffer pH 6.8 and Hanks buffer pH 6.8 (pH-controlled with pHysiostat®), respectively. Dissolution rates were continuously recorded with an UV spectrometer (Agilent 8453, Agilent, USA) equipped with 1.0 cm flow-through quartz cells at suitable wavelengths.

3 Results and discussion

3.1 Results and discussion of "Drug release from Eudragit® RL/L55 copolymer blend-coated theophylline pellets"[1]

The aim of the first study was to investigate the potential to modify drug release from theophylline pellets coated with ammonio methacrylate copolymer Type A (Eudragit® RL) by addition of methacrylic acid - ethyl acrylate copolymers (Eudragit® L-55). The pH-independent soluble drug theophylline was chosen as a model drug to identify changes in the drug permeability of the coating in dependence on the pH of the release medium.

In contrast to former studies where polymers with a similar chemical structure were combined, the present study compares coatings from blends of aqueous dispersions with a defined pH value with coatings from organic solutions of copolymer blends. Particularly, the dependency of drug release on the pH value of the release media and the copolymer blend ratio was investigated.

3.1.1 Drug release from theophylline pellets coated with RLD/L55D blends

Theophylline pellets were coated with three different aqueous coating suspensions containing the dispersions RLD and L55D in the weight ratios of (RLD:L55D) 1:0, 4:1, and 8:1 at pH 4.0. According to the literature, the pK_a value of L55D is 6.9 [169], hence at pH 4.0,

[1] This chapter has been published as shown in Section 5.2

L55D particles are practically uncharged and cannot interact with the cationic RLD particles. As expected, during mixing no aggregation was observed. After coating and curing, dissolution testing was performed in hydrochloric acid pH 1.2 and phosphate buffer pH 6.8. The release profiles are displayed in Fig. 10a and b.

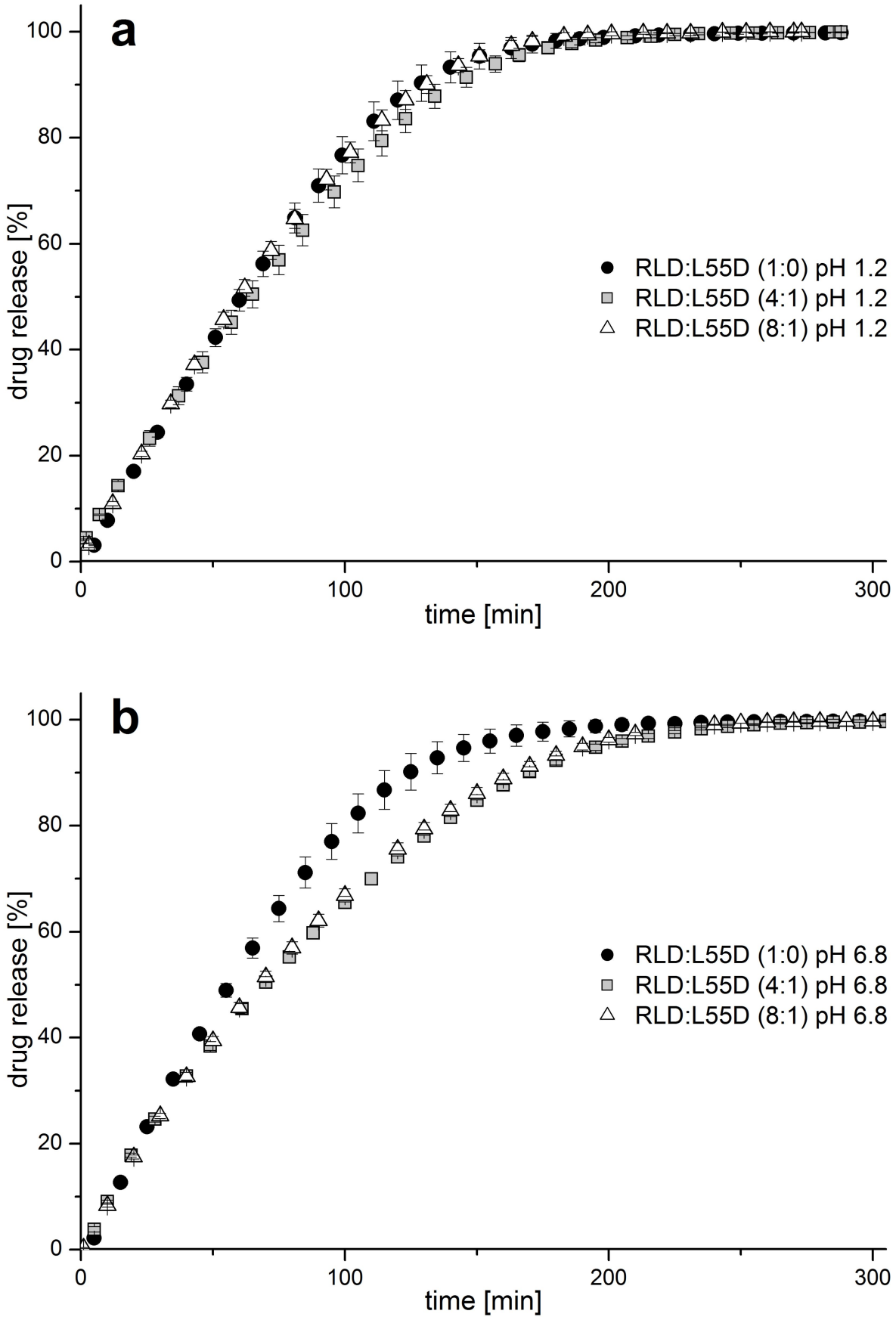


Fig. 10: Drug release from theophylline pellets coated with blends of RLD/L55D in weight ratios of 1:0, 4:1, and 8:1; n = 3, means ± SD. a) Drug release in hydrochloric acid pH 1.2; b) Drug release in phosphate buffer pH 6.8.

It was observed that films from aqueous dispersion caused only small differences in the release behavior of theophylline pellets. In Fig. 10a the release from pellets coated with the different aqueous dispersions in hydrochloric acid is displayed and no significant difference in the release can be detected. Obviously, there is no effect of the addition of L55D to RLD. With the same pellets leaching of L55D and therefore a faster drug release was expected in phosphate buffer pH 6.8 [138]. Surprisingly, drug release with both blend ratios was not increased but slightly decreased (Fig. 10b). To explain this behavior, it can be hypothesized that the QAGs of the RL copolymer interact electrostatically with the deprotonated carboxyl groups of the L55D and consequently prevent the leaching of the copolymer.

3.1.2 Drug release from theophylline pellets coated with RL/L55 blends

Theophylline pellets were coated with three different organic coating suspensions containing solutions of RL and L55 in the same copolymer weight ratios as the aqueous dispersions (RL:L55 1:0, 4:1, 8:1). Coating, curing, and dissolution testing were performed in accordance to the dissolution testing of pellets coated with RLD/L55D blends. The release profiles of pellets coated with organic copolymer solutions are displayed in Fig. 11a and b.

In hydrochloric acid a short lag time was observed for the 8:1 blend while the lag time for the 4:1 blend was longer. Longer lag times with increasing L55 portion can be attributed to the low permeability of L55 in hydrochloric acid.

The release profiles of the same pellets in phosphate buffer are different. Pellets coated with the 4:1 blend needed 100 min to release 10 % of theophylline, while the pellets coated with the 8:1 blend needed 473 min (data not shown). Obviously, no leaching of L55 out of the film coating occurs, as also observed with the coatings from aqueous dispersions. Instead, the coating becomes less permeable for theophylline. This could be either a result of an interaction between the functional groups within the blended film or of the blended film with the phosphate buffer. To investigate the reason for the decreased release rate and to characterize the release mechanism, further dissolution experiments were performed.

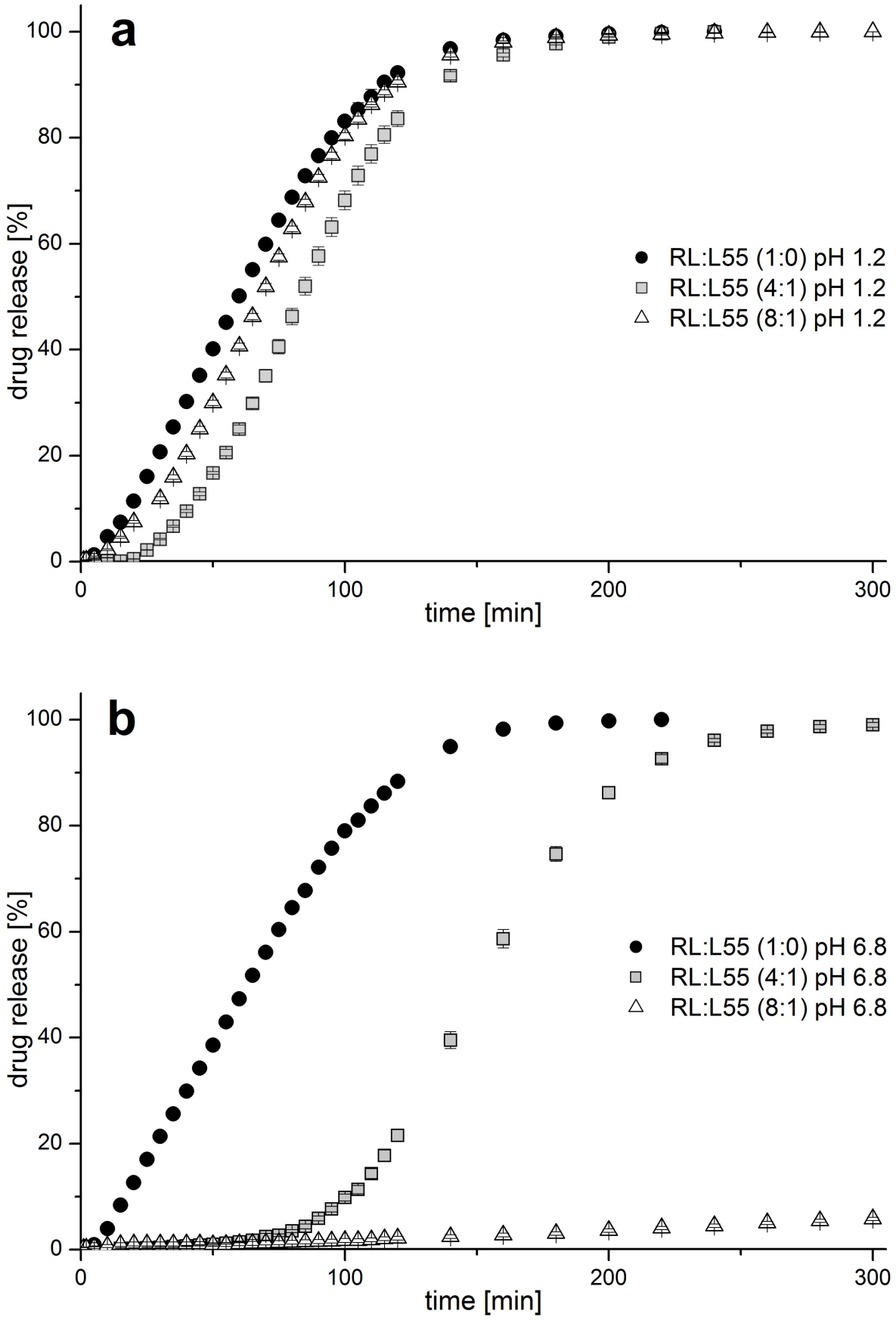


Fig. 11: Drug release from theophylline pellets coated with blends of RL/L55 in weight ratios of 1:0, 4:1, and 8:1; n = 3, means ± SD. a) Drug release in hydrochloric acid pH 1.2; b) Drug release in phosphate buffer pH 6.8

3.1.3 Release behavior of RL/L55-coated theophylline pellets

3.1.3.1 Influence of the buffer ions in the release media

To investigate a possible interaction of buffer ions with the blended film, dissolution tests in release media with pH 6.8 but different ion species (acetate buffer, TRIS buffer, citrate buffer) were performed. In addition, drug release in media with the same salts but different pH values (sodium chloride solution pH 3.0 and pH 4.0, acetate buffer pH 4.7) was investigated. In all release media the concentration of the respective buffer salt was 0.05 mol l^{-1}.

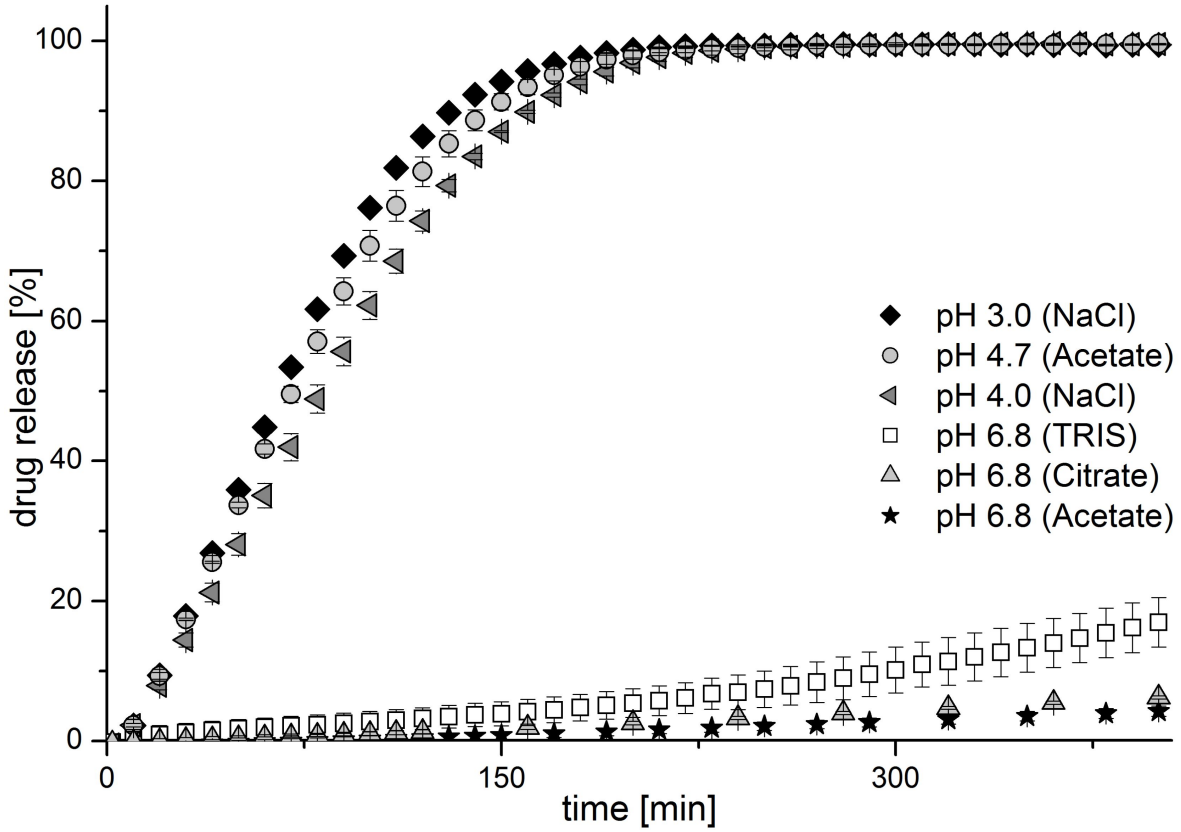


Fig. 12: Drug release from pellets coated with blends of RL/L55 in the weight ratios of 8:1 in various media; n = 3, means ± SD.

It could be shown that the pH of the release media is by far more relevant with regard to release rate, than the ion species (Fig. 12). Drug release in TRIS buffer pH 6.8 is slightly faster than the release in acetate and citrate buffer pH 6.8. However, these the release rates are very low compared to those at lower pH values.

When comparing drug release from pellets coated with ammonio methacrylate copolymers in media containing different ions, differences in release rates are very likely to be

seen [106]. Drug release from RL coated solid dosage forms depends on the exchange between the anions dissolved in the release media and the QAGs of the film [112]. Anions have different capabilities in interacting with the QAGs and thus influencing the permeability of the coating.

High sodium chloride concentrations decrease the permeability of RL coatings due to a reduced ion exchange [112]. In Fig. 13, the results of the dissolution testing of theophylline pellets coated with the 8:1 blend in sodium chloride solutions of different concentration at pH 4.0 are shown.

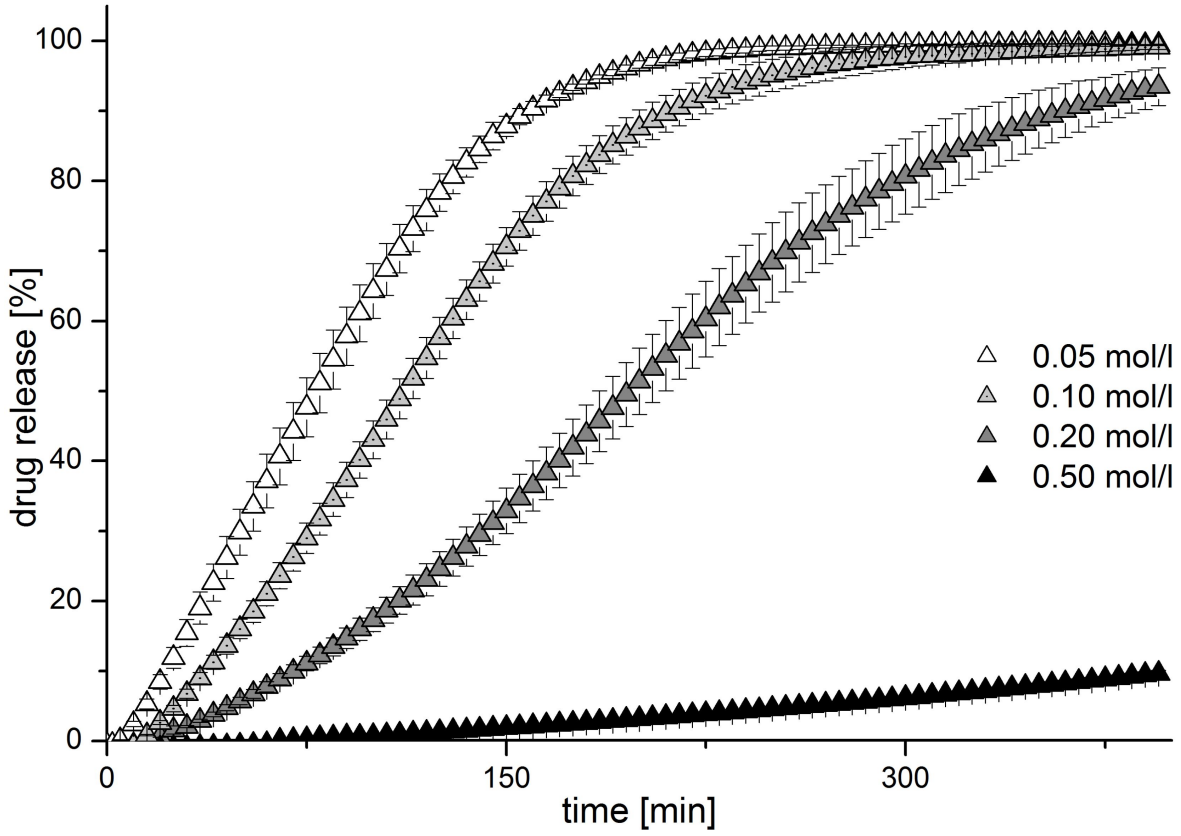


Fig. 13: Drug release from pellets coated with blends of RL/L55 in the weight ratio of 8:1 in sodium chloride solutions of various concentrations at pH 4.0; n = 3, means ± SD.

The release profiles displayed in Fig. 13 demonstrate that higher concentrations of sodium chloride result in a lower drug release rate, similar to plain RL coatings. This leads to the assumption that the theophylline release from RL/L55 blends is driven by ion exchange.

The obvious differences between drug release in media with pH 6.8 and drug release in media with lower pH are predominantly dependent on the pH value. L55 contains carboxyl groups that dissociate at a higher pH and might electrostatically interact with the QAGs thus

hindering the ion exchange with the anions in the release medium. These interactions are more pronounced in RL/L55 blends than in RLD/L55D blends as a consequence of higher polymer-polymer interpenetration [117].

3.1.3.2 Influence of the copolymer blend ratio and coating level

To characterize drug release from coatings with different blend ratios of RL/L55, theophylline pellets were coated with blend ratios of 4:1, 8:1, 12:1, and 16:1. The coating level was 10.0 % (w/w). To save time, the permeability of the coatings was increased by using talc with a smaller particle size. Insoluble platelet-shaped particles extend the diffusion path length for drug molecules. Larger platelet-shaped particles block diffusion routes more efficiently than smaller particles thus decreasing the release rate [9, 170]. The release profiles are displayed in Fig. 14a.

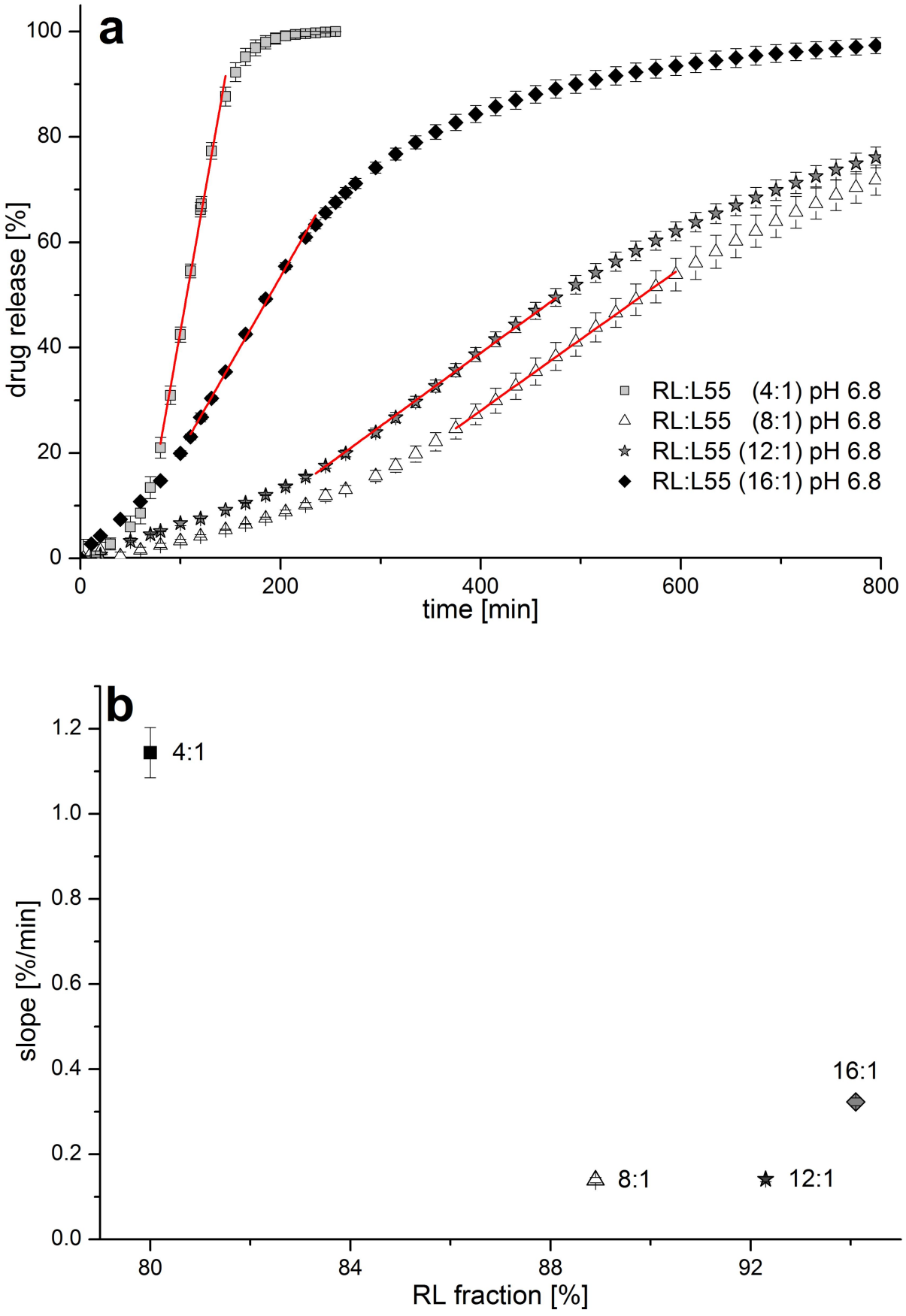


Fig. 14: a) Drug release profiles of theophylline pellets coated with 4:1, 8:1, 12:1, and 16:1 blends of RL/L55, n = 3, means ± SD; b) Slopes of the drug release profiles calculated from the linear release phase, n = 3, means ± SD

All release profiles in Fig. 14a can be described as sigmoidal-shaped where this sigmoidal shape is more pronounced with the 4:1 blend and less for the other blends. Theophylline release from RL/L55 blends is divided in three phases. In the first phase slow drug release is observed. Subsequently, in the second phase the release rate increases and the main portion of the drug is released following zero order release kinetics. In the third phase the drug release decreases as the reservoir depletes. To compare the drug release rates of the differently coated pellets, the slope of the linear release phases (second phase) was determined and plotted versus the percentage of the RL fraction in the coating film (Fig. 14b). The release rates are low for the 8:1 and 12:1 blends and high for the 4:1 blend. The 16:1 blend has a medium release rate.

The first phase of the sigmoidal-shaped drug release curves can be characterized with the time point of 10.0 % drug release ($t_{10.0\%}$), while the second phase can be described by its slope. To compare the shape of the curves, the data were fitted to the Weibull equation (Eq. 3) to determine the shape parameter β.

To gain deeper insight into the dependency of drug release on the blend ratio while taking the coating level into account, theophylline pellets with coating levels of 2.5 %, 5.0 %, and 10.0 % (w/w) were prepared. With these pellets dissolution experiments in hydrochloric acid pH 1.2 and phosphate buffer pH 6.8 were performed. To illustrate the release data, a two factor historical design was carried out. The fraction of RL in the coating blend and the coating level were used as factors. The three release profile characteristics ($t_{10.0}$, the slope of the linear release phase, and the shape parameter β) for drug release in hydrochloric acid and phosphate buffer, respectively, were used as responses. The settings of the factors and the corresponding responses are displayed in Table 6.

Table 6: Settings of the factors and the corresponding responses. *A* = RL fraction [% (w/w)]; *B* = coating level [% (w/w)], $t_{10.0\%}$ = time point of 10.0 % drug release [min]; *slope* = release rate [%/min]; β = shape parameter.

			hydrochloric acid pH 1.2			phosphate buffer pH 6.8		
Run	*A*	*B*	$t_{10\%}$	*slope*	β	$t_{10\%}$	*slope*	β
	[%]	[%]	[min]	[%/min]		[min]	[%/min]	
1	80.0	2.5	4.9	1.134	1.193	12.0	1.920	1.355
2	88.8	2.5	11.1	1.942	1.349	39.0	0.137	1.381
3	92.3	2.5	4.5	2.082	1.266	18.0	0.157	1.087
4	94.1	2.5	5.3	1.726	1.178	40.9	0.162	1.421
5*	94.1	2.5	5.5	2.398	1.306	20.0	0.291	1.225
6	80.0	5.0	18.7	1.525	1.792	22.5	1.972	2.494
7	88.9	5.0	9.8	1.992	1.680	68.3	0.125	1.342
8*	88.9	5.0	8.8	1.434	1.488	90.9	0.132	1.508
9	92.3	5.0	7.6	1.444	1.229	85.1	0.117	1.363
10*	92.3	5.0	8.7	1.678	1.488	89.6	0.085	1.375
11	94.1	5.0	9.4	1.151	1.320	43.1	0.224	1.310
12	80.0	10.0	40.7	1.132	2.659	48.1	1.144	3.479
13*	80.0	10.0	22.7	1.200	2.100	100.5	0.894	4.321
14	88.9	10.0	23.6	1.115	2.197	223.0	0.139	1.896
15*	88.9	10.0	11.0	1.418	1.891	246.5	0.119	1.725
16	92.3	10.0	15.2	1.590	1.902	183.7	0.144	1.438
17*	92.3	10.0	9.9	1.525	1.745	157.3	0.141	1.606
18	94.1	10.0	10.8	1.380	1.702	55.5	0.333	1.504

*Repeated run

To estimate a pure error and a Lack of Fit (LOF) for the models, six runs were repeated (Table 6). The calculated models for the time point of 10.0 % drug release in hydrochloric acid and the corresponding β value are described as equations which are displayed in Table 7 together with the correlation coefficients for the models and their factors. Although a decrease of drug release in hydrochloric acid depending on the coating level was expected, no model with satisfying predictive power for the shape of the linear release phase could be computed. This might be due to the relatively fast drug release and hence high deviations of the data.The computed models for the release in hydrochloric acid pH 1.2 show a reasonable R^2 in which the discussed deviations of the data are included. The predicted R^2 and adjusted R^2 are in good agreement. The dependency of the $t_{10.0\%}$ value on the factors *A* and *B* can be described with a linear function. For the β value an interaction of the factors *A* and *B* was found. The coating level is the most important factor for both models. The response surfaces derived from the equations in Table 7 is displayed in Fig. 15.

Table 7: Drug release in hydrochloric acid pH 1.2: Model factors and correlation coefficients for the RL/L55 blend ratios and coating levels. *A* = RL fraction; *B* = coating level, $t_{10.0\%}$ = time point of 10.0 % drug release; *slope* = release rate; β = shape parameter.

	$t_{10.0\%}$		β	
	Estimate	*P* value	Estimate	*P* value
A	-0.145	0.009	-0.194	0.021
B	0.198	<0.001	0.401	<0.001
AB	-	-	-0.152	0.022
$log\ t_{10.0\%} = 2.52 - 0.021A + 0.053B$				
R^2: 0.706	Adjusted R^2: 0.667		Predicted R^2: 0.482	*P* value LOF: 0.359
$\beta = 0.28 - 0.0083A + 0.61B - 0.0057AB$				
R^2: 0.874	Adjusted R^2: 0.848		Predicted R^2: 0.691	*P* value LOF: 0.978

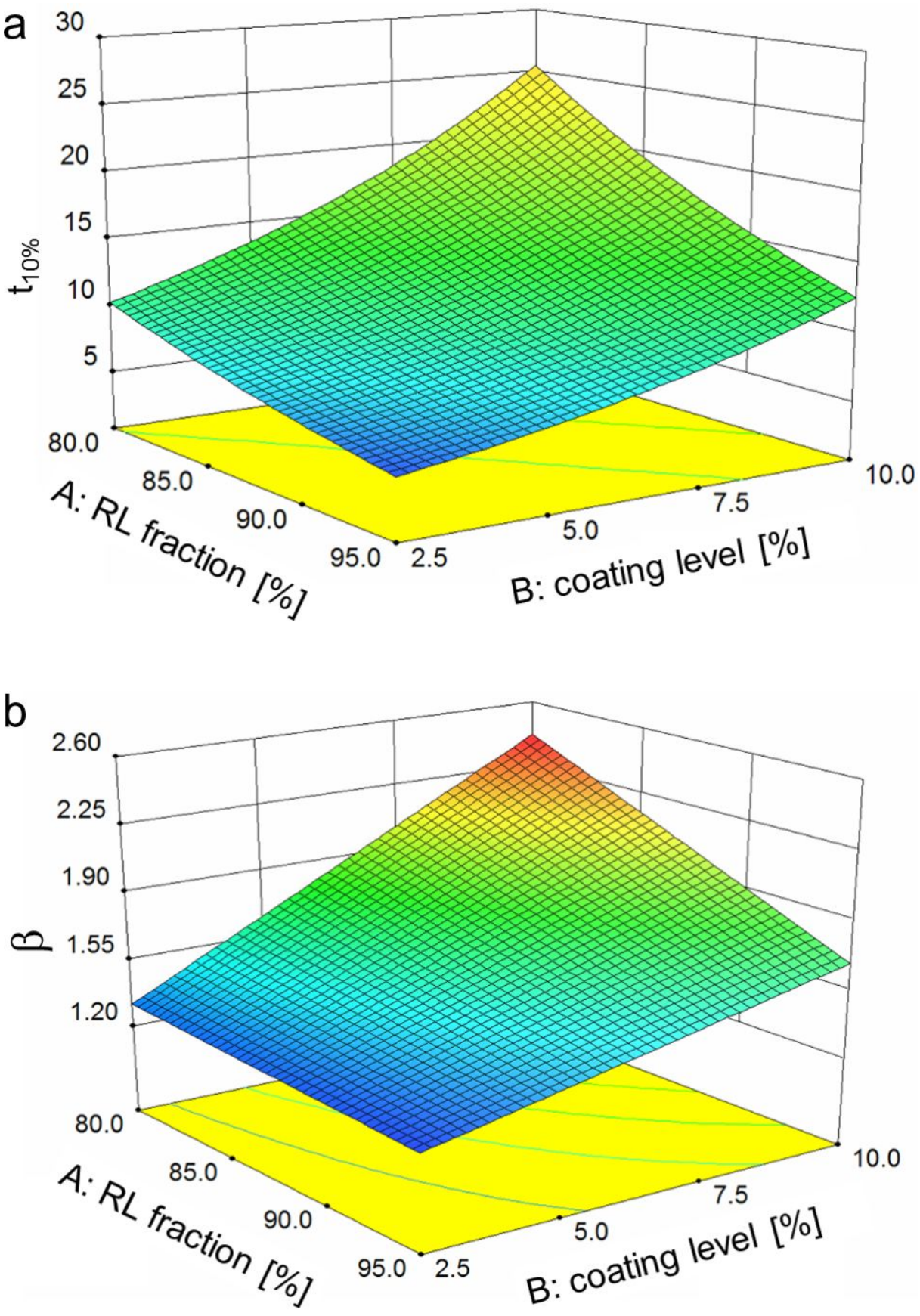


Fig. 15: Evaluation of the drug release data in hydrochloric acid pH 1.2: Response surfaces obtained by plotting RL fraction versus coating level; plotted responses are a) $t_{10\%}$; b) β.

The $t_{10.0\%}$ value increases with increasing coating level and decreasing RL fraction. A similar dependency can be found for the shape parameter β but in contrast to the $t_{10.0\%}$ value, β increases overproportionally due to the interaction between the factors *A* and *B*. Both effects can be attributed to longer lag times resulting from thicker films and a higher L55 fraction within the film.

Only a small effect of the blend ratio on the $t_{10.0}$ and β values could be found and the effect on the slope of the linear release phase was nonsignificant. Thus, drug release in hydrochloric acid is only marginally affected at least by small amounts of L55 in the RL/L55 blends.

For the release profiles in phosphate buffer pH 6.8 the same data analyzing methods as before were performed. Again, the calculated models for the responses are described as equations together with the correlation coefficients for the models and their factors (Table 8).

For all presented models the Adjusted R^2 and Predicted R^2 are in good agreement and R^2 is close to unity. The model for the time point of 10.0 % drug release can be described with a function in which the RL fraction is considered as a squared factor. The slope of the linear release phase can also be described with a quadratic model which also involves an interaction of the factors *A* and *B*. The model for the shape parameter β can be described with a two factor interaction equation. The response surfaces derived from these equations are displayed in Fig. 16.

Table 8: Drug release in phosphate buffer pH 6.8: Model factors and correlation coefficients of RL/L55 blend ratios and coating levels. A = RL fraction; B = coating level, $t_{10.0\%}$ = time point of 10.0 % drug release; *slope* = release rate; β = shape parameter.

	$t_{10.0\%}$		*slope*		β	
	Estimate	*P* value	Estimate	*P* value	Estimate	*P* value
A	0.117	0.050	-0.413	<0.001	0.107	<0.001
B	0.335	<0.001	-0.047	0.169	-0.090	<0.001
AB	-	-	0.107	0.020	0.066	<0.001
A^2	-0.428	<0.001	0.622	<0.001	-	-

$log\ t_{10.0\%} = -68.12 + 1.51A + 0.089B - 0.0085A^2$

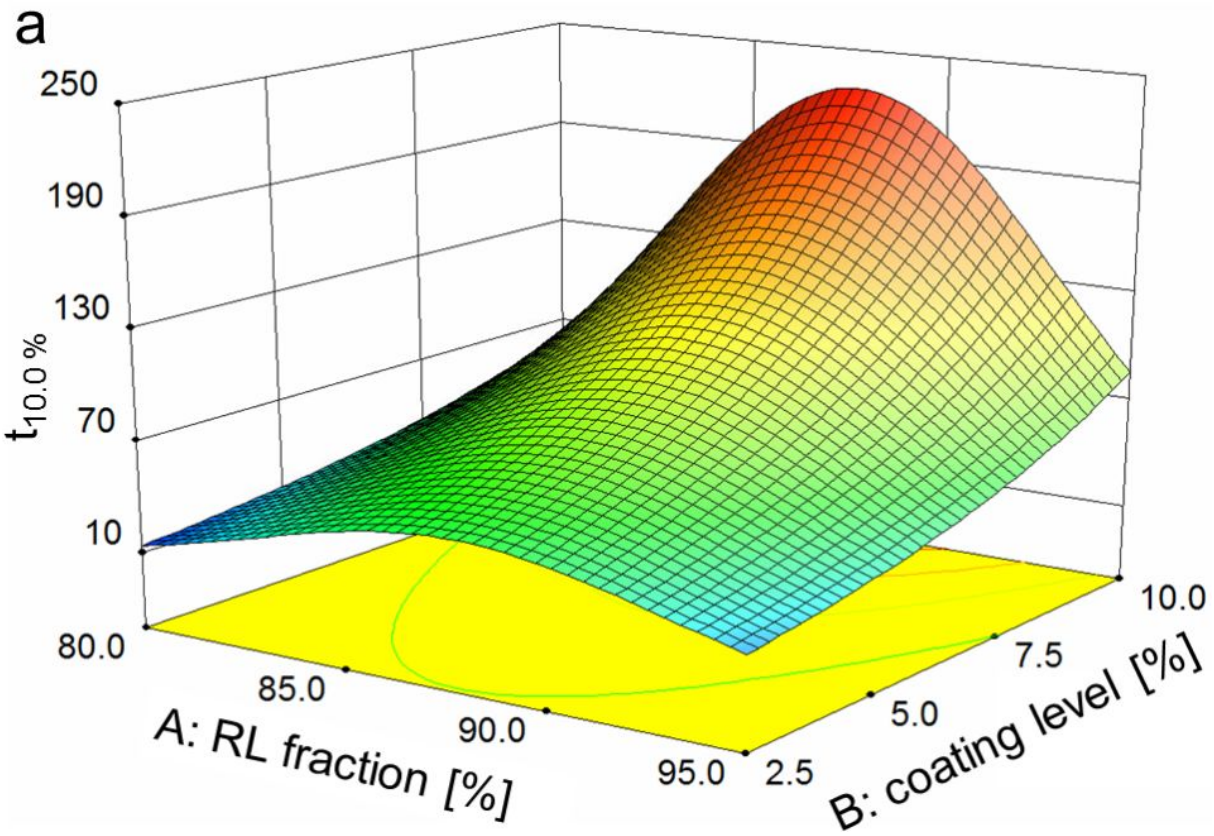
R^2: 0.850 Adjusted R^2: 0.818 Predicted R^2: 0.745 *P* value LOF: 0.244

$\frac{1}{\sqrt{\beta}} = 0.96 - 0.00045A - 0.24B + 0.0025AB$

R^2: 0.954 Adjusted R^2: 0.940 Predicted R^2: 0.916 *P* value LOF: 0.908

$log\ slope = 100.99 - 2.25A - 0.36B + 0.0040AB + 0.012A^2$

R^2: 0.908 Adjusted R^2: 0.888 Predicted R^2: 0.802 *P* value LOF: 0.190



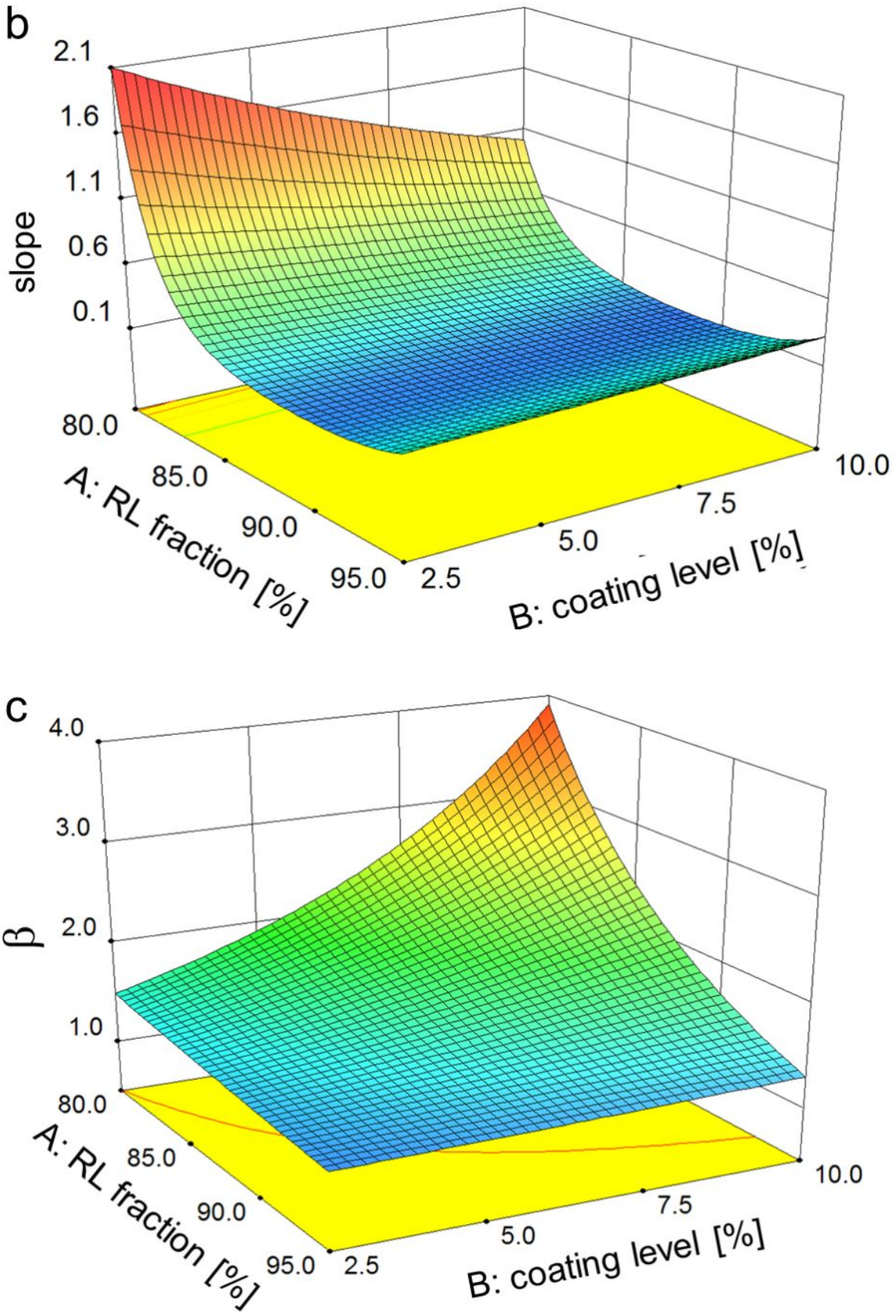


Fig. 16: Evaluation of the drug release data in phosphate buffer pH 6.8: Response surfaces obtained by plotting RL fraction versus coating level; plotted responses are a) $t_{10.0\%}$; b) *slope*; c) β.

In Fig. 16a a maximum at approximately 89 % (w/w) RL fraction and 10.0 % (w/w) coating level can be found. The $t_{10.0\%}$ value decreases with decreasing coating level.
When comparing the model factors for the slope of the linear release phase (Table 8), it can be stated that the coating level (*B*) only has a low influence. An influence of the coating level on the slope can be detected at lower RL fractions (Fig. 16b). Similar slopes for all three coating levels were detected for the 16:1 blend (~95 % RL fraction).

With lower RL fractions the β value increases and thus the sigmoidal shape of the release curves becomes very pronounced (Fig. 16c). The shape parameter is predominantly dependent on the coating level in the region of low RL fractions.

The pH value of the release medium is the key factor for the release behavior of RL/L55 blends coated pellets. The lowest slopes and highest $t_{10.0\%}$ values were found at approximately 89 % (w/w) RL fraction in phosphate buffer pH 6.8. At pH 1.2, the influence of the RL fraction is less pronounced than at pH 6.8 and the highest $t_{10.0\%}$ values were observed at a RL fraction of 80 % (w/w). This effect may be attributed to the dissociation of carboxyl groups and their interactions with the QAGs. Moreover, the blend ratio determines the amount of functional groups potentially available to interact. A large excess of carboxylate groups that cannot interact with QAGs raises the permeability of the coating. The 4:1 blend contains about two times more acidic groups than QAGs, many of them being dissociated at pH 6.8. In addition, only one out of sixteen monomers in RL is cationic whereas in L55 one out of two is acidic. Presumably, the different distances between the functional groups in the two copolymers sterically hinder their interaction. The excess carboxylate groups may contribute to the hydrophilicity and the swelling tendency of the film and lead to a fast drug release in phosphate buffer pH 6.8 (Fig. 14a).

3.1.3.3 Influence of the pH value of the phosphate buffers

The dissolution tests in hydrochloric acid pH 1.2 and phosphate buffer pH 6.8 showed a strong influence of the pH on the drug release behavior. To obtain more detailed information on the dependency of the release behavior on the pH value, dissolution tests with theophylline pellets coated with 4:1 and 8:1 blends (coating level 10.0 % (w/w)) were performed in phosphate buffers pH 5.8 and 7.6 (Fig. 17). These media were chosen because

they cover the wide pH range in the intestinal tract [73, 172]. Furthermore, these values are close to the lower and upper limits of the pH range of phosphate buffers. To exclude the influence of the salt concentration all release media were adjusted to a phosphate concentration of 0.05 mol l^{-1}.

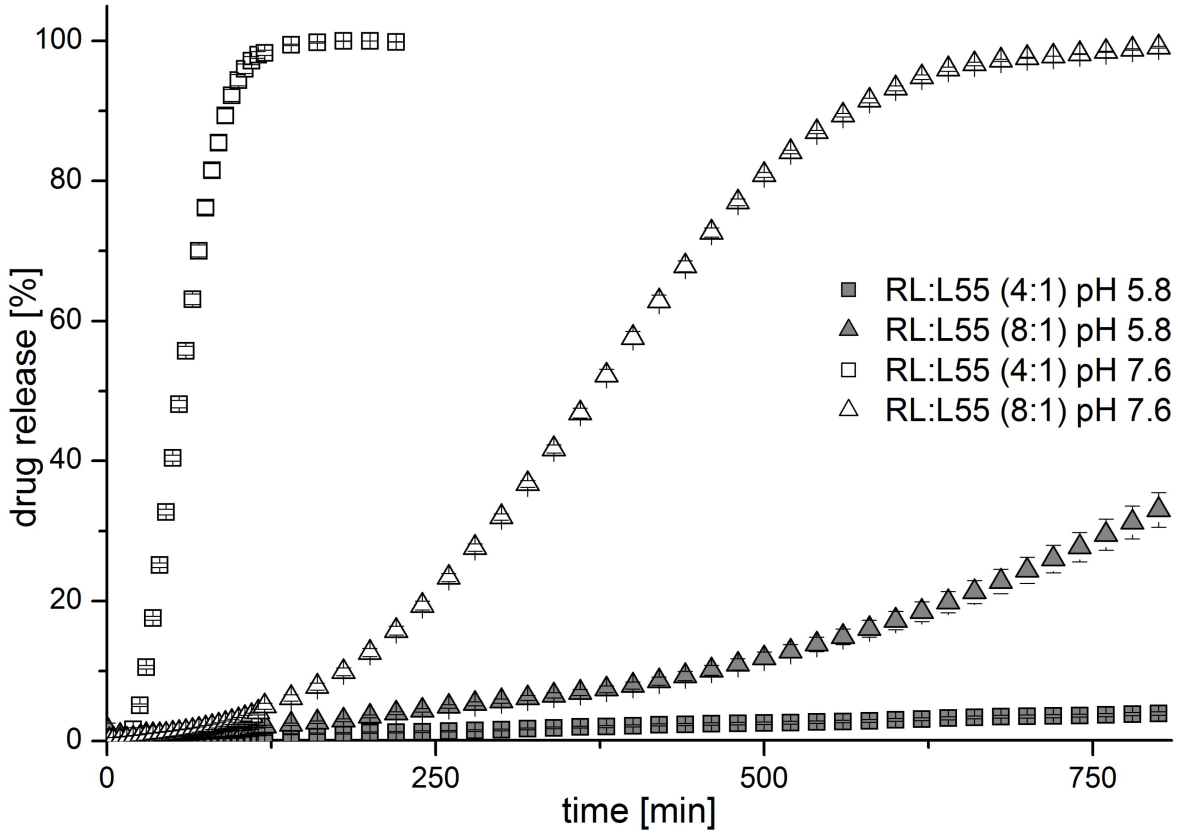


Fig. 17: Drug release from theophylline pellets coated with blends of RL/L55 in weight ratios of 4:1 and 8:1 in phosphate buffers pH 5.8 and 7.6; n = 3, means ± SD.

The lowest release rate was observed at pH 5.8 for the 4:1 blend. Drug release from pellets coated with the 8:1 blend was nearly identical to that at pH 6.8 (Fig. 14a) while it was faster at pH 7.6. To obtain a deeper insight into the interplay between the RL fraction and the pH value, additional RL/L55 blend ratios of 12:1 and 16:1 were investigated at pH 5.8 and 7.6. Along with the data from the release profiles in phosphate buffer pH 6.8 a Design of Experiments for historical data was performed. The settings of the factors and the corresponding responses are shown in Table 9.

Only one batch per blend ratio was used to determine the responses to minimize the influence of process variability. The calculated model factors are displayed in Table 10, along with the correlation coefficients and the model equations.

Table 9: Settings of the factors and the corresponding responses. A = RL fraction; C = pH; $t_{10.0\%}$ = time point of 10.0 % drug release; *slope* = release rate; β = shape parameter.

Run	A [%]	C	$t_{10.0\%}$ [min]	*slope* [%/min]	β
1	80.0	5.8	1926.3	0.017	2.53777
2	88.9	5.8	457.3	0.089	2.50144
3	92.3	5.8	60.9	0.556	1.56283
4	94.1	5.8	23.6	1.076	1.93979
5	80.0	6.8	100.5	0.894	4.32094
6	88.9	6.8	246.5	0.119	1.7252
7	92.3	6.8	183.7	0.144	1.43768
8	94.1	6.8	57.5	0.655	2.5139
9	80.0	7.6	29.5	1.509	2.54532
10	88.9	7.6	180.7	0.251	2.82444
11	92.3	7.6	251.5	0.100	1.73202
12	94.1	7.6	65.9	0.557	2.39953

Table 10: Drug release in phosphate buffers of various pH: Model factors and correlation coefficients of RL/L55 blend ratios and pH values.

	$t_{10.0\%}$		*slope*	
	Estimate	P value	Estimate	P value
A	-0.303	0.002	-0.035	0.518
C	-0.297	0.002	0.211	0.003
AC	0.625	0.001	-0.530	<0.001
A^2	-0.625	0.002	0.699	<0.001

$log\ t_{10.0\%} = -43.52 + 1.46A - 8.85C + 0.098AC - 0.012A^2$

R^2: 0.939 Adjusted R^2: 0.904 Predicted R^2: 0.745

$slope = 55.64 - 1.86A + 7.46C - 0.082AC + 0.014A^2$

R^2: 0.950 Adjusted R^2: 0.921 Predicted R^2: 0.876

With the shape factor β no significant model could be computed. For all models the Predicted R^2 and Adjusted R^2 are in good agreement. However, no pure error could determined as no replicate experiments were performed. The model factors in Table 10 show that the most prominent influencing factors for both responses are the *AC* interaction and the quadratic term A^2. In both cases the A^2 term promotes a fast drug release and the *AC* interaction decreases drug release. The contour plots derived from the equations in Table 10 are shown in Fig. 18.

The contour plots show that the release behavior of RL/L55 blends depends on the pH and the blend ratio. The slope of the release profiles has a minimum running diagonally from a RL fraction range between 80 and 89 % at a pH of 5.8 to a range between 87 and 93 % at pH 7.6. Areas with high values can be found in the upper left and lower right corner.

The dissociation of L55 must be taken into account to explain this release behavior. On the one hand, high dissociation promotes ionic interactions with the cationic copolymer and the formation of IPECs which hinder ion exchange. On the other hand, an excess of carboxylate groups promotes drug release via mechanisms as discussed in subsection 3.3.2.

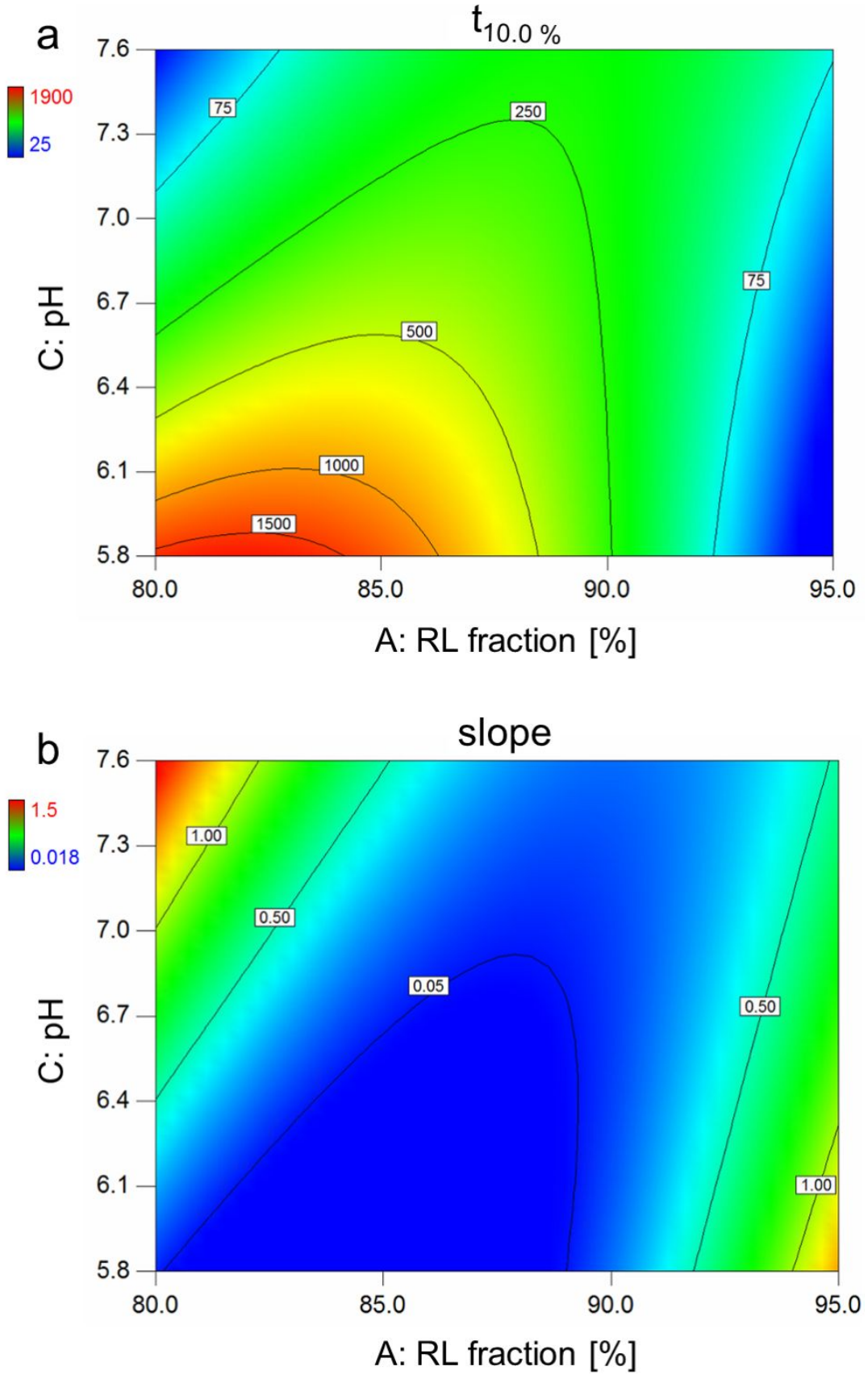


Fig. 18: Evaluation of the drug release data in phosphate buffers of various pH: Contour plots obtained by plotting the RL fraction versus the pH value; plotted responses are a) $t_{10.0\%}$; b) and *slope*.

3.1.3.4 Drug release from “delayed-release solid dosage forms” (Ph. Eur.)

Drug release rates from theophylline pellets coated with the investigated blends of RL/L55 are generally higher in hydrochloric acid than they are in phosphate buffer pH 6.8. The test for delayed-release solid dosage forms (Ph. Eur., Method A) was performed in a modified manner to evaluate the influence of a pH change from 1.2 to 6.8. The duration of the acidic stage was reduced to 60 min to prevent drug release from completion before the pH value is changed. The obtained release profiles are presented in Fig. 19.

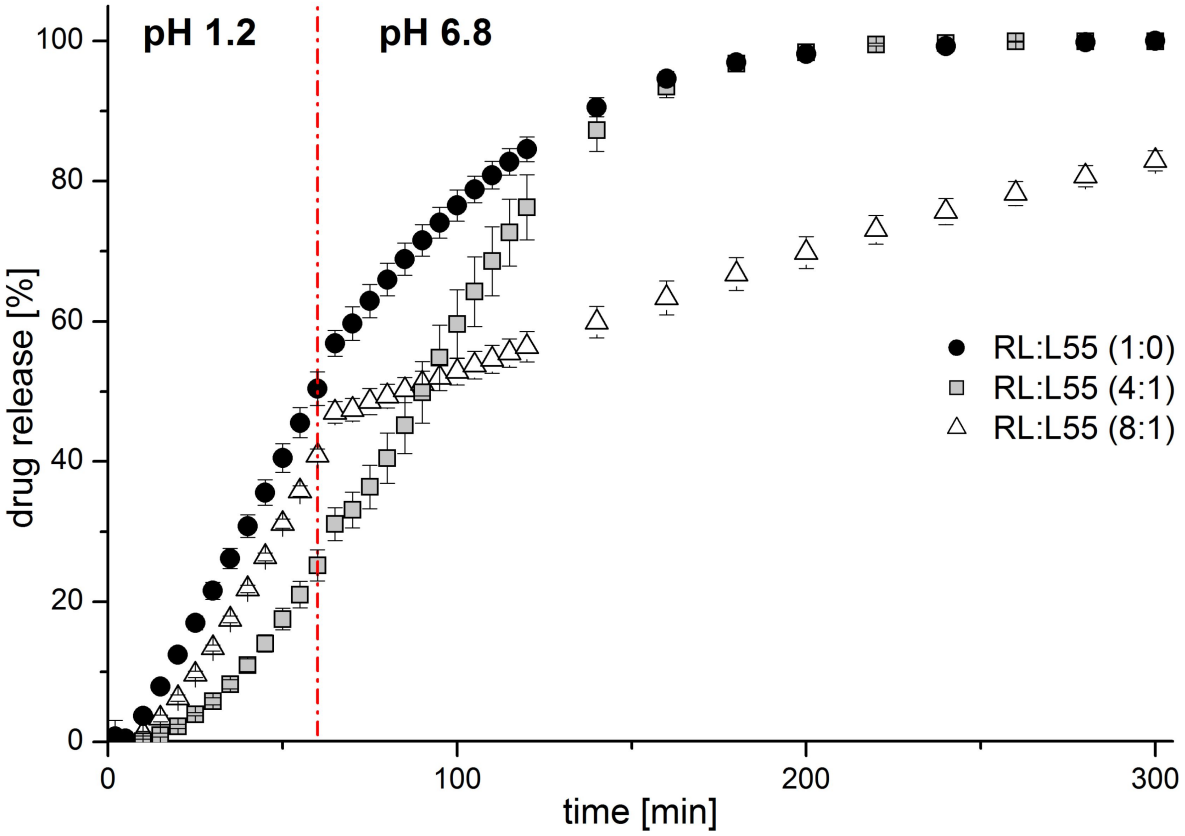


Fig. 19: Modified dissolution test for delayed-release solid dosage forms (Ph. Eur., Method A): Drug release from theophylline pellets coated with blends of RL/L55 in weight ratios of 1:0, 4:1, and 8:1; n = 3, means ± SD.

As expected, the release profiles over the first 60 min are nearly identical to those in Fig. 11a. It was observed that after changing the pH from 1.2 to 6.8 the theophylline pellets coated with plain RL and the 4:1 blend, respectively, did not show a significant change in the slope of the release profiles. This is in good agreement with the results in Fig. 11a where the slopes of the release profiles did not differ significantly. In contrast, the release rate from the pellets coated with the 8:1 blend decreased significantly after changing the

pH. This result is, again, in accordance with the results presented in Fig. 11b.

As expected, the interaction between the copolymers takes place in a neutral medium even after exposing it to an acidic medium. This release behavior could be a useful tool in controlled drug delivery as it provides the possibility of a tailor-made pH-dependent drug release while using well known pharmaceutical exipients.

3.1.4 Conclusion

Theophylline pellets coated with blends of RL and L55 from organic solutions were investigated with regard to their release behavior in dependence of the pH and the copolymer blend ratio. Blends with a RL content above 80 % were more permeable in hydrochloric acid (pH 1.2) than in neutral and basic media. This might be the result of interpolyelectrolyte complexes between the functional groups of the copolymers. These complexes are formed in neutral and basic media during drug release. Coatings applied to the pellets from aqueous dispersion are not significantly influenced in their permeability by the addition of the enteric copolymer. The pH-dependent permeability of RL/L55 blend coatings can be adjusted by varying the ratio of the copolymers in the film. The pH-dependent release behavior also occur if the coatings are exposed to hydrochloric acid pH 1.2 prior to drug release in neutral medium. The presented polymer blends may be suitable to achieve pH-independent release of weakly acidic drugs from a coated core while using well known pharmaceutical excipients. However, the reason for the dependency of the drug release on the coating process (organic vs. aqueous) is yet unknown. Furthermore, the exact release mechanism remained unclear.

3.2 Results and discussion of "Investigation on solid state interactions and homogeneity of free Eudragit® RL/L55 copolymer film blends from aqueous dispersion and organic solution"[2]

The results presented in section 3.1 showed that theophylline pellets coated with blends of RL and L55 reached higher drug release rates in acidic media than in neutral/basic media. However, this release behavior was only found with coatings from organic solution but not for coatings from aqueous dispersion. The pH-dependent release behavior might be attributed to ionic interactions between the copolymers that occur in neutral/basic media between the quaternary ammonium groups of RL and the dissociated methacrylic acid groups of L-55. The reason for the dependency of the drug release behavior on the coating technology remained unclear.

The aim of the second study was to identify reasons for the dependency of the release behavior of RL/L55 copolymer blends on the coating technology (aqueous vs. organic). Investigations were performed on their film forming properties out of organic solution and of aqueous dispersion with special regards to the pH value. Furthermore, the homogeneity of copolymer films from aqueous dispersion and organic solution was investigated, as well as interactions of the copolymers within the film.

3.2.1 Acid Value and the pK_a of L55D

For L55D an Acid Value of 319 $\pm$ 4.9 mg KOH /g polymer was determined by acidimetric titration. The value corresponds to the Acid Value in the specifications of L55D [173]. Furthermore, the acidimetric titration resulted in a pK_a value of 5.98 $\pm$ 0.06. A previous investigation on the pK_a led to a value of 6.9 [169]. However, unlike the Acid Value, the pK_a is not a continuously monitored parameter during L55D production. Thus the difference in the pK_a values might be a result of possible changes of the manufacturing process.

[2]This chapter has been published as shown in Section 5.2

3.2.2 Characterization of the polymer films

All prepared films were transparent and appeared homogeneous upon visual inspection. According to the determined pK_a value, approximately 1 % of the methacrylic acid groups in L55D are dissociated at pH 4.0. Consequently, 10 % of the acid groups are dissociated at pH 5.0 approximately.

Preliminary studies at pH 5.4 and above showed that L55D with 20 % and more dissociated groups often forms aggregates when mixed with RLD as a result of ionic interactions. Thus, most films derived from these mixtures were not transparent. Obviously, the pH has a significant influence on the film forming properties of RLD/L55D blends and on the homogeneity of the resulting films.

3.2.3 Investigations on the homogeneity of the copolymer films by ATR-FTIR spectroscopy

IR spectra of films from aqueous dispersions and organic solutions were recorded at least at four randomly chosen spots to verify the visually determined film homogeneity. A PCA was performed using the IR spectra of the plain copolymers as well as the copolymer film blends. The PCA scores plot of the aqueous dispersions at pH 4.0 and pH 5.0 are displayed in Figs. 20a and b.

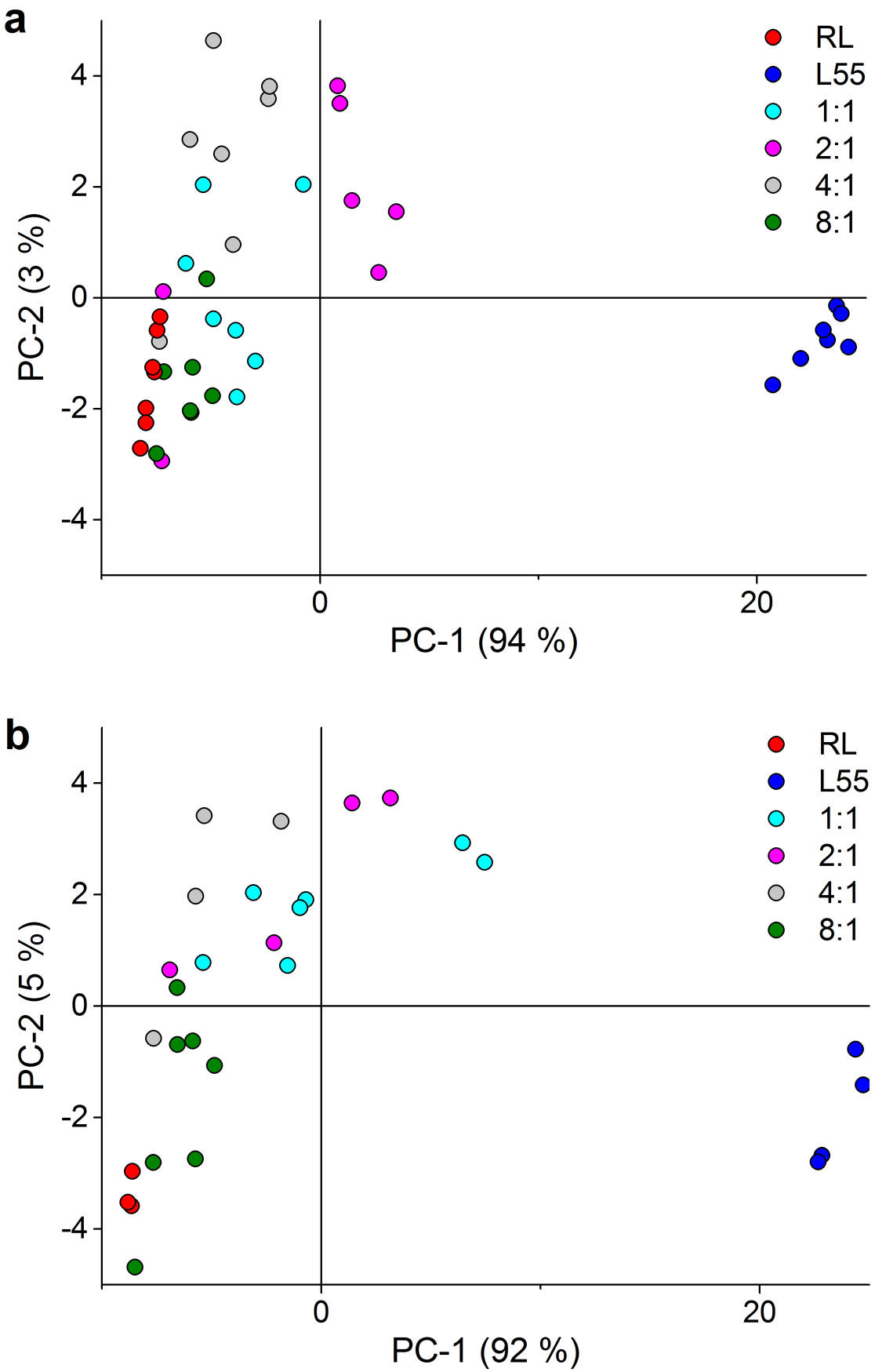


Fig. 20: PCA of plain copolymer films and copolymer film blends from aqueous dispersion at a) pH 4.0 and b) pH 5.0.

The IR spectra of the copolymer blends are not significantly clustering in the PCA scores plots. In contrast to the expectations after visual inspection, the copolymer films prepared from aqueous dispersions at both pH values cannot be considered homogeneous. It is postulated that the dispersed copolymer particles aggregate and form microclusters prior to film formation. Apparently, after film formation these microclusters are still present to some extent. Obviously, the mobility of the polymer chains is not sufficiently high to transform particles in the low micrometer range to a colloidal dispersion.

Film blends from organic solutions are expected to have a high degree of homogeneity [90, 117]. These colloidal copolymer solutions should form a homogeneous film if the copolymers are miscible. The results of the PCA for IR spectra of copolymer films from organic solution measured at four spots each is displayed in Fig. 21a, along with the spectra of the plain copolymer films, the corresponding difference spectrum and the loadings plot of PC-1 (Fig. 21b).

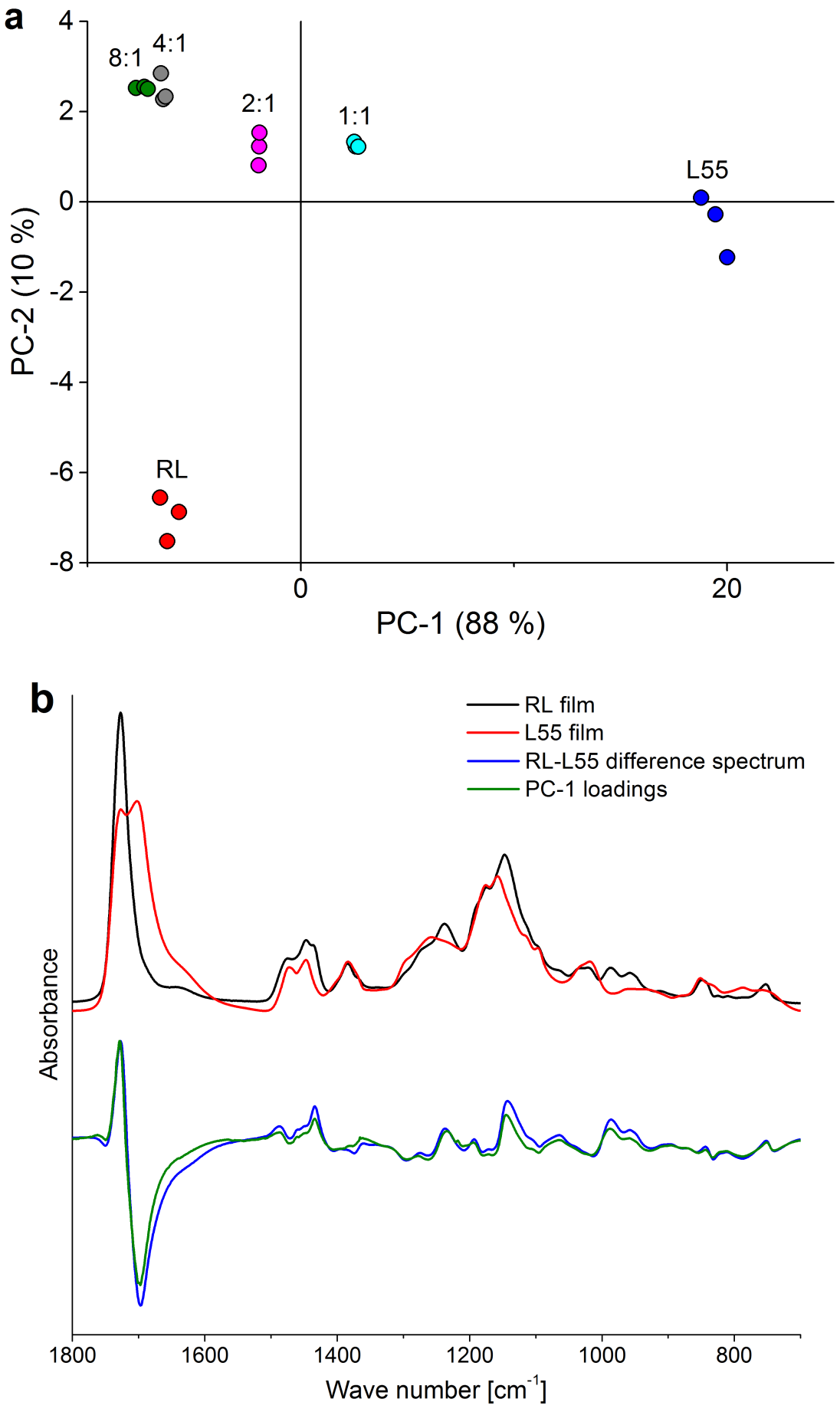


Fig. 21: PCA scores plot of plain copolymer films and copolymer film blends from organic solution; a) IR spectra of RL; b) L55, RL - L55 difference spectrum and PC-1 loadings plot.

As expected, the IR spectra of copolymer film blends from organic solution cluster in the PCA scores plot. Thus, they can be considered as homogeneous. The first PC (PC-1) describes the differences in the spectra of RL and L55 and significantly correlates with the difference spectrum of the two copolymer spectra (R^2 = 0.998). Consequently, the copolymer film blends are arranged in the scores plot according to their decreasing RL fraction along the PC-1 axis. The differences in the homogeneity between film blends from aqueous dispersion and those from organic solution are presumably the reason for their different drug release behavior if applied to theophylline pellets (Section 3.1).

Obviously, the spectra of the copolymer film blends from organic solution are not the addition of the two plain spectra but contain additional spectral information which is described by PC-2. This might be the result of interactions between the copolymers in the blends and the resulting changes in the corresponding spectra.

The additional spectral information determined by the PCA of RL/L55 copolymer blend films from organic solution cannot be caused by ionic interactions between dissociated methacrylic acid monomers of L55 and the QAGs of RL. Salts of carboxylic acids show bands between 1650 cm^{-1} and 1550 cm^{-1} [175]. In this spectral region no band was observed in the spectra of copolymer film blends from organic soluion. For further interpretation of the spectral information, the loadings plot of PC-2 is shown (Fig. 22).

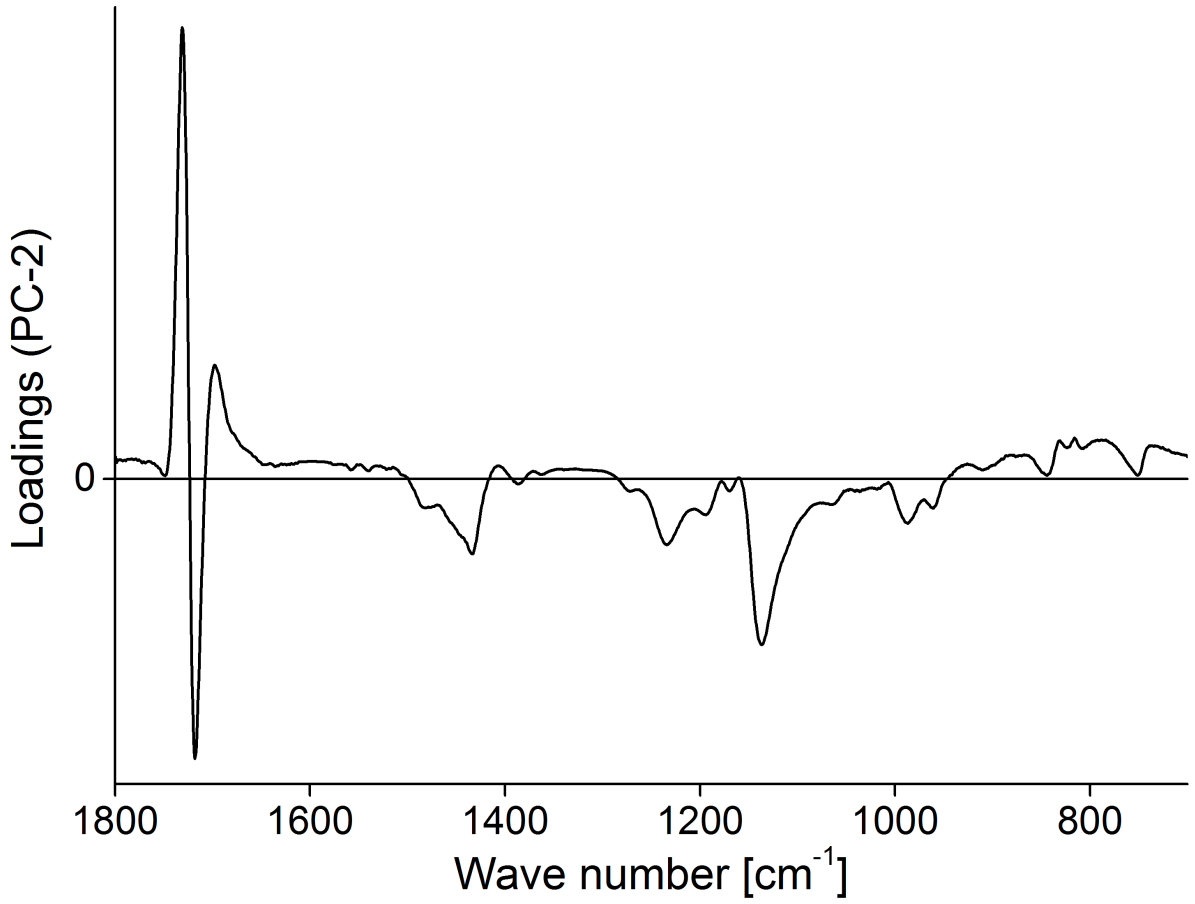


Fig. 22: Loadings plot of PC-2 from the PCA of plain films and blends from organic solution.

PC-2 distinguishes between the copolymer blends with positive scores and the plain copolymers with negative and neutral scores, respectively. The loadings plot of PC-2 reveals a shift of the C=O band to higher wave numbers (from 1717 cm^{-1} to 1731 cm^{-1}). To explain this shift the composition of the C=O band has to be considered.

The C=O band in the L55 spectrum results from the C=O stretching vibrations of the two monomers methacrylic acid and ethyl acrylate (1:1 molar ratio). The carbonyl groups can either be free or trapped in a hydrogen bond with acid groups. Such trapped carbonyl groups show bands at lower wave numbers. In addition, bound and free carbonyl groups can have different absorption coefficients. Plain L55 shows a C=O double band with peaks at 1727 cm^{-1} and 1702 cm^{-1} (Fig. 21b, red line). The peak at 1727 cm^{-1} can be attributed to free carbonyl groups and the peak at 1702 cm^{-1} to hydrogen bound carbonyl groups. Furthermore, the shape of the C=O double band is steeper at higher wave numbers then it is at lower wave numbers. This observation can also be attributed to hydrogen bonds, particularly to those of the methacrylic acid groups as they show absorption at lower wave numbers

in contrast to the bound ethyl acrylate groups [176, 177]. Unfortunately, the present data do not allow an exact differentiation of the origin and state of the carbonyl function.

The C=O band of the esterified acids in the ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride groups in plain RL films may be found at 1727 cm^{-1} (Fig. 21b, black line). The band is narrow and symmetric in shape. Obviously, the alcohol attached to the methacrylic acid does not influence the position of the band. Furthermore, no hydrogen bonds are present because proton-donors are missing.

The loadings plot in Fig. 22 indicates a decrease of absorption in the region between 1707 cm^{-1} and 1723 cm^{-1} (maximum: 1717 cm^{-1}) and an increase of absorption in the region from 1723 cm^{-1} to 1745 cm^{-1} (maximum: 1731 cm^{-1}) for the RL/L55 blends. Both spectral regions can be attributed to free C=O groups. These regions may be the result of new arrangement of hydrogen bonds resulting in an altered composition of unbound C=O groups.

The region between 1705 cm^{-1} and 1650 cm^{-1} can be attributed to hydrogen bound C=O groups [177]. In the loadings plot of PC-2 only a small peak is observable in this region. Thus, the amount of hydrogen bonds in the copolymer blends is similar to that in plain L55. In a homogeneous blend of L55 with a polymer that does not act as a proton acceptor or donor, the bands of the hydrogen bound C=O groups should be attenuated as the interaction between L55 chains are expected to be hindered. This leads to the conclusion, that RL and L55 interact via hydrogen bonds in films from organic solutions.

The remaining bands of the loadings plot cannot be interpreted with regard to hydrogen bonds. The predominantly negative values below 1600 cm^{-1} are the result of the increased absorption of C=O band. Results obtained by PCA considering only the interpreted region between 1800 cm^{-1} and 1650 cm^{-1} were similar to those obtained by analysis of the whole spectrum (data not shown).

To exclude the influence of residual organic solvent, a PCA with the the copolymer blends from organic solution and the PMs as references was performed. The resulting scores plot and loadings plot are displayed in Figs. 23a and b.

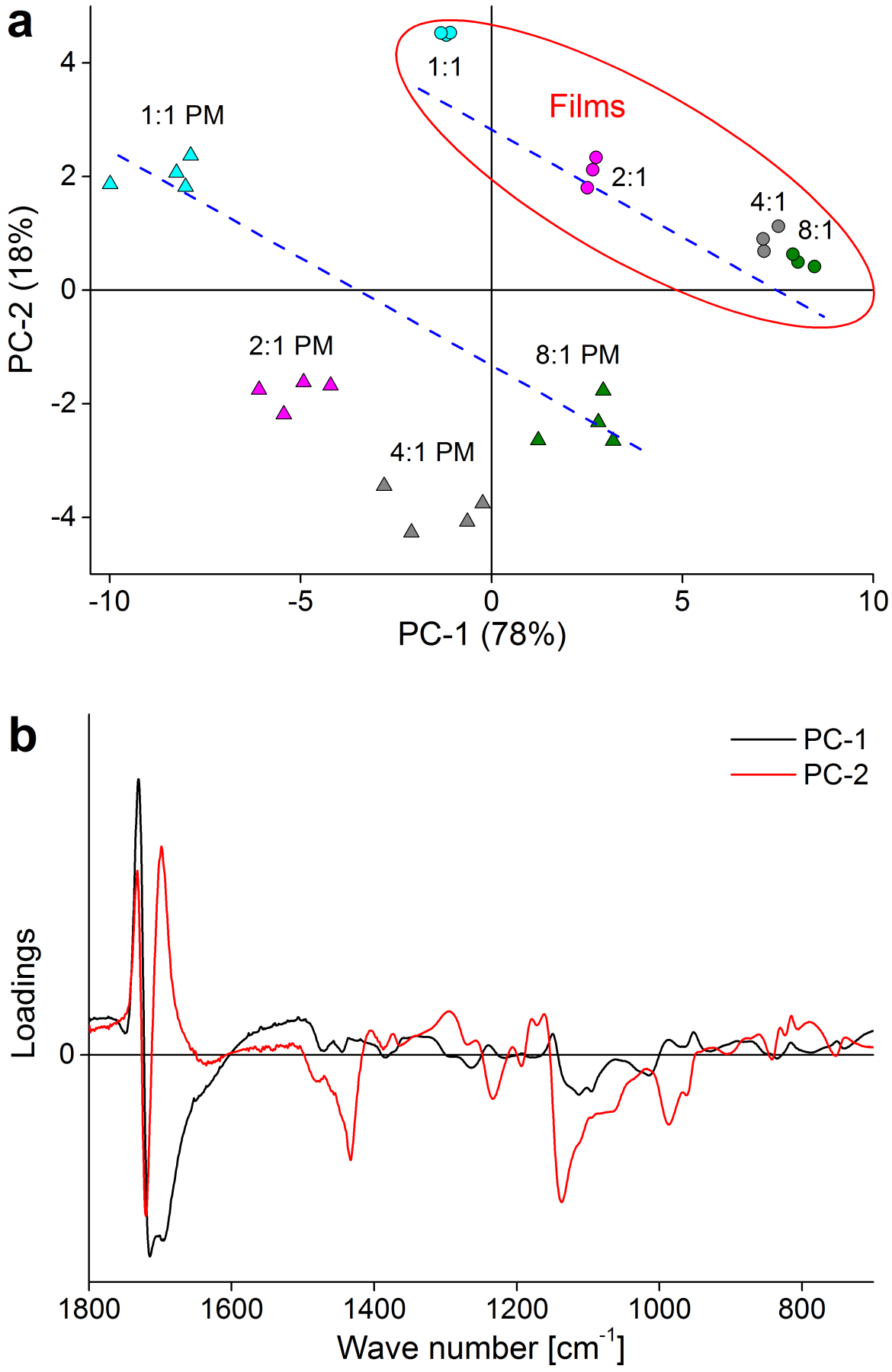


Fig. 23: PCA of film blends from organic solution and of the physical mixtures: a) Scores plot; b) Loadings plot.

The scores plot in Fig. 23a shows that PC-1 and PC-2 are needed to separate the PMs from the films blends from organic solution. The scores of the spectra are arranged along dashed lines which run parallel to each other.

The components of the organic solvent were acetone, isopropanol, and water. Only the IR spectum of the main component acetone has a C=O band that could influence the spectrum of the copolymer blends in the C=O region. The C=O band of acetone is located at 1717 cm^{-1}. However, the loadings of PC-1 and PC-2 reveal that the band at 1717 cm^{-1} is more even more pronounced in the PMs than in the film blends from organic solution. Hence, a significant influence of residual acetone on the IR spectra of the film blends from organic solution can be ruled out. Interestingly, the bands representing hydrogen bound C=O groups are more pronounced in the PM spectra. Hence, it may be assumed that more hydrogen bonds are present in the PMs than in the copolymer films from organic solution.

3.2.4 Thermoanalysis

To confirm the observed molecular interactions between the polymers in film blends from organic solution, thermal analyses were performed.

The interpretation of the DSC results regarding the T_g values was not meaningfull: differences in the heat capacity before and after the T_g were barely detectable in the copolymer films. Furthermore, within the investigated temperature range the films underwent additional thermal events such as solvent evaporation and dilatation of the films which resulted in mechanical stress and influenced the measurements. Consequently, instead of the T_g the decomposition temperatures determined by TGA were used for thermal characterization of the copolymer blends as these values were not influenced by the above mentioned interfering thermal events.

The decomposition temperatures of the prepared PMs, the films from aqueous dispersion at pH 4.0 and the films from organic solution were determined by TGA. The results are listed in Table 11.

Table 11: Decompositon temperatures of physical mixtures (PMs), films from aqueous dispersion at pH 4.0 (aq. films) and films from organic solution (org. films); means ± SD, n=3

	PMs [°C]	**aq. films** [°C]	**org. films** [°C]
RL	412.5 ± 1.7	384.6 ± 3.8	414.8 ± 1.0
L55	403.9 ± 0.6	382.1 ± 4.1	400.9 ± 2.5
4:1	409.4 ± 2.0	382.0 ± 0.9	419.2 ± 1.2
8:1	410.6 ± 2.2	381.4 ± 1.7	419.8 ± 2.3

The determined decomposition temperatures of the plain copolymer powders differ by 10 °C. However, the decomposition temperatures of the 4:1 and 8:1 PMs were not significantly different. Nonsignificant differences in the decomposition temperatures were observed with all films from aqueous dispersion. The values were significantly lower than those of the PMs. The determined decomposition temperatures of the plain copolymer films from organic solution were nonsignificantly different from the respective values of the plain copolymer powders but they were significantly higher than the determined decomposition temperatures of films from aqueous dispersion. Interestingly, the determined decomposition temperatures of the 4:1 and 8:1 films from organic solution were significantly higher than those of the plain copolymer films from organic solution.

The different decomposition temperatures of films from aqueous dispersion and organic solution can be attributed to altered heat conductivities and heat exchange rates as the structure of the films may differ according to the respective film forming processes. More importantly for this study are the significantly higher decomposition temperatures of the organic film blends compared to the plain copolymer films from organic solution. This may be the result of the more pronounced interactions between the two copolymers in film blends from organic solution. For instance, hydrogen bonds may stabilize polymer blends regarding their thermal stability [178, 179].

The results for the 4:1 and 8:1 film blends from organic solution confirm molecular interaction between RL and L55 in films from organic solution. However, due to the low accuracy of the method no closer information on the molecular interaction or the extent of molecular

interaction could be obtained. Therefore, no experiments on 1:1 and 2:1 blends as well as films from aqueous dispersion of pH 5.0 were performed.

3.2.5 Conclusion

The present study deals with RL/L55 film blends with regard to their film forming properties, solid state interactions and homogeneity. Ionic interactions between the QAGs of RL and the dissociated acidic groups of L55 could be identified as critical parameters in film formation from aqueous dispersion. Films from aqueous dispersion with a content of 1 % and 10 % dissociated groups were visually transparent. Surprisingly, ATR-FTIR spectroscopy in combination with Principal Component Analysis revealed that all investigated blends from aqueous dispersion were inhomogeneous on a microscale. In contrast, all films from organic solution were homogeneous. ATR-FTIR spectroscopy showed that RL and L55 form hydrogen bonds in films from organic solution, manifesting themselves in higher thermal stability, which could be confirmed by TGA.

The differences in homogeneity of films blends from aqueous dispersion and those from organic solution could be identified as the reason for the differences in their release behavior when coated onto theophylline pellets. The combination of ATR-FTIR and chemometrics has been proven to suitably characterize solid state interactions copolymers as well as film homogeneity.

3.3 Results and discussion of "Investigation on the drug release mechanism Eudragit® RL/L55 copolymer blend-coated solid dosage forms"[3]

Theophylline pellets coated with RL/L55 blends with RL fractions higher than 80.0 % showed lower release rates in phosphate buffers between pH 5.8 and pH 7.6 than in hydrochloric acid pH 1.2. However, the release behavior of theophylline from pellets coated with blends of aqueous dispersions of the same copolymers was not influenced by the pH of the release media. It was shown in Section 3.2, that the dependency of the release behavior on the coating process (organic vs. aqueous) was caused by the inhomogeneity of the copolymer blend films from aqueous dispersion. However, the reason for the pH-dependent release behavior of pellets coated with copolymer blends from organic solution remained unclear.

The object of the third study was to identify the mechanism behind this pH-dependent drug release. To obtain the necessary information, physicochemical transformations of free RL/L55 film blends from organic solution during swelling and their swelling behavior were investigated.

3.3.1 Raman spectroscopic investigation of swollen films

Raman spectra of copolymer films were recored during swelling in hydrochloric acid pH 1.2 and phosphate buffer pH 6.8 to obtain real-time information on the physicochemical transformations within the films during the swelling process. Copolymer films of blend ratios (RL:L55) of 1:0, 4:1, 8:1 and 0:1 were investigated. All obtained Raman spectra were of good quality with a reasonable signal to noise ratio. The spectra recorded from the samples swollen in hydrochloric acid pH 1.2 and phosphate buffer pH 6.8 were analyzed in separate PCAs. The corresponding scores plots are displayed in Fig. 24.

[3]This chapter has been published as shown in Section 5.2

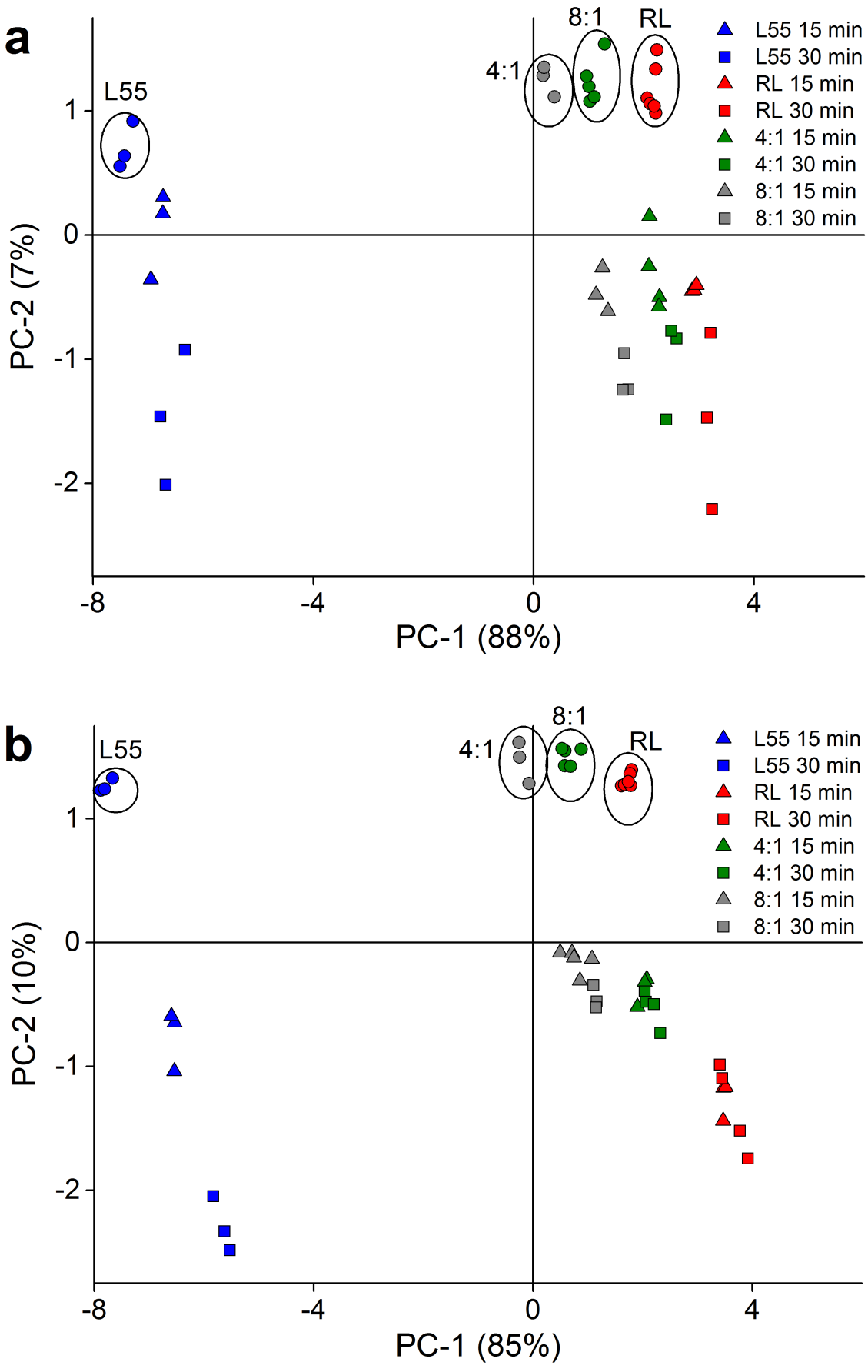


Fig. 24: Scores plots for PCAs of Raman spectra of copolymer films swollen in a) hydrochloric acid pH 1.2 and b) in phosphate buffer pH 6.8; the circled dots represent the unswollen samples (0 min values).

Both scores plots show a good separation of the different blend ratios along PC-1 axis. PC-2 separates swollen and unswollen films in both media were values of samples swollen in hydrochloric acid pH 1.2 are decreased with longer swelling time and can therefore be differentiated. A similar trend was found for samples swollen in phosphate buffer pH 6.8. Nevertheless, a distinct difference between the 15 min and 30 min samples in phosphate buffer was only detected for the L55 samples (Fig. 24b). The nonsignificant changes in the spectra of swollen copolymer films between 15 min and 30 min indicate a negligible progress of swelling in phosphate buffer pH 6.8.

The loadings for PC-2 of both PCAs are nearly identical (data not shown) and cannot be attributed to any known chemical or physical change within the copolymer films. For example, the uncharged and the ionized state of L55 cannot be differentiated in the respective Raman spectra. Furthermore, the C-N stretching vibration band of the QAGs in RL at 600 cm^{-1} does not contribute to the loading of PC-2, thus changes in the ionic state of QAGs are not described by PC-2 [180].

Although chemical or physical transformations of the polymers during swelling could not be identified, Raman spectroscopy was able to distinguish between swollen and unswollen films. Furthermore, the different PC-2 scores of the samples swollen in hydrochloric acid and those swollen in phosphate buffer pH 6.8 might be a result of different swelling behaviors. Hence, it may be possible to real-time monitor the swelling of polymer films with Raman spectroscopy.

3.3.2 IR spectroscopic investigation of swollen copolymer films

IR spectroscopic measurements were performed with swollen and subsequently dried copolymer films to observe physicochemical transformations in RL/L55 film blends resulting from swelling in different media. The investigated film blend ratios were 4:1 and 8:1; plain copolymer films were investigated as references in the same way.

The spectra of copolymer films swollen in hydrochloric acid pH 1.2 were nearly identical to the spectra of the unswollen copolymer films, whereas those of the films swollen in phosphate buffer pH 6.8 were significantly different. The effect of swelling in phosphate buffer pH 6.8 on the spectrum of copolymer film blends is displayed in Fig. 25; as a representative

example the 8:1 copolymer film blend was chosen.

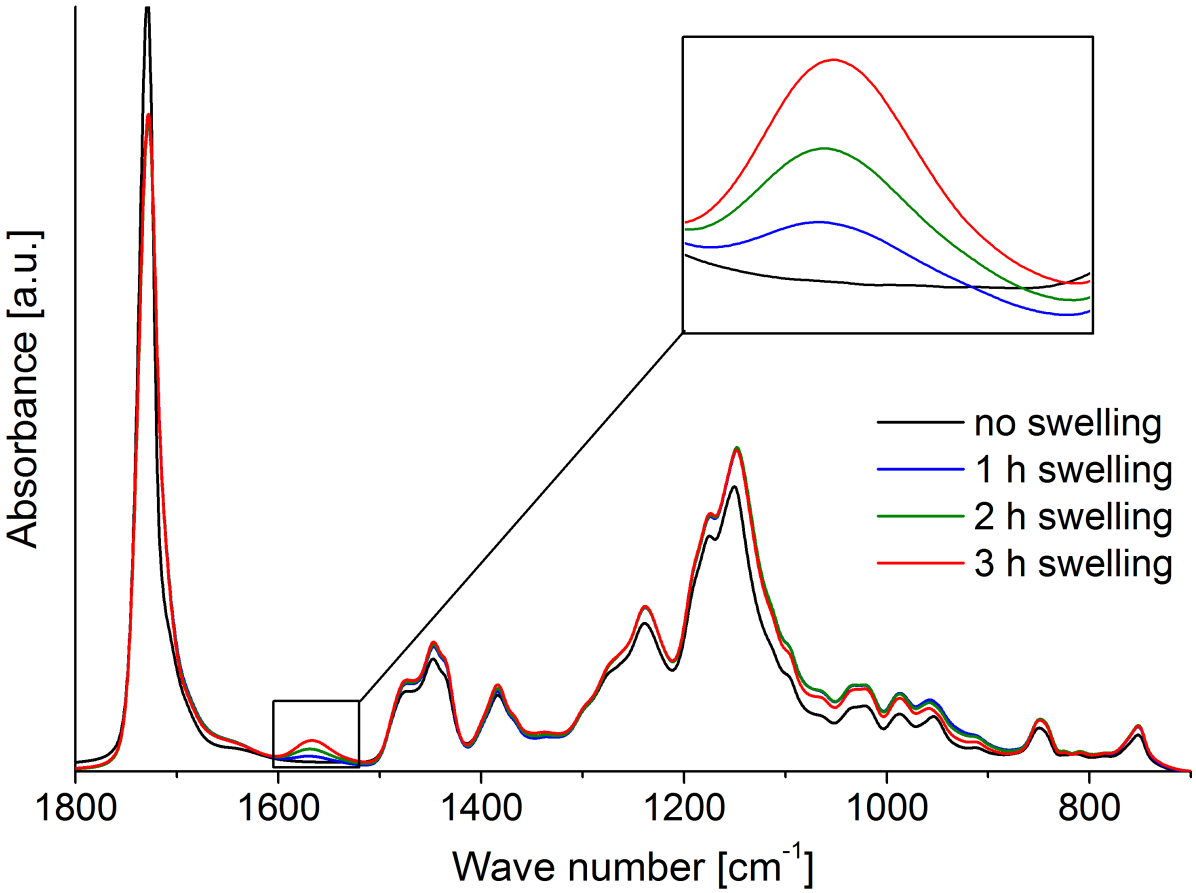


Fig. 25: IR spectra of 8:1 film blends swollen in phosphate buffer for 0 h, 1 h, 2 h, and 3 h and dried afterwards (n = 3).

The IR spectra of copolymer films in Fig. 25 show a additional at 1567 cm^{-1} induced by swelling. The inset in Fig. 25 reveals the increasing intensity of the band with progressing swelling time. This band was also found in the spectrum of the 4:1 copolymer blend swollen in phosphate buffer pH 6.8 and can be attributed to the carboxylate groups that originate from deprotonated L55. Interestingly, plain L55 films swollen in phosphate buffer pH 6.8 formed a carboxylate band at 1540 cm^{-1}. This shift of 27 cm^{-1} was assumed to be the result of ionic interactions between anionic carboxylate groups of L55 and cationic QAGs of RL. To verify this assumption, a PCA was performed with the IR spectra of unswollen copolymer films, samples swollen for 3 h in hydrochloric acid pH 1.2 and samples swollen for 3 h in phosphate buffer pH 6.8. Only spectral regions with bands of ionic groups were considered in the analysis. The stretching vibration band from the carboxylate group of L55 is located between 1600 cm^{-1} and 1510 cm^{-1}; the QAG groups of RL show a double band between 1000 cm^{-1} and 920 cm^{-1}. The results of the PCA are displayed in Fig. 26.

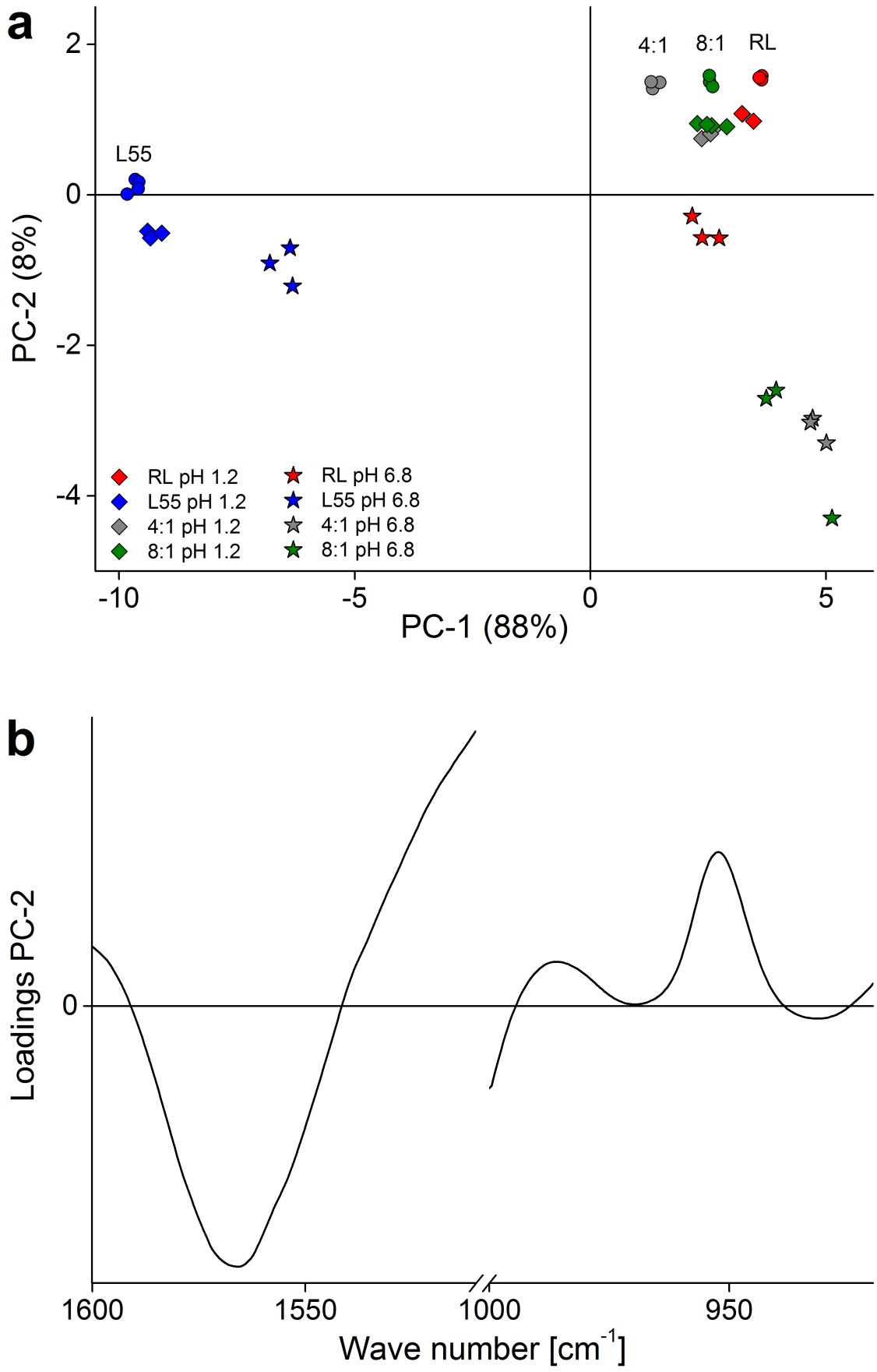


Fig. 26: a) Scores plot for PCA of IR spectra of unswollen copolymer films, copolymer films swollen in hydrochloric acid pH 1.2, and copolymer films swollen in phosphate buffer pH 6.8; b) Loadings plot for PC-2; the circled dots represent the unswollen samples.

The PCA scores plot in Fig. 26a shows clustering of spectra in different groups. PC-1 explains 88 % of the data variability and separates the data points for unswollen copolymer films according to their blend ratio. The spectra of copolymer films swollen in hydrochloric acid pH 1.2 showed slight attenuations in the region between 1000 cm^{-1} and 920 cm^{-1}. This effect overlaid the spectral differences between the copolymers resulting in a less distinct separation along PC-1. Copolymer films swollen in phosphate buffer pH 6.8 are not separated according to their blend ratio along PC-1 due to fundamental changes in their spectra compared to the spectra of unswollen copolymer films.

PC-2 explains 8 % of the data variability in the IR spectra and separates unswollen copolymer film blends from copolymer films swollen in the respective media. The loadings plot of PC-2 in Fig. 26b shows negative values at the carboxylate region with a minimum at 1567 cm^{-1}. Keeping in mind that the above mentioned carboxylate band of plain L55 was located at 1540 cm^{-1}, this band can be considered as a shifted carboxylate band. Additionally, positive values are observed in the region of the QAG double band from approx. 960 cm^{-1} to 940 cm^{-1} with a maximum at 952 cm^{-1}. The highly negative PC-2 scores of film blends swollen in phosphate buffer pH 6.8 indicate the appearance of a new carboxylate band and the attenuation of one of the QAG bands. This confirms an interaction between the ionic groups in the copolymer films after swelling in phosphate buffer. An attenuation of QAG bands and shifts of carboxylate bands resulting from ionic interactions has been described before [155, 176, 181].

All copolymer films swollen in hydrochloric acid showed slightly lower PC-2 scores resulting from the above mentioned spectral changes in the region between 1000 cm^{-1} and 920 cm^{-1}. The negative PC-2 scores for plain copolymer films swollen in phosphate buffer pH 6.8 are caused by new bands in the region between 1600 cm^{-1} and 1510 cm^{-1} and will be discussed later.

It can be hypothesized that the ionic interactions between the copolymers during swelling in phosphate buffer pH 6.8 decrease the extent of ion exchange of QAGs with the surrounding media and thus influencing drug release from dosage forms coated with these copolymer blends.

To investigate the ion exchange of the film blends and their differences compared to

the plain films, additional IR spectra of film blends and plain copolymer films swollen in TRIS buffer pH 6.8 and acetate buffer pH 6.8 were recorded. Regarding ion exchange, the spectral region between 1600 cm^{-1} and 1500 cm^{-1} is the most interesting. This region of the IR spectra of plain copolymer films and RL:L55 film blends swollen in different media is displayed in Fig. 27.

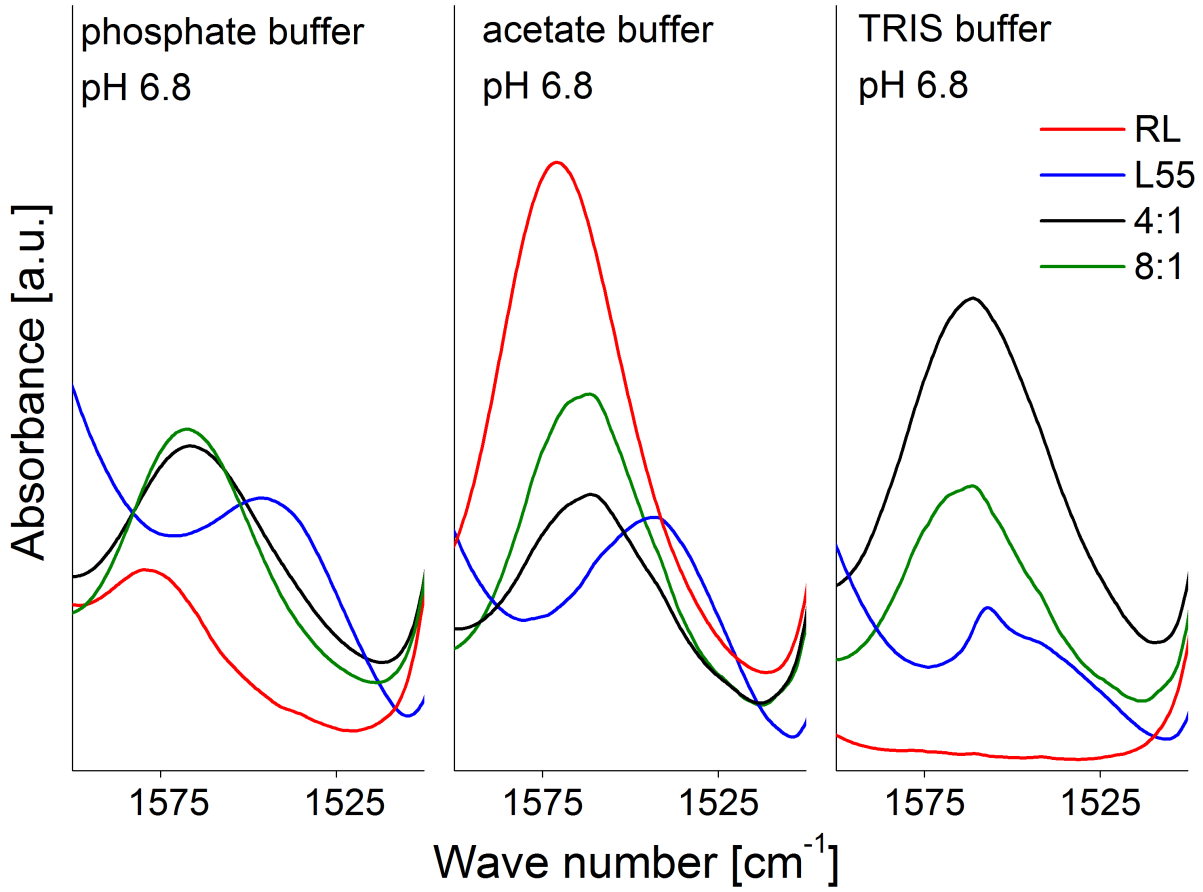


Fig. 27: IR spectra of copolymer films swollen in various media for 3 h and dried afterwards (n = 3).

The plain RL copolymer films showed a small band at 1580 cm^{-1} after swelling in phosphate buffer pH 6.8. This might be the result from phosphate anions interacting with QAGs. After swelling in acetate buffer pH 6.8, a band appears at 1571 cm^{-1} that might be attributed to the carboxylate group of acetate. However, free sodium acetate shows a carboxylate band at 1573 cm^{-1}. This shift of two wave numbers can be the result of ionic interactions between the carboxylate group af acetate and the QAGs of the RL copolymer. Obviously, the negatively charged phosphate and acetate ions migrated at least to a certain extend into the positively charged RL films and interacted electrostatically with the QAGs. After swelling in TRIS buffer pH 6.8, no band in the region between 1600 cm^{-1} and 1510 cm^{-1}

was observed. At pH 6.8 TRIS is cationic and therefore its migration into the positively charged RL film is hindered.

L55 copolymer films showed the expected carboxylate band at 1540 cm^{-1} in phosphate buffer pH 6.8 and in acetate buffer pH 6.8. The spectra of L55 swollen in TRIS buffer is superimposed by strong bands from the TRIS spectrum, for example the N-H stretching vibration at 3180 cm^{-1} (data not shown). Obviously, TRIS was at least adsorbed to the surface of L55 films because of electrostatic interactions with the L55 carboxylate groups.

The 4:1 and 8:1 RL/L55 film blends showed the earlier discussed carboxylate band at 1567 cm^{-1} during swelling in all three media. Interestingly, the intensities of the bands cannot be attributed to the blend ratios but vary between the media. Most probably, this is the result of different swelling a behavior depending on the media.

The IR spectra of all investigated film blends swollen in media of pH 6.8 showed a carboxylate band at the same wave number independent of the swelling medium. This indicates that all film blends underwent the same ionic interactions in all media of pH 6.8. Furthermore, the spectra indicate that the film blends did not exchange ions with the media of pH 6.8 to an extent that is detectable by IR spectroscopy. In contrast, ion exchange of plain copolymer films with the surrounding medium was clearly detectable. This leads to the assumption, that ionic interactions between RL and L55 in film blends at neutral/basic pH decreased the ion exchange with the surrounding media. As a consequence, the drug release rate from dosage forms coated with these blends is lower in neutral/basic media than in acidic media, similar to the “sealing” effect of bivalent ions described by Wagner and Grützmann [105]. Nevertheless, these ionic interactions alone cannot explain the differences in the release rates from dosage forms coated with RL/L55 blends. The intensity of the carboxylate band and hence the amount of interacting functional groups was not dependent on the copolymer ratio but on the swelling media. To obtain further information on the differences between the copolymer blends, erosion and swelling experiments were performed.

3.3.3 Investigation of the erosion of plain copolymer films and film blends

Erosion studies can provide valuable information on the integrity of a polymer film during the swelling process. Films might be subject to mechanical stress or leaching out of ingredients into the surrounding medium resulting in changes in drug permeability.

The results of the erosion studies of plasticized copolymer films are displayed in Fig. 28a, the results for unplasticized films are displayed in Fig. 28b.

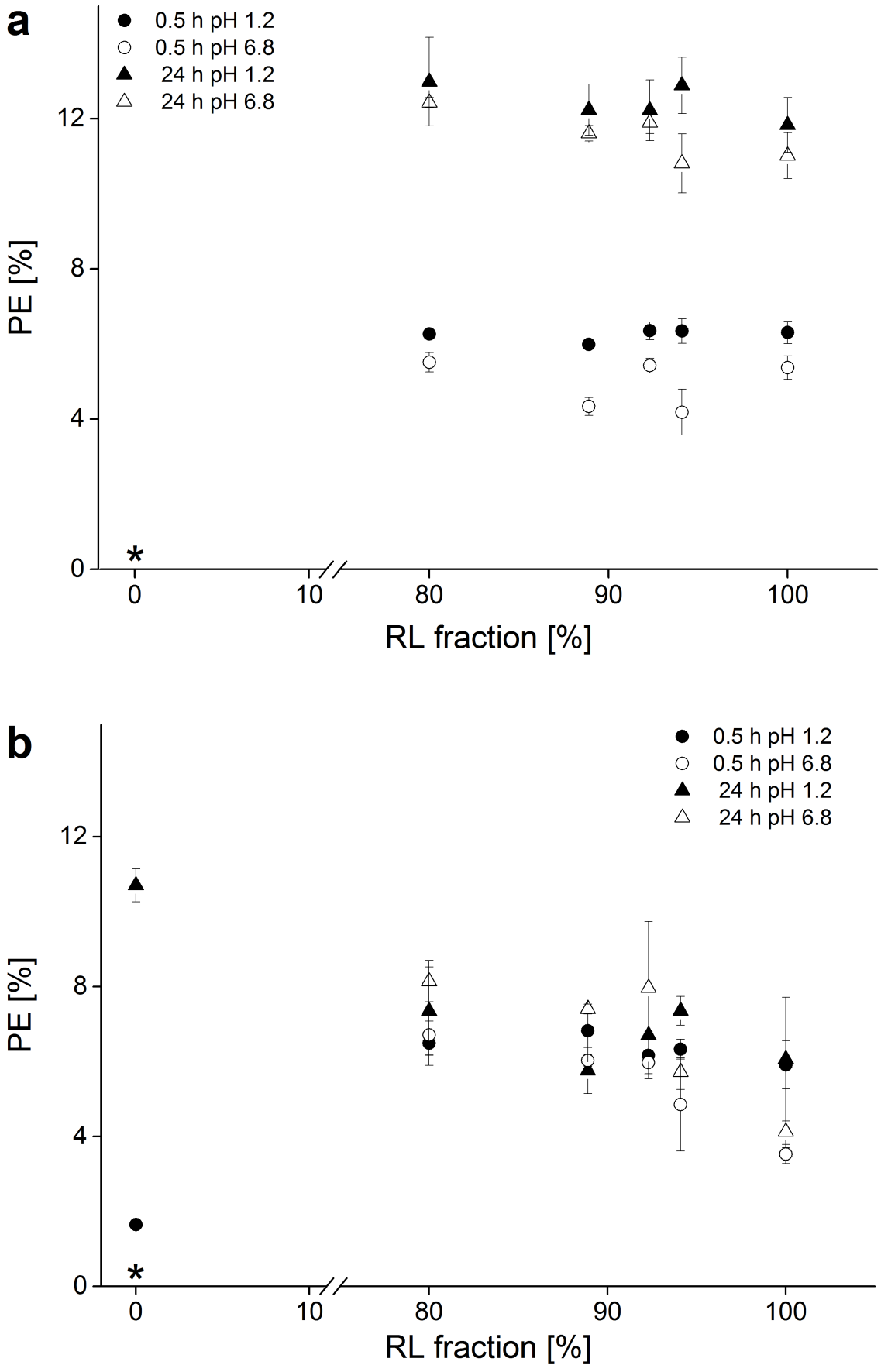


Fig. 28: a) PE values of various plasticized copolymer films in hydrochloric acid pH 1.2 and phosphate buffer pH 6.8; b) PE values of various copolymer films in hydrochloric acid pH 1.2 and phosphate pH 6.8; means ± SD, n = 3. *: Not all samples were measurable.

In phosphate buffer pH 6.8 all L55 films dissolved in less than 0.5 h. In hydrochloric acid pH 1.2 the swelling of plasticized L55 films swollen was not measurable, as it was not possible to detach them from the Teflon® mat after drying. The PE values of plasticized RL films and plasticized RL/L55 blends were differ significantly. The PE values of plasticized RL films and all plasticized film blends swollen in hydrochloric acid pH 1.2 were about 6 % after 0.5 h and about 12 % after 24 h. The respective PE values in phosphate buffer pH 6.8 were slightly lower than those in hydrochloric acid pH 1.2.

The erosion of unplasticized film blends (Fig. 28b) was about 6 % after 30 min and increased nonsignificantly after 24 h. This indicates that the weight loss between 0.5 h and 24 h of the plasticized films results from TEC leaching out of the copolymer film. The PE value of unplasticized RL copolymer films was slightly lower than the PE values of the copolymer film blends; the PE value of unplasticized L55 was higher after 24 h. This might be explained by differences in the resistance against mechanical erosion caused by the agitated media which could already be observed during handling of the film samples.

The weight loss after 0.5 h can be explained by leaching of residual organic solvent out of the copolymer films and mechanical erosion of the films. Leaching of the pH-dependent soluble L55 out of the film blends was not observed at any time point. The PE values of film blends swollen in phosphate buffer pH 6.8 were lower than the respective values of samples swollen in hydrochloric acid pH 1.2 in most cases. A dependency of PE on the L55 fraction was not found. All film blends were prepared from organic solution resulting in a high polymer-polymer interpenetration of RL and L55. Thus, RL and L55 copolymer chains are highly entangled and therefore leaching out of L55 into the surrounding medium is minimized. Such behavior has been described before for film blends of ethyl cellulose and L55 prepared from organic solution [117]. Additionally, the ionic interactions between the copolymers might also contribute to the prevention of leaching out of L55 during exposure to phosphate buffer pH 6.8.

3.3.4 Investigation of the swelling behavior of plain copolymer films and film blends

Polymer swelling is a prerequisite for drug release from coated solid dosage forms. Even though the extent of swelling cannot be correlated with the release behavior of RL-coated dosage forms, knowledge on the swelling behavior of RL/L55 film blends may provide information on the drug release mechanism. Moreover, previous studies have reported an altered polymer swelling behavior as a result of ionic interactions between oppositely charged coating polymers and consequently an altered drug release behavior [149, 154]. The drug permeability of RL/L55 coating blends is generally lower in phosphate buffer pH 6.8 than in hydrochloric acid pH 1.2. The most unusual RL/L55 copolymer with regard to its release behavior was the 4:1 blend. Theophylline pellets coated with the 4:1 blend showed a remarkably long lag time followed by a fast drug release. To identify a relationship between the swelling behavior and the drug permeability of RL/L55 film blends swelling experiments were performed. The results are displayed in Fig. 29.

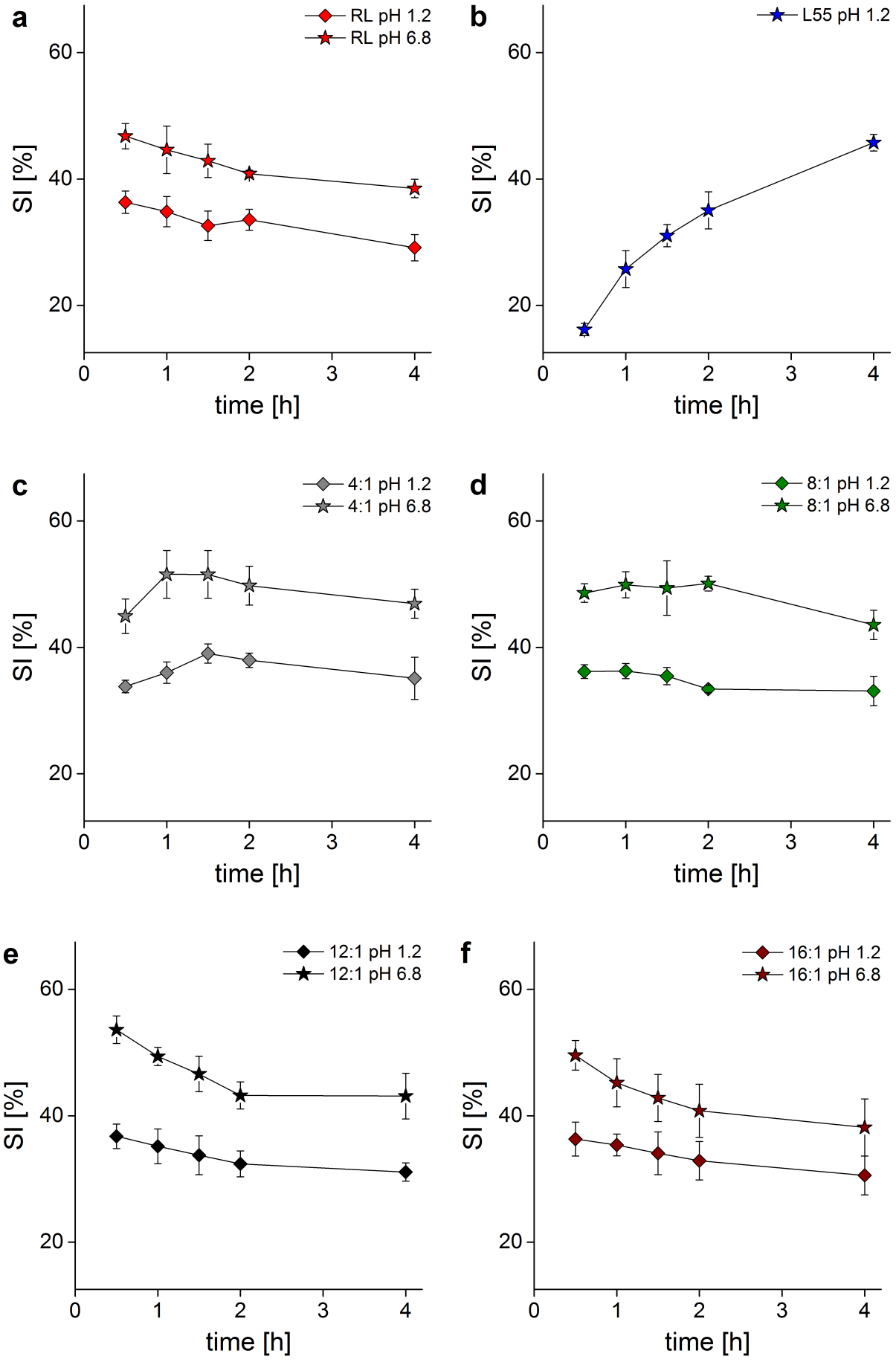


Fig. 29: SI values of various copolymer films (a-f) in hydrochloric acid pH 1.2 and phosphate buffer pH 6.8; means ± SD, n = 3.

For all investigated film samples swelling in phosphate buffer pH 6.8 led to higher SI values than swelling in hydrochloric acid pH 1.2, with the exception of L55 film samples that dissolved completely in less than 0.5 h at pH 6.8.

The highest SI value of RL was observed after 0.5 h and decreased afterwards (Fig. 29a). The decrease of the SI after the first 0.5 h can be explained by the extraction of plasticizing agents (TEC, residual organic solvents). After fast diffusion of buffer into the plasticized copolymer films, plasticizing agents are leached out of the copolymer films. A decrease of the plasticization is accompanied by a decrease of the swelling capacity; thus, buffer is squeezed out of the film to a certain extent. This phenomenon has been described before for drug loaded RL films [182]. The swelling of L55 films in hydrochloric acid pH 1.2 was initially low and reached an SI value of approximately 45 % after 4 h (Fig. 29b).

The 4:1 and 8:1 film blend samples reached slightly higher SI values in both media than plain RL films (Fig. 29c,d). Furthermore, the maximum of swelling was observed at later time points. For swelling in hydrochloric acid pH 1.2, this can be explained by the high L55 fraction, a copolymer which initially swells slower but reaches higher SI values than plain RL films after 4 h. Therefore, the swelling behavior of the 4:1 and 8:1 copolymer blends at pH 1.2 can be considered as a combination of the swelling behavior of RL and L55. A similar swelling behavior was observed for swelling of the 4:1 copolymer blend in phosphate buffer pH 6.8 within the first 4 h. Interestingly, the 4:1 blend swollen in phosphate buffer pH 6.8 reached a exceptionally high SI values of 83.2 % $\pm$ 3.0 % after 24 h (data not shown) while with all other samples the SI value determined at the 4 h time point remained constant. This swelling behavior may be caused by the high amount of carboxylate groups that increase the swelling capacity of the films.

With the 12:1 and 16:1 blends SI values were highest at the 0.5 h time point and decreased afterwards, similar to plain RL copolymer films (Fig. 29e,f).

The swelling behavior of the plain RL film was only slightly different compared to that of the 8:1, 12:1 and 16:1 film blends. The differences in the drug permeability of these coatings described in Section 3.1 could not be correlated to the presented differences in their swelling behavior. Only the 4:1 blend in phosphate buffer leads to a different result with extensive swelling within 24 h.

The long lag time of theophylline pellets coated with the 4:1 copolymer blend can be explained with the decreased extent of ion exchange that decreased the drug release rate in the initial phase as discussed above. The fast drug release in the later phase can be explained by the extensive copolymer swelling that might have induced domains of highly hydrated L55. Thus, the release mechanism changed from an ion exchange-driven to a diffusion controlled process with enhanced drug release. Film coatings are usually much thinner than the investigated film samples in the present study and therefore their swelling process might be finished earlier. Hence, the lag time is expected to be shorter than 24 h.

3.3.5 Conclusion

Free films prepared from organic solutions of RL, L55 and blends thereof were investigated with regard to their swelling behavior, physicochemical transformations during swelling and ion exchange with the surrounding media. The overall goal was to obtain a deeper insight into the drug release mechanism of RL/L55-coated dosage forms.

Raman spectroscopy was found to be a promising tool for real-time monitoring of polymer swelling. Nevertheless, the desired information on physicochemical transformations could not be obtained with the applied method. ATR-FTIR spectroscopic measurements confirmed the formation of interpolyelectrolyte complexes between the QAGs of RL and the carboxylate groups of L55 during swelling in media at pH 6.8. These ionic interactions decreased the extent of ion exchange between the QAGs and the swelling media. The decrease in the extent of ion exchange was responsible for the reduced drug permeability of RL/L55 blend coatings in media at pH 6.8 compared to that at pH 1.2 which has been described in Section 3.1.

The swelling behavior of RL/L55 film blend samples was not considerably different from that of plain RL films, except for the swelling of the RL/L55 4:1 blend ratio. Film samples of the 4:1 copolymer blend were found to swell extensively within 24 h. This swelling behavior explains the high drug permeability of 4:1 coatings after a long lag time.

The present study gives important information on the underlying drug release mechanism of RL/L55-coated dosage forms and contributes to the development of tailor-made coated drug delivery systems.

3.4 Results and discussion of of "Controlled release of acidic drugs in compendial and physiological hydrogen carbonate buffer from Eudragit® RL/L55 blend-coated oral solid dosage forms"[4]

The aim the fourth study was to investigate the ability of RL/L55 blend coatings to provide a pH-independent drug release of acidic drugs from coated mini tablets. Further objectives were to analyze drug release from RL/L55 coated mini tablets in different release media mimicking the physiological conditions of the gastrointestinal passage and to investigate the influence of various factors on drug release, including buffer capacity and composition of the release medium as well as pH changes.

3.4.1 Optimization of drug release from coated ketoprofen and naproxen mini tablets with the aim of a pH-independent drug release

Drug release from mini tablets coated with sustained release polymers is affected by the solubility of the drug in the surrounding release medium. For instance, the release of weakly acidic drugs is generally lower at the acidic stage of the "dissolution test for delayed-release solid dosage forms" (Ph. Eur.) than at the buffer stage. To prevent this increase of the dissolution rate at the buffer stage, RL/L55 copolymer blends were used to coat mini tablets containing weakly acidic drugs such as ketoprofen and naproxen to obtain a pH-independent drug release. The coating thickness and the blend ratio of the two copolymers were varied to achieve this aim. The release of ketoprofen from mini tablets with various coatings is displayed in Fig. 30.

[4]This chapter has been published as shown in Section 5.2

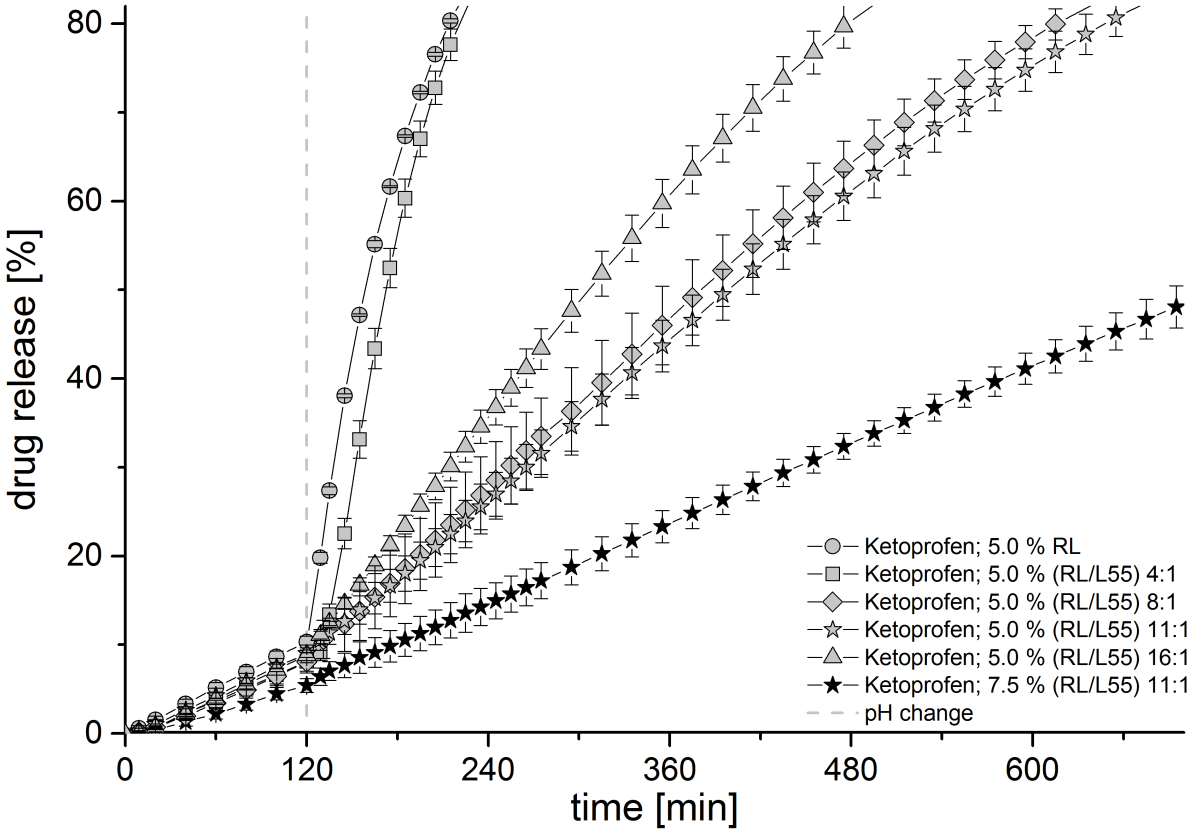


Fig. 30: Dissolution test for "delayed-release solid dosage forms" (Ph. Eur., Method A): Drug release from coated ketoprofen mini tablets; n = 3, means ± SD.

The release rates of mini tablets with a coating thickness of 5 % weight gain were very similar during the first 120 min. After the pH change, drug release rates from all formulations with 5 % weight increased. The strongest increase of the release rate was observed with the RL and the 4:1 blend coating followed by the 16:1 blend coating. Drug release from coatings with blend ratios of 8:1 and 11:1 was almost identical. These results are in good agreement with prior studies on coated theophylline pellets. For further optimization, 7.5 % of the 11:1 copolymer blend was applied onto the ketoprofen mini tablets leading to a slightly reduced release rate within the first 120 min compared to coatings with a coating thickness of 5.0 % weight gain. After the pH change the release rate remained almost constant.

The dissolution profiles of naproxen mini tablets coated with RL and the 8:1 blend (5.0 % and 7.5 % weight gain) are displayed in Fig. 31.

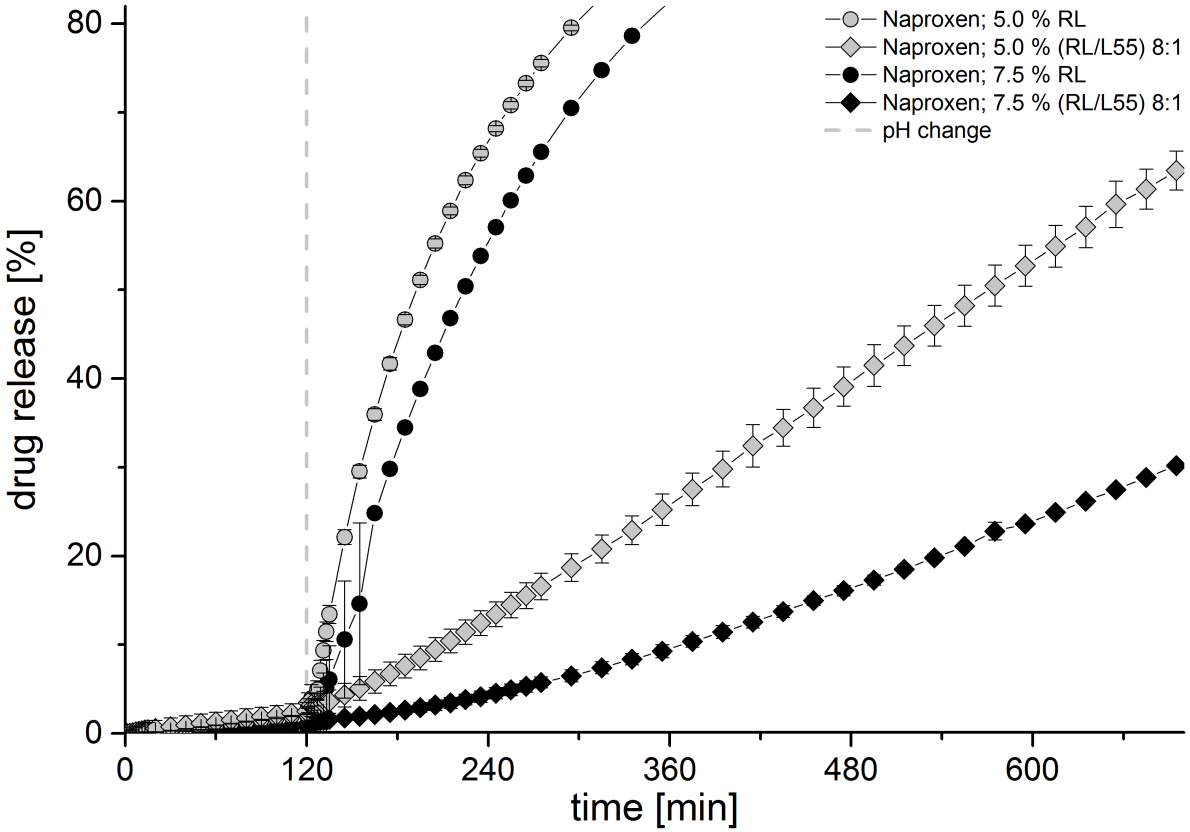


Fig. 31: Dissolution test for "delayed-release solid dosage forms" (Ph. Eur., Method A): Drug release from coated naproxen mini tablets; n = 3, means ± SD.

Drug release from naproxen mini tablets with the 5.0 % 8:1 blend coating showed a markedly less pronounced increase in the drug release rate after the pH change compared to mini tablets coated with plain RL. Naproxen mini tablets coated with 7.5 % 8:1 blend showed a constant release rate for approximately 240 min. However, naproxen release in hydrochloric acid pH 1.2 is very low with RL and 8:1 blend coatings because of the low solubility of naproxen in acid [168]. Drug release from naproxen mini tablets coated with the 4:1, 11:1, and 16:1 blends cannot be expected to show a faster drug release at pH 1.2. Therefore, drug release experiments with these coatings were not performed.

The dissolution profiles of coated ketoprofen and naproxen tablets showed that variation of the blend ratio of RL/L55 blends can be used to adjust the permeability of coatings at different pH values. Optimization of the coating composition resulted in a pH-independent drug release as observed with the micro-environmental pH adjustment approach [139, 140]. Nevertheless, the release rate was limited to the drug solubility in the respective medium. However, the release in compendial media can be significantly different from drug release

in the GI tract due to the pH change throughout the GI tract and the low buffer capacity compared to compendial media.

3.4.2 Influence of hydrogen carbonate buffer mimicking physiological conditions on drug release from RL/L55 blend coated mini tablets

Drug release from coated solid dosage forms is influenced by the drug permeability of the coating and the drug solubility in the release medium. Thus, intrinsic dissolution rates of the investigated drugs were determined in hydrochloric acid pH 1.2, Hanks buffer pH 6.8 and phosphate buffer pH 6.8. The results are displayed in Table 12.

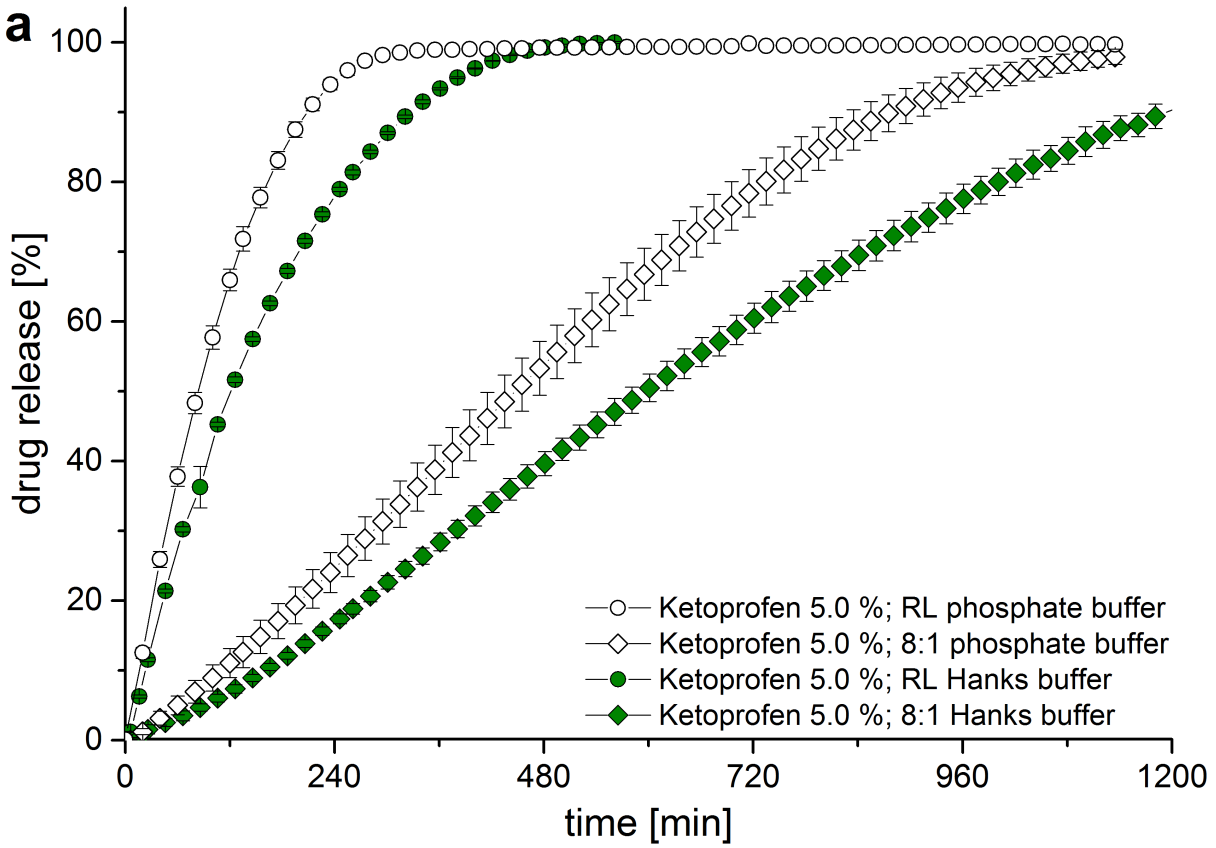
Table 12: Intrinsic dissolution rates of ketoprofen, naproxen and theophylline in various media; β = buffer capacity; n = 3, means $\pm$ SD.

Drug	Medium	Intrinsic dissolution rate [µg min^{-1} cm^2]
Ketoprofen	Hydrochloric acid pH 1.2	25.2 $\pm$ 2.8
	Phosphate buffer pH 6.8, β = 23 mmol	812.1 $\pm$ 53.8
	Hanks buffer pH 6.8, β = 3.1 mmol l^{-1}	141.4 $\pm$ 7.0
Naproxen	Hydrochloric acid pH 1.2	5.1 $\pm$ 0.7
	Phosphate buffer pH 6.8, β = 23 mmol	357.2 $\pm$ 9.0
	Hanks buffer pH 6.8, β = 3.1 mmol l^{-1}	56.4 $\pm$ 1.8
Theophylline	Hydrochloric acid pH 1.2	2599.3 $\pm$136.4
	Phosphate buffer pH 6.8, β = 23 mmol	2954.2 $\pm$145.8
	Hanks buffer pH 6.8, β = 3.1 mmol l^{-1}	2543.1 $\pm$139.2

The dissolution rates of the acidic drugs ketoprofen and naproxen are significantly lower in Hanks buffer pH 6.8 than in phosphate buffer pH 6.8. Besides the pH value, the buffer

capacity (β) is a dominating factor influencing the intrinsic dissolution rate. Hanks buffer pH 6.8 has a significantly lower buffer capacity than compendial phosphate buffer pH 6.8. Hence, the dissolution rates are decreased in Hanks buffer pH 6.8 [183]. As expected, theophylline was not influenced by the pH value of the dissolution medium. However, the intrinsic dissolution rate of theophylline in phosphate buffer pH 6.8 was slightly higher than the dissolution rates in hydrochloric acid pH 1.2 and Hanks buffer pH 6.8.

Moreover, drug release experiments with mini tablets (ketoprofen, naproxen, and theophylline) coated with RL and RL/L55 blends were performed in phosphate buffer pH 6.8 and Hanks buffer pH 6.8 to investigate the influence of the media on drug release. The respective release profiles are displayed in Fig. 32.



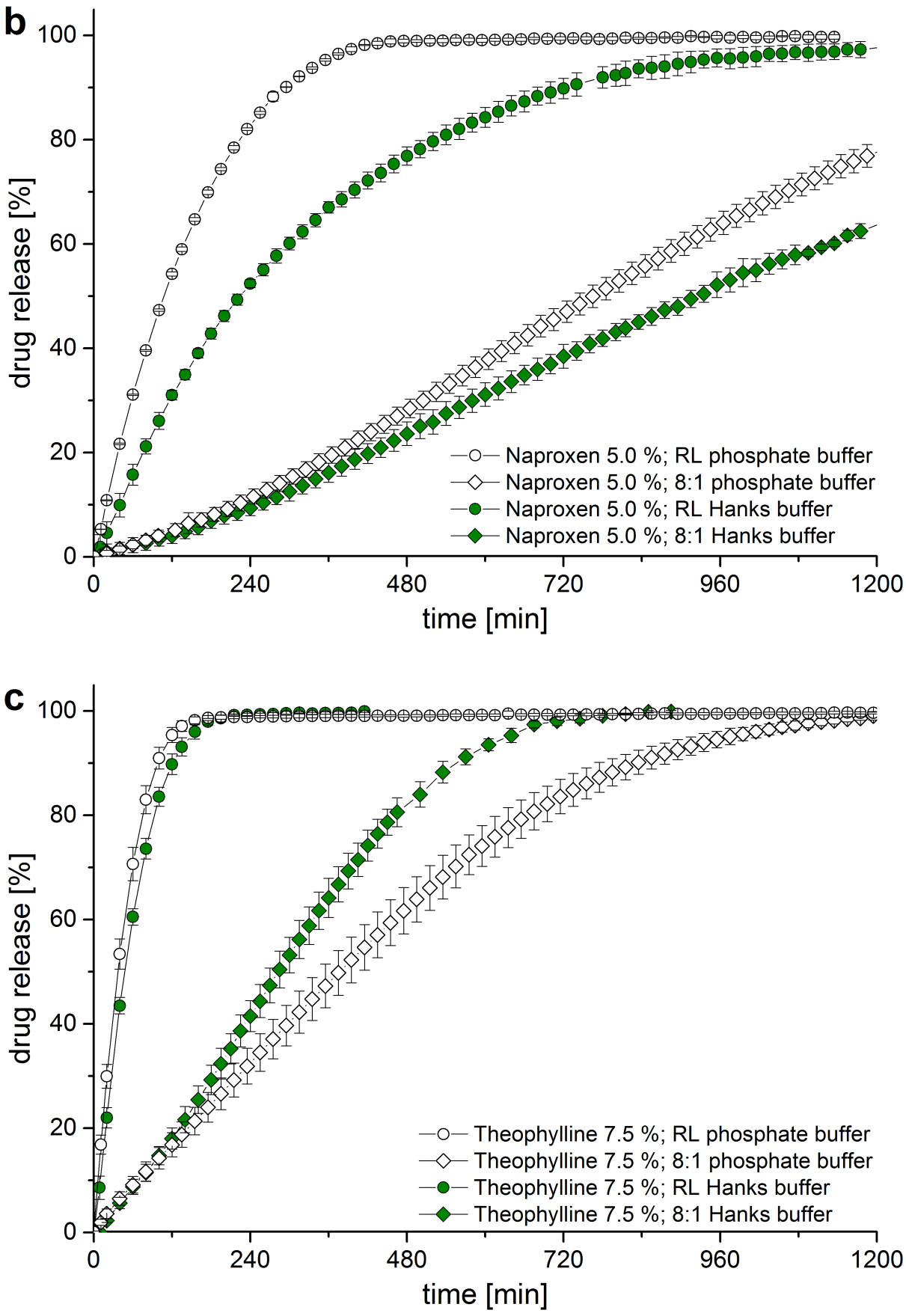


Fig. 32: Drug release profiles in Hanks buffer and phosphate buffer pH 6.8 of coated mini tablets containing 10 % of a) ketoprofen, b) naproxen, and c) theophylline; n = 3, means ± SD.

When comparing the drug release profiles of all investigated drugs, the release rate of RL-coated mini tablets was lower in Hanks buffer pH 6.8 than in phosphate buffer pH 6.8. The reduced solubility of all drugs in Hanks buffer pH 6.8 can be assumed to be the dominating factor for the observed decrease in drug release. Furthermore, a reduced permeability of RL coatings in Hanks buffer pH 6.8 was expected, resulting from the higher chloride concentration in this medium. The permeability of RL coatings is predominantly influenced by the anions in the release medium, in particular by chloride ions [104].

In accordance with the results in section 3.4.1, the 8:1 blend coatings exhibited a significantly stronger retarding effect on drug release from mini tablets at pH 6.8 than RL coatings. Similar to the drug release from RL coated mini tablets, the release rate from 8:1 blend coated mini tablets corresponded to the intrinsic dissolution rate of ketoprofen and naproxen. Surprisingly, drug release from theophylline tablets coated with the 8:1 blend was faster in Hanks buffer pH 6.8 than in phosphate buffer pH 6.8, whereas drug release from ketoprofen and naproxen tablets was faster in phosphate buffer. However, considering that the intrinsic dissolution rates of ketoprofen and naproxen were about six times higher in phosphate buffer pH 6.8 than in Hanks buffer pH 6.8, the differences between the drug release rates in both media were relatively small. As the release of theophylline, which showed similar intrinsic dissolution rates in both media, was faster in Hanks buffer pH 6.8, it can be assumed that the drug permeability of 8:1 blend coatings was higher in Hanks buffer than in phosphate buffer.

Further drug release experiments were performed to investigate the dependency of drug release from RL/L55 blend coated mini tablets on the composition of the release medium. The influence of the buffer capacity of the medium was investigated using carbonate buffer with a buffer capacity equal to that of phosphate buffer and a further phosphate buffer with a buffer capacity equal to that of Hanks buffer (Table 12). To investigate the influence of the other salts present in Hanks buffer pH 6.8, a Hanks buffer without sodium carbonate was used. Hence, the buffer capacity of this buffer was very low ($< 0.01\,\mathrm{mmol\,l^{-1}}$) whereas the pH value remained at pH 6.8.

Only theophylline mini tablets coated with the 8:1 blend were used in these drug release experiments. The results are displayed in Fig. 33 along with the drug release profiles in

Hanks buffer pH 6.8 and phosphate buffer pH 6.8 for comparative purposes.

Drug release in Hanks buffer was independent of the presence of carbonate ions. Furthermore, the drug release profiles obtained in the carbonate buffer were comparable to those measured in both phosphate buffers. This led to the assumption that the differences in coating permeability in phosphate buffer pH 6.8 and Hanks buffer pH 6.8 were predominantly caused by the different anion concentrations. It is assumed that the anions in the release media competed with the deprotonated carboxylate groups of L55 for the formation of ionic bonds with the QAGs of RL. Therefore, the amount of IPECs in the copolymer film decreased and the drug release rate increased.

The release of the acidic drugs ketoprofen and naproxen from RL coated mini tablets and RL/L55 blend coated mini tablets was generally slower in Hanks buffer pH 6.8 than in phosphate buffer pH 6.8. This was attributed to the lower buffer capacity and higher anion concentration of Hanks buffer pH 6.8. In contrast, the permeability of 8:1 RL/L55 blend coatings was higher in Hanks buffer pH 6.8 than in phosphate buffer pH 6.8. This

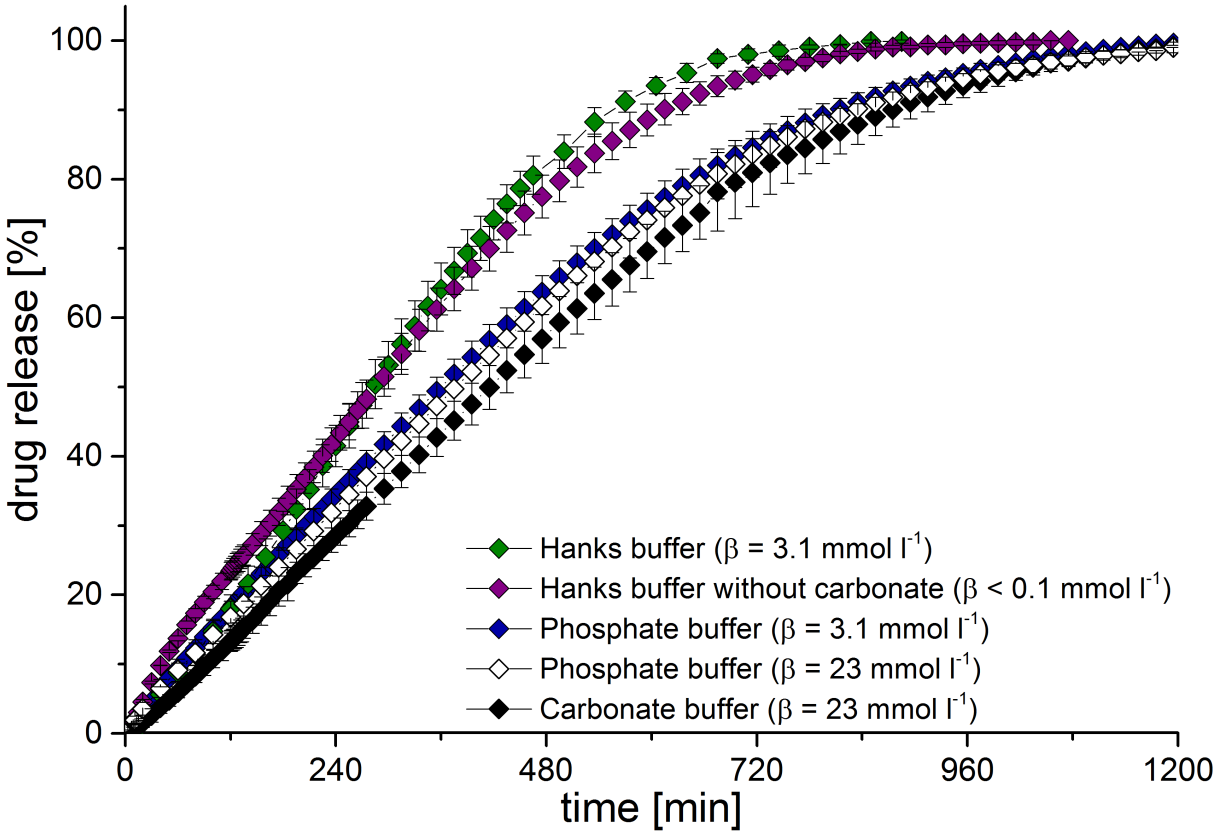


Fig. 33: Drug release profiles of theophylline mini tablets coated with 8:1 RL/L55 film blends in various media at different buffer capacities (β) at pH 6.8; n = 3, means ± SD.

phenomenon was most likely caused by the higher anion concentration in Hanks buffer pH 6.8 and the resulting decrease of the formation of IPECs. A similar decrease of ionic interactions has been described by Jenquin et al. [156] for the ionic adsorption of salicylate to RL powder. Despite the influence of the different anion concentrations in the media, RL/L55 blend coated mini tablets exhibited comparable release profiles in physiological hydrogen carbonate buffers and compendial release media.

3.4.3 Influence of pH sequences in the media on drug release from mini tablets coated with RL/L55 blend coatings

Previous investigations showed that blends of RL and L55 copolymers exhibit ionic interactions in media of neutral/basic pH values. This pH-dependent formation of IPECs is associated with changes in the drug permeability of RL/L55 blend coatings. During the gastrointestinal passage, controlled release tablets are exposed to a sequence of pH values which is assumed to have an influence on the drug permeability of the coating [32]. To estimate the changes in coating permeability, which RL/L55 blend coatings undergo during the gastrointestinal passage, the influence of changing pH values was investigated with a simulation of the pH conditions in the GI tract. Hydrochloric acid pH 1.2 was used to simulate fasted state gastric conditions followed by Hanks buffer as physiologically relevant hydrogen carbonate buffer solution. Two different pH sequences simulating the intestinal passage were applied. Ketoprofen and theophylline mini tablets coated with RL and the RL/L55 8:1 blend, respectively, were tested. The applied pH sequences and the obtained release profiles are shown in Fig. 34.

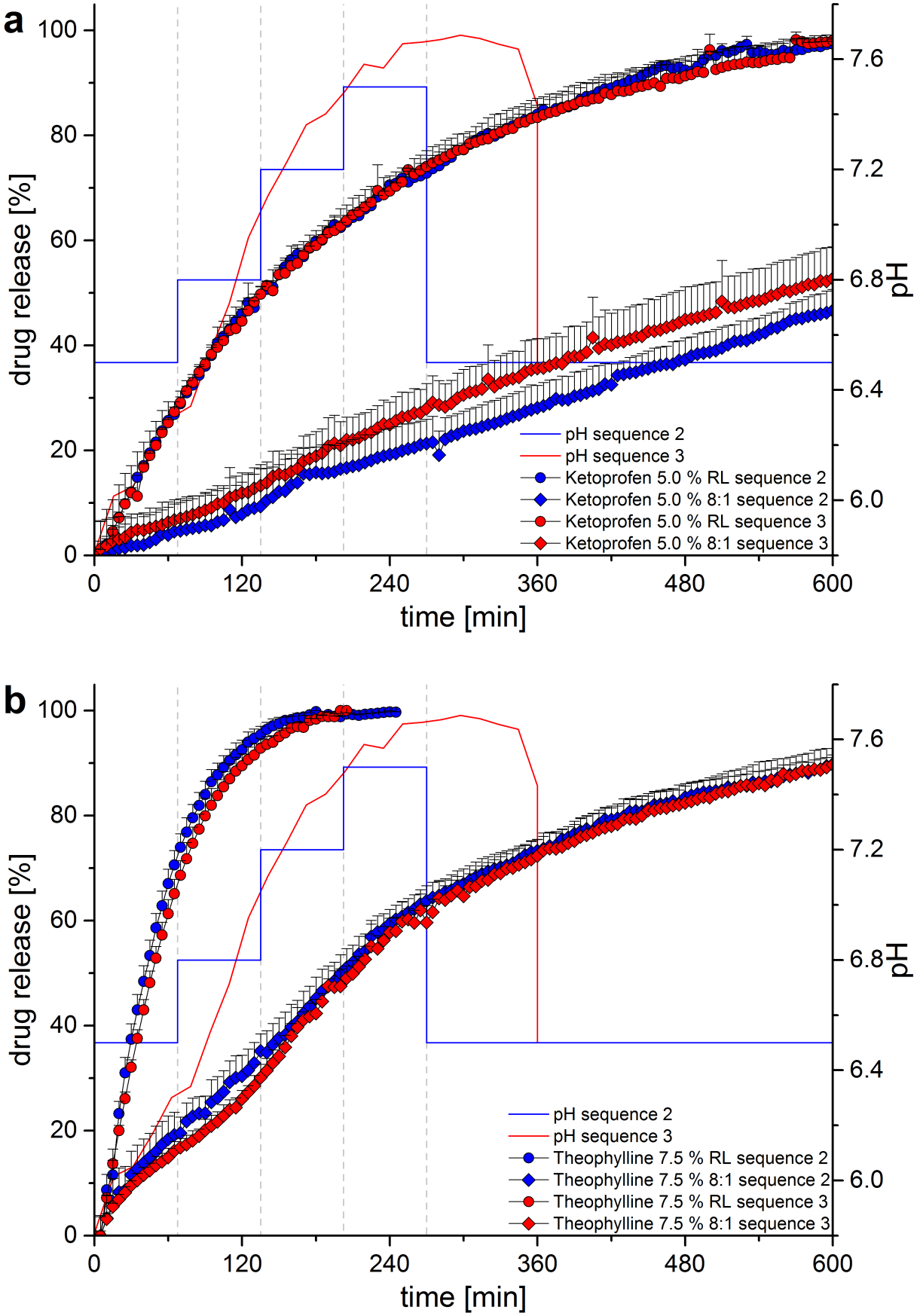


Fig. 34: Release profiles in Hanks buffer with different pH sequences of mini tablets containing 10 % of a) ketoprofen and b) theophylline; n = 3, means + SD.

The drug release profile of ketoprofen mini tablets coated with plain RL was expected to show an increase in the drug release rate with increasing pH value. Interestingly, no increase in drug release was observed at higher pH values. Furthermore, drug release was nearly identical with regard to the two pH sequences despite the significant change of the pH values in the range between pH 5.8 and 7.7. Ketoprofen mini tablets coated with the 8:1 blend showed a slightly slower drug release with pH sequence 2. In general, drug release was comparable with both pH sequences.

As expected, drug release profiles of theophylline mini tablets coated with RL in Hanks buffer showed only small differences between the two pH sequences. Theophylline mini tablets coated with the 8:1 blend also exhibited nearly identical drug release profiles with both applied pH sequences. The expected dependency of drug permeability of the RL/L55 blend coatings on the actual pH value in the release medium was not observed.

Overall, the two different pH sequences did not lead to significant differences in the resulting release profiles. The applied changes in the pH value could not be correlated with changes in the drug release rate. This was probably a result of the low buffer capacity of Hanks buffer which might not be able to transfer the pH changes of the surrounding medium into the micro-environment inside the mini tablets and the coating fast enough. In addition, acidic drugs such as ketoprofen stabilize the local pH value inside the mini tablet and in its diffusion boundary layer. Therefore, the drug release rate remains nearly unchanged regardless of the pH of the surrounding medium.

Nevertheless, dissolution testing using a physiological hydrogen carbonate buffer combined with gastrointestinal pH sequences allowed an estimation of the pH effect as well as the effect of the buffer and its capacity on drug release within the GI tract. Even though the unique release behavior of RL/L55 blend coated mini tablets was also found in hydrogen carbonate buffers, the obtained drug release profiles were significantly different from those obtained by drug release testing in compendial media. The experiments showed that both, the release of ketoprofen from coated mini tablets and the drug permeability of RL/L55 blend coatings, were less sensitive to pH changes than indicated by prior investigations with compendial media (Section 3.1.3.3). Furthermore, the almost zero order ketoprofen release from mini tablets coated with the RL/L55 8:1 blend during both simulated gastroin-

testinal pH sequences confirmed the potential of RL/L55 blend coatings to deliver acidic drugs at a constant rate. To date, RL/L55 blends are the only coatings which may cause a release behavior suitable for a constant rate delivery of acidic drugs from solid oral dosage forms. In this case the addition of pH-adjusting excipients to the tablet core is unnecessary. Overall, patients benefit from a constant and more predictable delivery of acidic drugs as it may reduce intra- and inter-patient variations of drug absorption [184, 185].

3.4.4 Conclusion

RL/L55 copolymer blend coatings were investigated with regard to their suitability for pH-independent release of weakly acidic drugs using compendial release media and the physiological Hanks buffer. A constant drug release rate based on the "dissolution test for delayed release solid dosage forms" (Ph. Eur.) was achieved with mini tablets containing the acidic drugs naproxen or ketoprofen with RL/L55 blend coatings. For both drugs suitable RL/L55 blend ratios and coating thicknesses were determined.

Release of weakly acidic drugs from mini tablets was slower in Hanks buffer pH 6.8 than in phosphate buffer pH 6.8. This was attributed to the reduced solubility of acidic drugs in Hanks buffer due to the lower buffer capacity of Hanks buffer compared to phosphate buffer pH 6.8. Drug release from theophylline mini tablets coated with RL/L55 blends indicated an increased permeability of these blend coatings in Hanks buffer pH 6.8. It was hypothesized that the high ion concentration in the buffer hindered the formation of interpolyelectrolyte complexes, which resulted in higher drug permeability.

The simulation of the intestinal passage using pH sequences in Hanks buffer resulted in a constant release rate of an acidic and a pH-independent soluble drug from mini tablets coated with RL/L55 (8:1) copolymer blend. Drug release testing in physiological hydrogen carbonate buffer with static as well as dynamic pH proved to be a useful tool for realistic estimation of the drug release behavior in the intestinal tract.

In conclusion, the coating of solid dosage forms with RL/L55 copolymer blends is a promising approach for a pH-independent drug release of weakly acidic drugs.

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5 Appendix

5.1 Curriculum Vitae

Entfällt aus Datenschutzgründen.

5.2 Publication list

Poster Presentations

R. Wulff, C.S. Leopold
Infrared study on blends of Eudragit® RL and Eudragit® L-55 using Principal Component Analysis
8th World Meeting on Pharmaceutics, Biopharmaceutics & Pharmaceutical Technology 2012, Istanbul

R. Wulff, C.S. Leopold
Comparison of pellets coated with organic solutions and aqueous dispersions of Eudragit® RL/L-55 blends: Investigation of drug release
AAPS Annual Meeting & Exposition 2012, Chicago

R. Wulff, C.S. Leopold
Investigation of the dissolution behavior of Eudragit® RL/L-55 blends using a response surface methodology
40th Annual Meeting & Exposition of the Controlled Release Society 2013, Honolulu

R. Wulff, M. Klukkert, C.S. Leopold
How to Achieve Zero Order Release Kinetics of Acidic Drugs by Coating with Blends of Eudragit® RL/L55
AAPS Annual Meeting & Exposition 2013, San Antonio

R. Wulff, C.S. Leopold
Drug release from mini tablets coated with Eudragit® RL and Eudragit® L55 in biorelevant media
8th World Meeting on Pharmaceutics, Biopharmaceutics & Pharmaceutical Technology 2014, Lisbon

Publications

R. Wulff, C.S. Leopold
Coatings from blends of Eudragit® RL and L55: A novel approach in pH-controlled drug release
International Journal of Pharmaceutics 476, 78-87 (2014)
Reference Chapters: 2.1, 3.1

R. Wulff, C.S. Leopold
Coatings from blends of Eudragit® RL and L55: Investigation on solid state interactions and homogenity of free films from aqueous dispersion and organic solution
submitted, (2015)
Reference Chapters: 2.2, 3.2

R. Wulff, C.S. Leopold
Coatings of Eudragit® RL and L-55 blends: Investigations on the drug release mechanism
AAPS PharmSciTech, accepted, (2015)
Reference Chapters: 2.3, 3.3

R. Wulff, G. M. Rappen, M. Koziolek, G.Garbacz, & C. S. Leopold
Controlled release of acidic drugs in compendial and physiological hydrogen carbonate buffer from polymer blend-coated oral solid dosage forms
European Journal of Pharmaceutical Sciences, 77, 246-253 (2015)
Reference Chapters: 2.4, 3.4

5.3 Hazardous materials

Substance	Supplier	Danger symbol	Hazard statements	Precautionary statements
Acetone	Biesterfeld Spezial-chemie, Germany		225 - 319 - 336	210 - 233 - 305 + 351 + 338
Calcium chloride	Merck, Germany		319	305 + 351 + 338
Citric acid	Carl Roth, Germany		319	305 + 351 + 338
Hydrochloric acid (1 N)	Carl Roth, Germany		290 - 314 - 335	234 - 260 - 304 + 340 - 303 + 361 + 353 - 305 + 351 + 338 - 309 + 311 - 501
Isopropanol	Biesterfeld Spezial-chemie, Germany		225 - 319 - 336	210 - 233 - 305 + 351 + 338
Ketoprofen	Kreussler Pharma, Germany		301 - 315 - 319 - 335	261 - 301 + 310 + 305 + 351 + 338
Naproxen	Roche, Switzerland		301	301 + 310
Sodium hydroxide (1 N)	Carl Roth, Germany		314 - 290	280 - 301 + 330 + 331 - 309 + 310 - 305 + 351 + 338
Theophylline	Caelo, Germany		301	301 + 310
TRIS	Carl Roth, Germany		315 - 319 - 335	261 - 305 + 351 + 338
Trisodium phosphate	Carl Roth, Germany		314	305 + 351 + 338 - 310

6 Eidesstattliche Versicherung

Hiermit versichere ich an Eides statt, die vorliegende Arbeit selbstständig und ohne fremde Hilfe sowie nur mit den angegebenen Hilfsmitteln und Quellen erstellt zu haben. Ich versichere zudem, keinen weiteren Promotionsversuch an einer anderen Einrichtung unternommen zu haben.

Hamburg, den

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Robert Wulff