Development and characterization of poly(vinyl acetate) based oral dosage forms

Dissertation

zur Erlangung des akademischen Grades

doctor rerum naturalium (Dr. rer. nat.)

vorgelegt der

Naturwissenschaftlichen Fakultät I

der Martin-Luther-Universität Halle-Wittenberg

von

Sandra Strübing

geboren am 20.10.1977 in Waren (Müritz)

Gutachter:

1. Prof. Dr. Karsten Mäder
2. Prof. Dr. Dr. h.c. Reinhard Neubert
3. Prof. Dr. Jürgen Siepmann

urn:nbn:de:gbv:3-000014858
[http://nbn-resolving.de/urn/resolver.pl?urn=nbn%3Ade%3Agbv%3A3-000014858]

Halle, den 02. Oktober 2008

Contents

Abbreviations

API	Active pharmaceutical ingredient
BCS	Biopharmaceutical classification system
CW	Continuous wave
DDS	Drug delivery system
DMSO	Dimethyl sulfoxide
DSC	Differential scanning calorimetry
EC	Ethyl cellulose
EPR	Electron paramagnetic resonance
ESR	Electron spin resonance
FLT	Floating lag time
GI	Gastrointestinal
GRDF	Gastro retentive dosage form
HBS	Hydrodynamically balanced system
HCl	Hydrochloric acid
HLB	Hydrophilic lipophilic balance
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropyl methylcellulose
IMMC	Interdigestive migration myoelectric complex
LOD	Limit of detection
Log P	Log octanol/water partition coefficient
MCC	Microcrystalline cellulose
MRI	Magnetic resonance imaging
NMR	Nuclear magnetic resonance
NSAID	Non steroidal antiinflammatory drugs
PCM	N-3-carbamoyl-2,2,5,5-tetramethylpyrrolidin-1-yloxy = 3-Carbamoyl-proxyl
PEG	Poly(ethylene glycol)
Ph. Eur.	Pharmacopoea Europaea
PVA	Poly(vinyl alcohol)
PVAc	Poly(vinyl acetate)
PVP	Poly(vinyl pyrrolidone)
rpm	rotations per minute

SEM	Scanning electron microscopy
TEC	Triethyl citrate
TEM	Transmission electron microscopy
TMA	Thermal mechanical analysis
TMS	Tetramethyl silane
TPI	Terahertz pulsed imaging
USP	United States Pharmacopeia

1. Introduction

The peroral administration of drugs represents nowadays the most common way of drug application not least due to its high patient acceptance. Applicable devices may be classified into single unit dosage forms such as tablets, dragées and capsules as well as multi particulate dosage forms like for example pellets, granulates and powders [1]. In principle immediate release drug delivery systems have to be distinguished from modified release dosage forms. Immediate release DDSs are, particularly with regard to drugs with a short biological half-life, associated with a fast increase and decrease and hence fluctuations of drug plasma levels. Therefore, therapeutic drug plasma levels are under-run or exceeded, leading to a reduction or loss in drug effectiveness or an increased incidence of side effects. Modified release DDSs include systems with pH-dependent, extended, delayed or pulsed drug release. Sustained, extended or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery devices. By contrast, delayed release dosage forms have to be distinguished from the ones mentioned above as they exhibit a more or less pronounced lag time before drug release.

Extended release oral DDSs offer the opportunity to provide constant or nearly constant drug plasma levels over a certain time period after administration [2]. As therapeutic drug plasma concentrations are maintained over prolonged periods by applying extended release dosage forms, an attenuation of adverse effects, the application frequency and thus improved patient compliance can be achieved, especially when used in long-term treatment [3,4]. Sustained release drug delivery systems include single-unit and multiple-unit dosage forms as well as coated and matrix devices [5]. Sustained release oral dosage forms have to conform to the following requirements:

- Increase the duration of drug's action in the body
- Controlled drug delivery over a long period of time
- Improved effectiveness of drug therapies
- Safe drug release without the risk of dose dumping.

Drugs administered by using a sustained release oral dosage form are subjected to the following parameters:

- The necessity to maintain constant plasma levels over prolonged time periods
- A broad therapeutic window ensuring that in case of undesirable burst release of the nominal dose the health of the patient is not endangered [6].

The maximum achievable sustained drug release is restricted by the transit time of the dosage form in the gastro intestinal tract, which is subjected to interindividual variations of 12 hours up to 48 hours [7]. The transit time is effected by the age, the gender, the body mass index and the state of health of the individual as well as the composition of meals and dietary conditions. Additionally the impact of administered drugs such as opioid analgesics or metoclopramide affecting the gastric motility has to be taken into account.

The present thesis intended to analyze drug release mechanisms from two different types of extended release dosage forms, namely coated tablets and matrix devices. Regarding coated tablets it is possible to modify the drug release by the application of polymer coats which determine either pH-dependent or pH- independent drug liberation [8]. In this thesis, a main focus is on the pH-independent drug release from tablets with membrane controlled drug delivery.

Polymers used for the manufacturing of these dosage forms include ethyl cellulose, ammonio methacrylate copolymers such as Eudragit® RL and Eudragit® RS as well as ethyl acrylate methyl methacrylate copolymer Eudragit® NE. Since the variation in coating thickness is in some cases limited due to formation of cracks at lower coating levels, alterations in coating formulation play a major role in adjustment of drug release profiles. In this connection many efforts have been made to affect drug release rate by choosing different excipients as pore forming components in coating formulations. For achieving a controlled porosity in the tablet coating leachable small water-soluble molecules may be incorporated in the film. For this purpose components like sucrose, urea, potassium chloride and sodium chloride are used [9-11]. Moreover, systems using non-ionic surfactants like polysorbate 20 or even varying amounts of plasticizer were described [12,13]. The latter solution implies the risk of brittle or sticky coatings in case of too low or to high plasticizer amounts.

Avoiding these issues the use of polymer blends consisting of a water insoluble and in the end remaining polymer such as ethyl cellulose and a leachable water soluble

polymer like i.e. polyethylene glycol, poly(vinyl alcohol)-poly(ethylene glycol)-graft-copolymer, polyvinyl pyrrolidone or hydroxypropyl methylcellulose represents an interesting approach for achieving membrane controlled drug delivery [14-17]. Drug liberation may be adjusted by the combination of polymers exhibiting the desired physicochemical characteristics such as solubility in different parts of the GI tract, permeability and mechanical strength [18]. In this case, drug release profiles are dependent on the amount and solubility of the pore-forming polymer, the coating thickness, the osmotic pressure difference and the solubility of the drug.

The main polymer used in the formulations presented in this thesis is Kollicoat® SR, a polyvinyl acetate exhibiting an averagemolecular weight of 450.000. It is marketed as Kollicoat® SR 30 D, a ready to use coating suspension composed of 27 % poly(vinyl acetate) stabilized with 0.3 % sodium lauryl sulphate and 2.7 % povidone, which acts as a pore former [19].

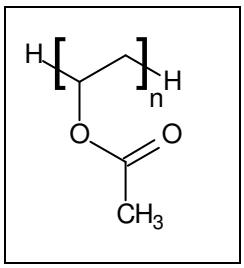


Fig. 1.1 Chemical structure of Kollicoat® SR (n ~ 5226).

Kollicoat® SR is characterized by water insolubility and a low minimum film forming temperature of 18 °C. It shows exceptional sustained release characteristics for both water soluble and poorly water soluble drugs and provides drug release independent of pH and ionic strength of the release medium [20-22].

An exceptional characteristic of Kollicoat® SR lies in its high tensile strength. Elongation at break is up to about 400 % with an amount of 15 % propylene glycol as a plasticizer [23]. Thus, the compression of pellets without rupture of the polymer film is possible by adding 10% TEC or propylene glycol respectively [24,25].

Though Kollicoat® SR represents a relatively new controlled release polymer on the market it has already been used as the water insoluble part in membrane controlled drug delivery coatings of some formulations [25,26]. When in contact with dissolution medium, PVP dissolves leaving pores for the drug diffusion through the polymer film. Since April 2004 a Kollicoat® SR monograph is registered in the European Pharmacopoeia [27].

In addition to the application as a polymeric coat Kollicoat® SR is used as a granulation agent due to its binding characteristics [28].

Drug release profiles of Kollicoat® SR coated tablets were adjusted by the addition of soluble, pore forming polymer Kollicoat® IR. The latter represents a spray dried powder of poly(ethylene glycol)-poly(vinyl alcohol) graft copolymer. It is produced by grafting of vinyl acetate onto polyethylene glycol (PEG) and subsequent saponification of the poly(ethylene glycol)-poly(vinyl acetate) graft copolymers. PEG units and PVA units are related to each other as 25 %:75 %, forming a comb-like structure. Kollicoat® IR was launched in 2002 and approved by BfArM in 2005 and by the FDA in 2008.

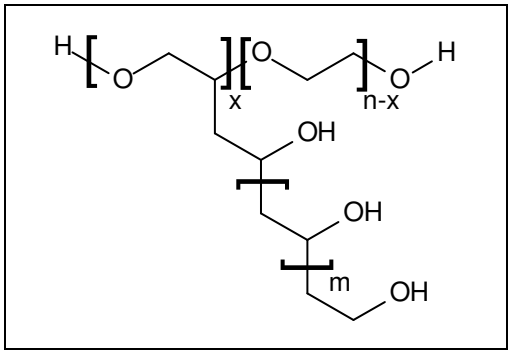


Fig. 1.2 Chemical structure of Kollicoat® IR (m ~ 175, n ~ 136, x = 2 - 3).

Kollicoat® IR is characterized by a high water solubility and a high dissolution rate. The low viscosity of coating solutions causes a fast and simple processibility. PEG-PVA grafted copolymer forms highly flexible films, as the plasticizer is covalently bonded to the polymer.

A main field of application lies in the function of a fast dissolving film forming polymer for taste masking or protection against humidity and light [29]. Janssens et al. utilized the good water solubility of Kollicoat® IR in the development of solid dispersions via melt extrusion to improve the bioavailability of poorly water soluble drugs [30,31]. Some approaches have been performed by the use of Kollicoat® IR in orally fast dissolving films for drug application [32,33].

In membrane controlled drug delivery systems PEG-PVA grafted copolymer acts as a pore forming agent, whereas drug release rates may be adjusted by a change in Kollicoat® IR concentration [34]. Combined with PVAc a pH independent sustained release coating is obtained that is characterised by a much lower risk of dose dumping due to its highly flexible film.

Regarding matrix tablets as the second type of oral dosage form characterized in this thesis, various polymers exhibiting different physicochemical properties have been investigated in last decades as matrix forming excipients to retard drug liberation. In this connection, hydrophilic, hydrophobic and plastic matrices have to be distinguished. The most commonly used polymers in for the realization of hydrophilic matrix systems are cellulose ethers such as hydroxyethyl cellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose. After contact with aqueous dissolution medium a gel layer controlling the drug release is formed. Hydrophobic matrix systems are often consisting of waxy materials, whereas the drug liberation is controlled by the drug diffusion through the porous material and erosion of the matrix. In contrast to this, inert, plastic matrix systems do not exhibit erosion. The diffusion of aqueous medium into the matrix device represents the rate limiting step unless pore forming agents are added [35]. Polymers such as ammonio methacrylate copolymer (Eudragit® RSPO) have been applied in the past to realize this kind of matrix systems.

For the preparation of plastic matrix systems characterized in this thesis Kollidon® SR was used as a matrix forming agent. Kollidon® SR represents a physical mixture of 80 % poly(vinyl acetate) and 20 % poly(vinyl pyrrolidone) (Figs. 1.1 and 1.3).

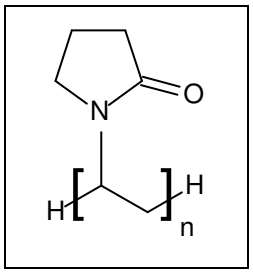


Fig. 1.3 Chemical structure of poly(vinyl pyrrolidone) (n = 396 – 486).

Kollidon® SR shows strong dry binding characteristics, whereas the optimized ratio of PVP and PVAc provides a partly water soluble binder with a high plasticity [36]. Poly(vinyl pyrrolidone) improves the compressibility and acts as a pore forming agent allowing a controlled drug diffusion. Kollidon® SR based matrix tablets with a high crush resistance preventing the misuse of opioid analgetics such as oxycodon have been prepared [37]. Excerted compression forces for the manufacturing of these tablets are comparatively low. Formulations with solely poly(vinyl acetate) as matrix forming excipient as well as in combination with HPMC, maize starch, lactose, calcium phosphate have been published [38-40]. Due to the low glass transition

temperature of PVAc even a preparation of matrix tablets via melt extrusion can be considered [41].

Two different model drugs were chosen to analyze the impact of drug solubility on drug release characteristics. In this context, Propranolol HCl represents a mixture of R- and S-1-(Isopropylamino)-3-(naphthalen-1-yloxy)propan-2-ol hydrochloride. As a non-selective antagonist on β1- and β2-adrenoceptors and is used as an anti-arrhythmic and blood pressure lowering drug.

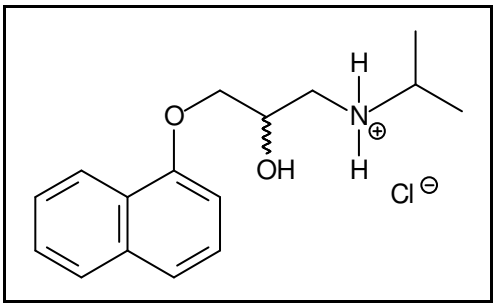


Fig. 1.4 Chemical structure of R,S - Propranolol HCl.

Due to its relativly good water solubility of 220 mg/ml in 0.1 N HCl and 254 mg/ml in phosphate buffer as well as a sufficient permeability in vivo, Propranolol HCl is classified as a BCS I drug [42,43]. In consequence of a strong first pass effect the bioavailibility of Propranolol HCl is decreases to 30 % - 55 %, depending on the age of the subject [44]. In general, extended release Propranolol HCl formulations are subjected to a lower bioavailability compared to conventional tablets. Nevertheless, various bioequivalence studies comparing immediate and sustained release Propranolol HCl formulations found equivalent or increased Propranolol HCl plasma levels [45,46]. Propranolol HCl was selected as a model drug to show the drug release from the developed DDSs which is only marginally influenced by solubility issues. Therefore, these systems were expected to mainly exhibit the influence of the drug delivery system on drug release retardation.

On the other hand, Theophylline exhibits poor water solubility characteristics of 8.3 mg/ml and has been classified as BCS IV [43]. Theophylline has been reported to act as an adenosin A1 receptor antagonist which is additionally inhibiting phosphodiesterases and releases calcium from intracellular reservoirs to the cytoplasma. Its use is mainly focused on the treatment of medium to severe asthma bronchiale as it contributes to the release of bronchial spasms [47].

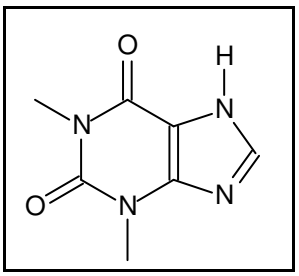


Fig. 1.5 Chemical structure of Theophylline.

As Theophylline exhibits a small therapeutic window, the development of a dosage form ensuring reliable and controlled drug release rates has up to now been in the focus of interest. In contrast to Propranolol HCl, Theophylline was expected to show a more pronounced retardation in release patterns when formulated with the same DDSs due to its decreased solubility.

For the characterization of solid oral dosage forms up to now various techniques have been described. In case of coated tablets the analysis of physicochemical properties of the polymer films plays an essential role. Up to now only a few publications regarding the thermal characterization of Kollicoat® SR/Kollicoat® IR films by means of DSC and TMA can be found [48]. For the determination of glass transition temperatures not only DSC and TMA but also differential thermo analysis, dilatometry and refractometry come into consideration. Films can be formed by spreading or spraying of the coating formulation onto plates and subsequent drying. Another application of the DSC technique lies in the analysis of the interaction potential of PVAc with incorporated drugs [49].

Molecular and morphological properties of polymeric films can be obtained by the utilization of Raman spectroscopy [50,51]. Further characterization of film surfaces can be performed by using ESEM [50,51]. Compared to SEM, environmental scanning electron microscopy allows the measuring of humid samples and thus may provide information on the swelling characteristics of polymer films. Up to the present no publications regarding the morphological characterization of Kollicoat® SR/ Kollicoat® IR based films are available.

Apart from standard pharmacopoeial methods, various techniques were used for a deeper analysis of the prepared tablets and the manufacturing process. Tableting characteristics of Kollidon® SR at different humidities in combination with the model drug Theophylline have been studied by Hauschild and Picker-Freyer using the 3D model [52].

Recently terahertz pulsed imaging has been applied to the characterization of solid dosage forms. It offers the possibility to analyze film coatings in a non-destructive manner, as terahertz radiation is capable of penetrating most pharmaceutical excipients. Thus, detailed information regarding coating thickness, coat uniformity and reproducibility, phase transitions, polymorph identification and polymorph quantification is gained [53,54].

MRI proved to be a powerful method concerning the monitoring of swelling processes of HPMC based matrix tablets [55-57]. ^{19}F NMR imaging has been used to determine drug distributions in swelling HPMC matrix tablets [58]. Unfortunately, the application of MRI on solid oral dosage forms consisting of poly(vinyl acetate) has been neglected so far.

Today, electron paramagnetic resonance spectroscopy has been utilized in the field of pharmaceutical research to determine water penetration behaviour into systems of interest as well as their homogeneity. It has been applied to HPMC matrix systems to further characterize drug release processes [59,60]. EPR offers furthermore the possibility to detect the oxidative degradation of active pharmaceutical ingredients in the solid state as well as the pH measurement [61]. EPRI was applied to monitor ph values inside HPMC based matrix tablets affected by incorporated pH modifying agents, their solubility and leaching behaviour [62]. Furthermore, oxygen permeation kinetics through HPMC coated tablets was studied using EPR spectroscopy [63].

Summarizing it is obvious, that due to the short period of time since Kollicoat® IR, Kollicoat® SR and Kollidon® SR entered the market, only a few drug delivery systems consisting of these polymers have been analyzed more deeply regarding their drug release mechanism. On the other hand it has to be pointed out, that despite the long history of solid oral dosage forms some processes governing drug release are still unexplored. The basic mechanism of drug release from coated oral dosage forms with membrane controlled drug delivery is related to the diffusion of the solubilized drug through the polymer coat. In this connection the further characterization of water penetration behaviour into the tablet initialiting drug solubilization leads to a deeper understanding of mechanisms related to drug liberation. Surprisingly, despite the long history of membrane controlled DDSs, the leaching of water-soluble components from the film and its impact on drug release pattern has not been investigated in detail.

Furthermore, not only extended release oral dosage forms but gastroretentive drug delivery systems based on PVAc were put in the focus of this work. The retention mechanism for the gastroretentive tablets proposed in this thesis was based on the ability of these devices to float. At this juncture matrix devices were compared to coated floating tablets, whereas in the latter the required lower density was obtained by carbon dioxide development inside the tablet core. As Kollicoat® SR/Kollicoat® IR blends were utilized likewise for the development of coated floating tablets, it was possible to apply some of the results obtained in the previous characterization of drug release processes from non-floating tablets. Despite the development of various DDSs proposed for gastric retention in the last three decades, still some questions concerning the retention mechanism of the dosage form remained unanswered. Although magnetic resonance imaging has been used to monitor water penetration and swelling behaviour of HPMC matrix systems the application of the MRI technique has been neglected in the characterization of floating drug delivery systems up to now.

Research objectives

The research objectives of the present doctoral thesis can be summarized as follows:

- Thermal analysis of polymer films to study the compatibility of Kollicoat® SR/ Kollicoat® IR blends and receive information regarding the glass transition temperatures of the polymers
- Investigation of the impact of polymer film composition and coating thickness on drug release characteristics from Kollicoat® SR/Kollicoat® IR coated tablets
- Non-invasive monitoring of the solubilized drug amount inside the coated tablet by EPR spectroscopy
- Evaluation of water uptake characteristics into coated tablets by using thermogravimetric methods
- Monitoring of morphological changes in film coat composition induced by dissolution by means of scanning electron microscopy
- Characterization of dissolution induced changes in film coat composition by the application of ^{1}H NMR spectroscopy
- Development of Kollicoat® SR/Kollicoat® IR coated floating tablets
- Development of poly(vinyl acetate)-based floating matrix tablets
- Quantitative determination of the floating strength of the devices
- Non-invasive and continuous monitoring of swelling, hydration and carbon dioxide development characteristics
- Determination of drug release kinetics of floating matrix devices

2. Thermal analysis of polymer films

2.1 Introduction

DSC and TMA are widely used to determine the glass transition temperature T_g of free films [48,64-67]. The glass transition temperature is defined as the transformation of a substance from the amorph and glassy to a rubbery state. It is related to increased polymer chain segment motion and depends on molecular weight, internal strain in the polymer and residual solvents [68,69]. As an amorphous solid is not in a thermodynamically balanced state, the transition to the rubbery state represents a kinetically controlled relaxation process. Therefore, the process of glass transition is not fixed to a certain temperature but a temperature range.

DSC studies are performed either by detecting the heat flux (heat flux DSC) being proportional to the temperature difference or by measuring the electrical power needed to keep both sample and reference at a constant temperature (power compensating DSC).

TMA experiments are realizable utilizing two different measuring setups. By using the penetration mode a copped measuring sensor under load is penetrating the sample in relation to temperature. Measuring the T_g by means of TMA is predicated on the principle that due to the acquirement of thermal energy at glass transition temperature polymer chains are beginning to move. Thus, the transition from the brittle to the ductile state is detected as the glass transition temperature [69]. A deep penetration of the measuring sensor indicates the softening temperature T_s of the polymer film. Using the expansion method a flat measuring sensor is in contact with the sample, registering the temperature dependent increase of the free volume of the sample which is caused by an increased mobility of the polymeric chains at higher temperatures.

In this chapter the film forming polymers Kollicoat® SR and Kollicoat® IR were analyzed regarding their glass transition temperatures by using heat flux DSC and TMA operating in penetration mode. Furthermore, the compatibility of both polymers was characterized by determining the glass transition temperatures of Kollicoat® SR/IR films. Therefore, the total amount of film forming polymer as a sum of Kollicoat® SR and Kollicoat® IR as well as the total amount of plastcizer triacetin

remained the same in both film formulations. Solely the Kollicoat® SR/IR ratio was varied to study the influence of PEG-PVA on the glass transition temperature.

2.2 Materials

Kollicoat® SR, Kollicoat® IR and Kollidon® 30 were obtained by BASF (Ludwigshafen, Germany). Triacetin and Talc were purchased from Sigma Aldrich (Taufkirchen, Germany). Titanium dioxide was supplied by Kronos Titan GmbH (Leverkusen, Germany).

2.3 Methods

2.3.1 Preparation of free films

Pure Kollicoat® IR films were prepared by mixing 60.0 g PEG-PVA with 140.0 ml distilled water to receive a polymer solution of 30 % (m/m). Kollicoat® SR 30 D was used as received and only blended before casting the films. Polymer dispersions with different Kollicoat® SR/IR ratios according to Table 2.1 were prepared by adding triacetin, Kollicoat® IR and Kollicoat® SR 30 D to 60 ml distilled water and subsequent blending. Mixing was always carried out for 3 min using an Ultra Turrax (T 18 basic, Ika, Germany) at 18.000 rpm. PVP was diluted in 35 ml distilled water. After adding talc and titanium dioxide to the PVP solution the suspension was dispersed. Then the pigment suspension was incorporated into the polymer suspension and mixed again.

Table 2.1 Composition of Kollicoat® SR/ Kollicoat® IR films.

Components (g)	**SR/IR:9/1**	**SR/IR:8/2**
Kollicoat® SR 30 D	87.0	84.6
Kollicoat® IR	2.6	5.0
Triacetin	1.4	1.4
Kollidon® 30	1.0	1.0
Titanium dioxide	1.0	1.0
Talc	7.0	7.0
Distilled water	95.0	95.0

Amounts of 20 ml polymer dispersions were cast onto teflon coated plates and subsequently dried to constant weight in a heater at 60 °C for 12 hours. Polymer

films were removed from the Teflon plates and stored at 20 °C and 60 % relative humidity for 3 days. The thickness of the films was determined using a manual micrometer at 15 random positions of the film. The mean standard deviation did not exceed 3.5 % of the average thickness, which exhibited values as shown in Table 2.2.

Table 2.2 Film thickness of free films casted on Teflon plates.

Film	Kollicoat® IR	Kollicoat® SR	SR/IR:9/1	SR/IR:8/2
Film thickness	143 ± 3 µm	150 ± 5 µm	148 ± 5 µm	142 ± 4 µm

2.3.2 Thermal mechanical analysis experiments

Thermal mechanical analysis detects changes of a dimension or mechanical properties of samples subjected to a predefined temperature program.
TMA experiments were carried out with a TMA 202 (Netzsch, Selb, Germany), working with expansion mode. Samples were heated from 0 °C to 100 °C with a heating rate of 5 K/min. Nitrogen was used as a washing gas with a rate of 50 ml/min. The glass transition temperature was determined by the change of the slope of the obtained curves. Experiments were performed in duplicate.

2.3.3 Differential scanning calorimetry experiments

DSC measurements were performed on a DSC 200 (Netsch, Selb, Germany), operating with a heating rate of 10 K/min within a range of 0 °C to 100 °C. After an equilibration phase the samples were first heated, afterwards cooled down to 0 °C and then heated again following the same regimen like before. Nitrogen was used as a flushing gas with a flow rate of 10 ml/min. The weight of the free film samples used for the DSC measurements varied from 4.5 to 7.8 mg. The samples were placed into aluminium pans with a pierced lid. For the determination of the glass transition temperature T_g the data of the second heating curve were analyzed. DSC experiments were carried out in triplicate.

2.4 Results and discussion

2.4.1 Thermal mechanical analysis experiments

TMA curves are characterized by two inflection points, whereas the first indicates the glass transition temperature. At the T_g the mobility of the polymer chains and thus the free volume of the sample increases, leading to a penetration of the measuring sensor into the sample. Therefore, the onset in TMA thermograms indicates the glass transition temperature of the polymer (Fig. 2.1). Thermal mechanical analysis experiments revealed a lower T_g for Kollicoat® IR compared to Kollicoat® SR 30 D (Table 2.3).

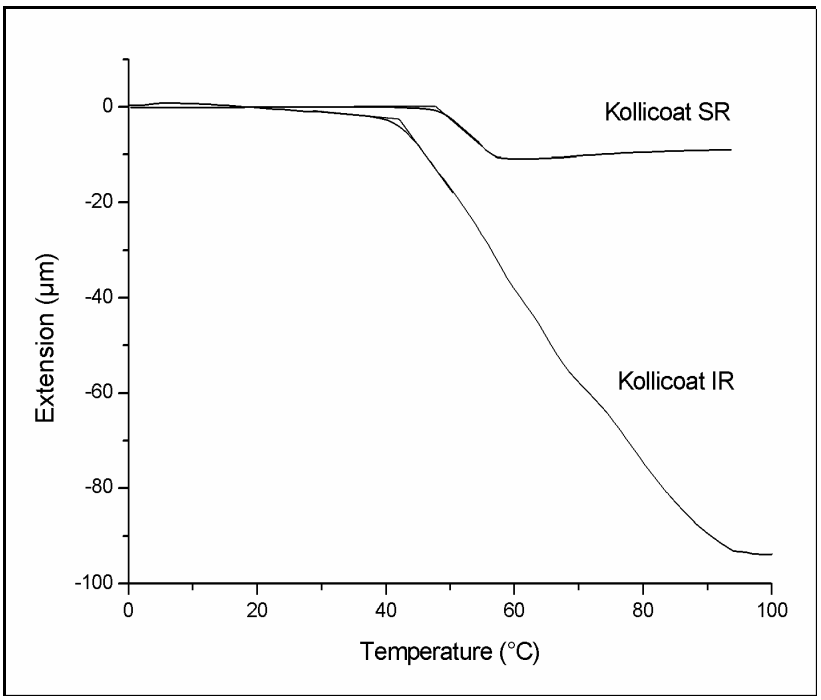


Fig. 2.1 TMA curves of Kollicoat® SR and Kollicoat® IR free films.

2.4.2 Differential scanning calorimetry experiments

The glass transition temperature is apparent in DSC curves as an endothermic step and is determined as the intersection point of the baseline and the tangent of the gradient DSC curve. As DSC curves often exhibit a gradient baseline, the correct determination of the T_g is possibly hindered. To simplify the comparison of the results obtained by DSC and TMA the midpoint of the steps in the DSC curves, which also

represents the inflection point of the curve, is used for the determination of the glass transition temperature (Fig. 2.2).

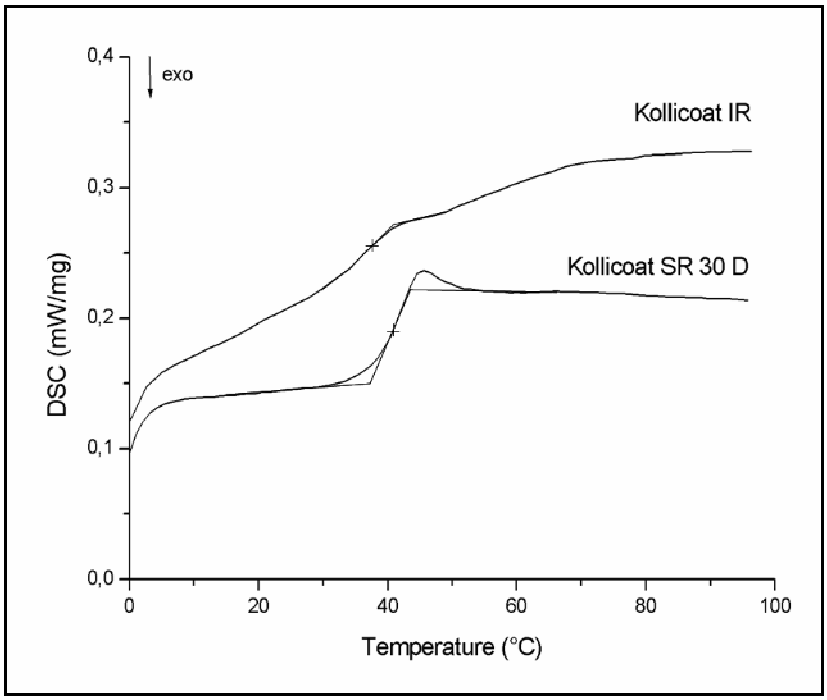


Fig. 2.2 DSC curves of Kollicoat® IR and Kollicoat® SR free films.

The glass transition temperatures obtained by both methods are compared in Table 2.3. Determined T_g values of polymers often tend to vary depending onthe technique used for determination [69]. Values determined by TMA tend to be higher than those acquired by DSC. This phenomenon has already been described in the literature, whereas values determined by TMA exceed DSC values by 6 °C in average [70,71]. Thus, a comparison of T_g obtained by different methods remains difficult.

Table 2.3 Glass transition temperatures of Kollicoat® IR and Kollicoat® SR 30 D films determined by TMA and DSC.

Polymeric film	**T_g determined by TMA**	**T_g determined by DSC**
Kollicoat® IR	41.6 °C	37.4 °C
Kollicoat® SR 30 D	47.9 °C	40.6 °C

Free films with a Kollicoat® SR/ Kollicoat® IR ratio of 9:1 exhibited a glass transition temperature of 27.4 °C, which was lower compared to pure free films. The decrease

in T_g value was expected due to the addition of the plasticizer triacetin (Fig. 2.3). Interestingly, the increase in PEG-PVA content resulted in further decreased glass transition temperature to a value of 25.8 °C. Since the plasticizer PEG is covalently bound to the film forming polymer, Kollicoat® IR acts as a polymeric plasticizer. Thus, PEG-PVA improves film coat properties such as mechanical strength and facilitates the film formation at lower temperatures due to the further lowering of the glass transition temperature.

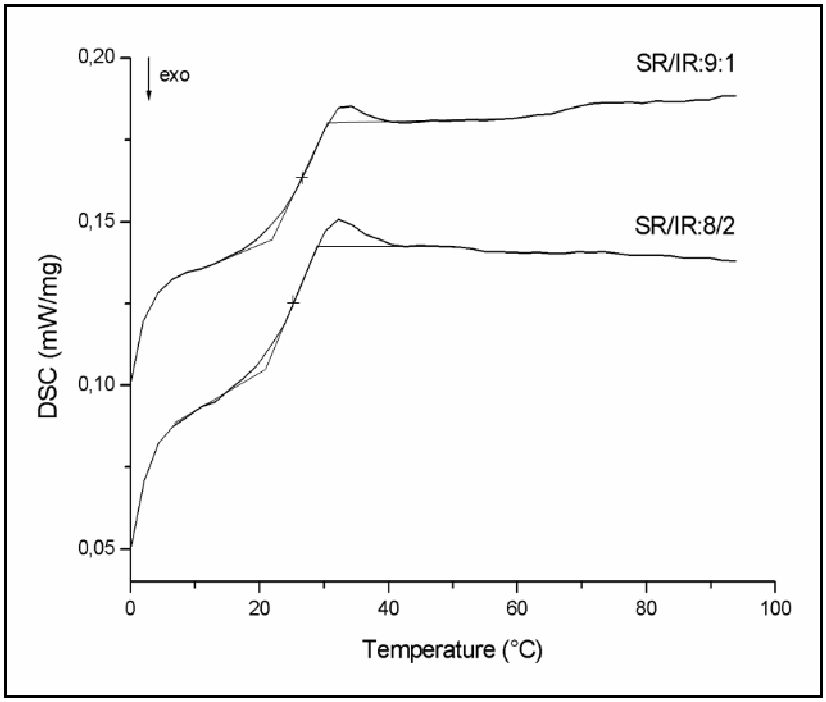


Fig. 2.3 DSC measurements of SR/IR:9:1 and SR/IR:8/2 films.

The appearance of only one glass transition temperature of the polymer films with different Kollicoat® SR/Kollicoat® IR ratios indicates the compatibility of both polymers.

2.5 Conclusion

DSC and TMA allowed the T_g determination of pure Kollicoat® IR and Kollicoat® SR films as well as of polymer films with different Kollicoat® SR/IR ratios. The condition of film coats during the dissolution process is expressed by the glass transition temperatures of the swollen polymer films. Lower T_g values of polymer films are related to a higher probability of being exceeded by the physiological temperature. Thus, an increased mobility of the polymer chains will contribute to a higher permeability of the film coat facilitating drug release. It was shown, that both coating formulations are effectively plasticized by the addition of triacetin and Kollicoat® IR acting as a polymeric plasticizer.

3. Mechanistic analysis of drug release

3.1 Introduction

In the present chapter drug release characteristics from MCC based tablet cores coated with two different coating compositions for membrane controlled drug delivery were analyzed. Therefore film coats with Kollicoat® SR/Kollicoat® IR ratios of 9/1 and 8/2, which were already characterized in the previous chapter by means of thermal analysis, were used.

Kollicoat® SR was utilized as a coating polymer allowing membrane controlled drug delivery. The addition of a water soluble polymer Kollicoat® IR was expected to accelerate the drug release. After contact with the dissolution medium polymers will first begin to swell and absorb water. Swelling will continue until an equilibrium state is reached between the ambition of hydration that will promote the diffusion and the elastic strength of the polymer network on the opposite. As a second process dissolution of the polymer occurs which is eroding the film coating [72,73]. For this step a linear polymer or a sufficient hydrophylicity of the polymer is required for it can be solvated by the water in the dissolution medium. The water which penetrated the film coating is reaching the tablet core and increases the polarity and molecular mobility inside the tablet so that dissolution of the drug and water soluble excipients occurs.

Regarding the composition of the tablet core MCC was chosen as an excipient allowing direct compression without the need of a time consuming granulation step. Since MCC contributes to a fast disintegration of the tablet core, the characteristics of the tablet coat will mainly influence the drug release profile.

Propranolol HCl and Theophylline were incorporated into the tablet cores as water soluble and slightly water soluble model drugs respectively. In addition to investigate the impact of drug solubility characteristics, coating composition and film coat thickness on drug release the focus in this chapter was to explore the drug release mechanisms in more detail. A detailed understanding of the release mechanisms is required for a rationale based improvement of the drug liberation characteristics. Therefore, the water uptake was quantified by gravimetric measurements. Additionally, EPR spectroscopy was applied to analyze the microenvironment inside the tablet core. EPR spectroscopy (Electron Paramagnetic Resonance spectroscopy,

syn. ESR spectroscopy) is a powerful tool to get unique information on drug delivery processes [74-79]. In this chapter EPR spectroscopy was applied to monitor drug solubilization processes within the tablet core. Propranolol HCl and Theophylline are both EPR silent as they do not exhibit the molecular structure of a radical possessing an unpaired electron. Therefore, the hydrophilic, water soluble spin probe PCM (N-3-carbamoyl-2,2,5,5-tetramethylpyrrolidin-1-yloxy) was incorporated into tablets as a model drug. Exhibiting a logP value of 0.68, except for the radical character the spin probe 3-Carbamoyl-proxyl shows physical properties comparable to Propranolol HCl with a logP value of 0.62 (logP value of Theophylline = -0.008) [80,81]. Thus, results obtained by EPR spectroscopy will allow drawing conclusions regarding the dissolution behaviour of the model drug inside the tablet.

3.2 Materials

Kollicoat® IR, Kollicoat® SR 30 D, Kollidon® 30 and Theophylline monohydrate were purchased from BASF (Ludwigshafen, Germany). MicroceLac® 100 was obtained from Meggle GmbH & Co. KG (Wasserburg, Germany). Talc and Propranolol HCl were purchased from Sigma Aldrich (Taufkirchen, Germany). Titanium dioxide was supplied by Kronos Titan GmbH (Leverkusen, Germany). EPR spin probe PCM (N-3-carbamoyl-2,2,5,5-tetramethylpyrrolidin-1-yloxy) was obtained by Prof. V.V. Khramtsov, Institute of Chemical Kinetics and Combustion, Novosibirsk, Russia.

3.3 Methods

3.3.1 Preparation of tablet cores

Two different tablet cores were prepared with a composition according to Table 3.1. All formulation ingredients, except the magnesium stearate were blended in a z-arm mixer (AR 400, Erweka GmbH, Heusenstamm, Germany) for 10 min. After adding the magnesium stearate the powder mixture was blended for another 2 min. Biconvex tablets were compressed on a rotary tablet press (RL 12, Kilian GmbH & Co KG, Germany) with a compression force of 6 kN. Tablets weighed 310 mg (±15mg) and measured 9 mm in diameter.

Table 3.1 Tablet core composition.

Components	**m (mg)**
API (Propranolol HCl or Theophylline)	62.00
MicroceLac® 100	243.35
Aerosil® 200	3.10
Magnesium stearate	1.55

For tablets containing the hydrophilic EPR spin probe PCM (Fig. 3.1) 0.05 mmol of this substance were dissolved in ethanol 70 % and mixed in the z-arm mixer with 100 g of the powder mixture. The powder was dried at 40°C in a drying oven for 48 h. This procedure was carried out to obtain a tablet powder with molecularly dispersed EPR spin probe PCM. Biconvex tablets were compressed on a rotary tablet press

(Pharmapress 100, Korsch Pressen GmbH, Germany). Tablets weighed 500 mg (±25 mg) and measured 11 mm in diameter.

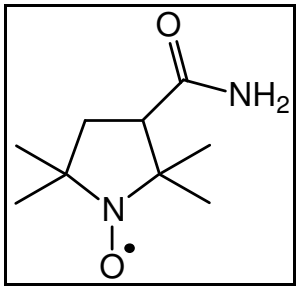


Fig. 3.1 Chemical structure of spin probe PCM.

3.3.2 Film coating of tablet cores

Coating dispersions with two different Kollicoat® SR/IR ratios were modified according to Kolter et al. [82] and contained coating polymers in a 90 %/10 % and 80 %/20 % Kollicoat® SR/IR rate respectively, related to each other as dry mass (Table 3.2).

Table 3.2 Composition of coating dispersions.

Components (g)	SR/IR:9/1	SR/IR:8/2
Kollicoat® SR 30 D	435.0	422.0
Kollicoat® IR	13.0	26.0
Triacetin	7.0	7.0
Kollidon®30	5.0	5.0
Titanium dioxide	5.0	5.0
Talc	35.0	35.0
Distilled water	475.0	475.0

Triacetin, Kollicoat® IR and Kollicoat® SR 30 D were added to 300 ml distilled water and blended. Mixing was always carried out for 3 min using an Ultra Turrax (T 18 basic, Ika, Germany) at 18.000 rpm. PVP was diluted in 175 ml distilled water. After adding talc and titanium dioxide to the PVP solution the suspension was dispersed. Then the pigment suspension was incorporated into the polymer suspension and mixed again. The coating dispersion was stirred during the whole coating run to prevent settling using a blade stirrer (MR 25, MLW, Germany) at 100 rpm.

The tablets were coated in a drum coater (Lab-Coater GC-300, Glatt GmbH, Switzerland). The coating conditions were: inlet air temperature: 50 °C, air flow rate: 100 m³/h, spray rate: 7.5 g/min, atomizing air pressure: 2.0 bar, drum speed: 10 rpm. During the coating process samples of 100 tablets were taken at 4, 6 and 8 mg polymer/cm² respectively.

3.3.3 Determination of dissolution characteristics

The dissolution tests were performed according to paddle method 2 in the USP 30 [83]. Therefore an automatic dissolution tester (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) was used. The dissolution conditions were set to 37 °C dissolution temperature and 50 rpm paddle speed. The dissolution medium was hydrochloric acid with a pH of 1. After two hours the medium was changed to phosphate buffer with a pH of 6.8. The dissolved drug amount was determined by measuring the UV absorption at 290 nm (Propranolol HCl) and 272 nm (Theophylline) respectively and calculated using the calibration equations of both drugs. Dissolution tests were carried out in triplicate.

3.3.4 Comparison of lag times before drug release

After extrapolating the approximately linear part of the dissolution slope to the abscissa it is possible to calculate the lag times at the initial phase of drug dissolution profiles.

3.3.5 Determination of water uptake behaviour

Propranolol HCl tablets were placed into hydrochloric acid (pH 1) for the first two hours and then transferred into phosphate buffer (pH 6.8). In predetermined intervals samples were taken and adhering water on the surface was removed using paper tissues. Then tablets were weighed and dried in a drying oven at 70 °C until mass was constant. Water uptake was calculated as amount of penetrated water related to dry tablet mass. Measurements were carried out in triplicate.

3.3.6 Monitoring of water diffusion characteristics by means of EPR spectroscopy

Propranolol HCl tablets containing EPR spin probe PCM in addition were used. Measurements were performed with an L-band EPR spectrometer (Magnetech GmbH, Berlin, Germany) working at a microwave frequency of about 1.3 GHz. Measurements were carried out using the following parameters: B_0-field 49.0 mT, scan range 12 mT, scan time 60 s and modulation amplitude 0.21 mT.
Tablets were placed into a dissolution tester containing 900 ml 0.1 N hydrochloric acid. After 2 hours the dissolution medium was changed to phosphate buffer with a pH of 6.8. Before measuring the tablets were removed from dissolution medium and adhering water on the surface was removed carefully using paper tissues. Each measurement was performed in triplicate.

3.4 Results and discussion

3.4.1 Determination of dissolution characteristics

In order to guarantee a reliable release, coating application was not lower than 4 mg polymer/cm². In all dissolution tests Theophylline tablets showed lower drug release rates compared to tablets with Propranolol HCl due to the poorer water solubility of the drug (Figs. 3.2 and 3.3).
According to the law of Noyes and Whitney the dissolution rate of a drug substance is given by the following equation:

$$-\frac{\delta m}{\delta t} = \frac{D}{h} \cdot A \cdot (c_s - c_t) \qquad (1)$$

where $\delta m/\delta t$ represents the dissolution rate, δm the mass of the unsolubilized drug at time t, D the diffusion coefficient, h the thickness of the diffusion layer, A the surface area of the drug particles, c_s the drug solubility and c_t the drug concentration at time t. As Theophylline is characterized by a lower solubility in aqueous media (c_s = 8.3 mg/ml) compared to Propranolol HCl (c_s = 220 mg/ml in 0.1 N HCl and 254 mg/ml in phosphate buffer) the drug dissolution rate was expected to be lower for Theophylline, which in consequence was detected in the dissolution experiments.

Tablets with coating formulation SR/IR:9/1 exhibited no complete drug release for Theophylline and Propranolol HCl.

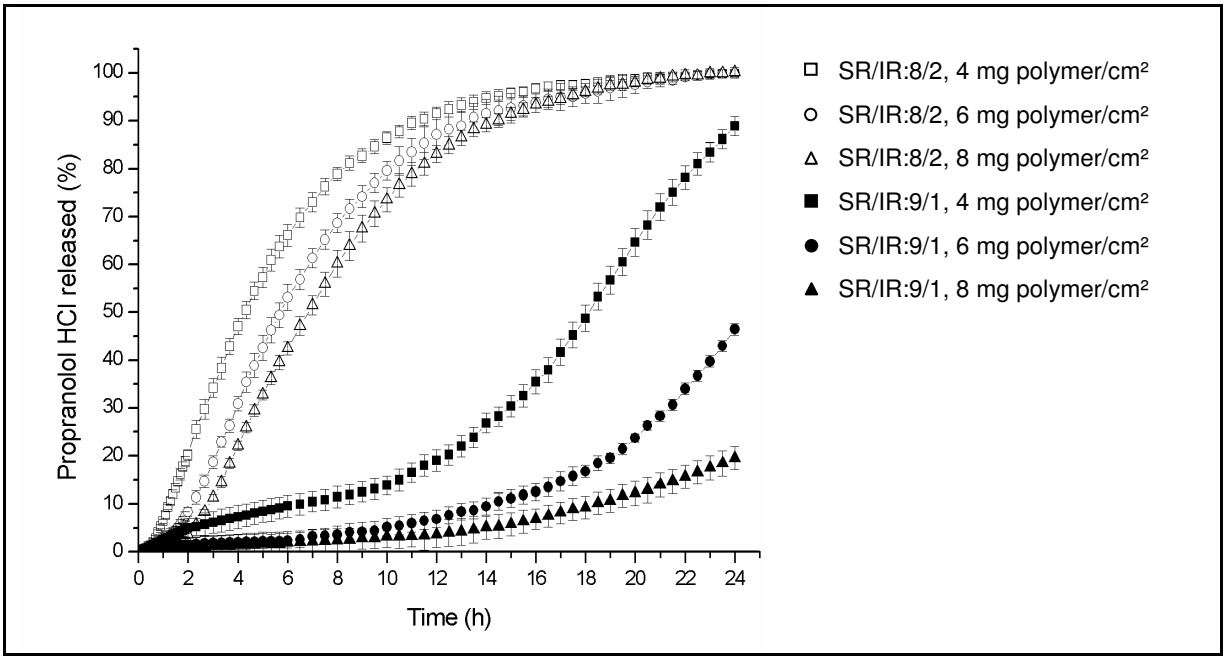


Fig. 3.2 Influence of coating level on Propranolol HCl release from tablets with coating formulation SR/IR-9/1 and formulation SR/IR:8/2.

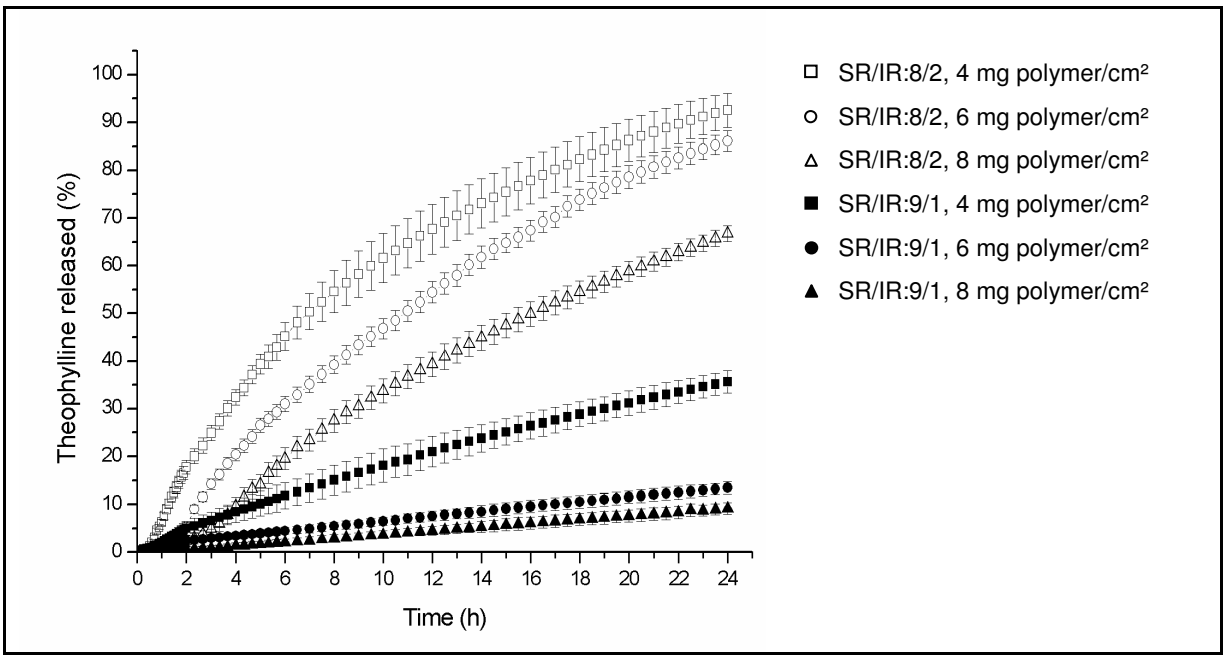


Fig. 3.3 Influence of coating level on Theophylline release from tablets with coating formulation SR/IR:9/1 and formulation SR/IR:8/2.

The release rate of both model drugs from SR/IR:9/1 coated tablets was to slow due to a small amount of water soluble polymer Kollicoat® IR. Within 24 hours the total amount of drug released from tablets with an 8 mg polymer/cm² coat yielded

maximum values of only 20 % Propranolol HCl and 9 % Theophylline respectively. Due to a lower permeability an increased coating thickness led to decreased drug release rates. Theophylline release behaviour was approximately linear whereas Propranolol HCl delivery increased after an almost linear initial phase. The Kollicoat® SR/IR ratio showed a stronger impact on drug release rates compared to coating thickness. This effect was strongly apparent from the Propranolol HCl release profiles. The lower solubility of Theophylline compared to Propranolol HCl masked the influence of the coating composition on drug release characteristics. As expected, drug delivery increased with a higher Kollicoat® IR concentration in coating formulation SR/IR:8/2. Dissolution profiles were characterized by an initial lag time with no drug release and a suddenly increased permeability of the film coat. Poor water solubility prevented complete Theophylline liberation, whereas Propranolol HCl tablets showed complete drug release within 24 hours.

3.4.2 Comparison of lag times before drug release

During the lag time at the beginning of the dissolution test the concentration of permeant in the film is building up. After water penetration through the film the drug inside the tablet is dissolved. It begins to diffuse through the film as permeability increases. The lag times for coating formulation SR/IR:8/2 were calculated and are given in Table 3.3.

Table 3.3 Lag times prior to drug release for coating formulation SR/IR:8/2.

Coat thickness	Lag time of Propranolol HCl tablets (min)	Lag time of Theophylline tablets (min)
4 mg/cm²	28 (± 4)	28 (± 1)
6 mg/cm²	82 (± 2)	84 (± 2)
8 mg/cm²	104 (± 2)	124 (± 4)

A higher coating thickness led, due to extended diffusion pathways, to slower water diffusion and increased lag times (Fig. 3.4). For formulations with the same coating level comparable lag times prior to drug release were obtained for both model drugs, except for tablets with 8 mg polymer/cm² coat thickness. Slight differences in lag times may be caused by the lower water solubility of Theophylline. Due to the

decreased drug permeability of the polymeric film coat the calculation of lag times for tablets with coating formulation SR/IR:9/1 was not feasible.

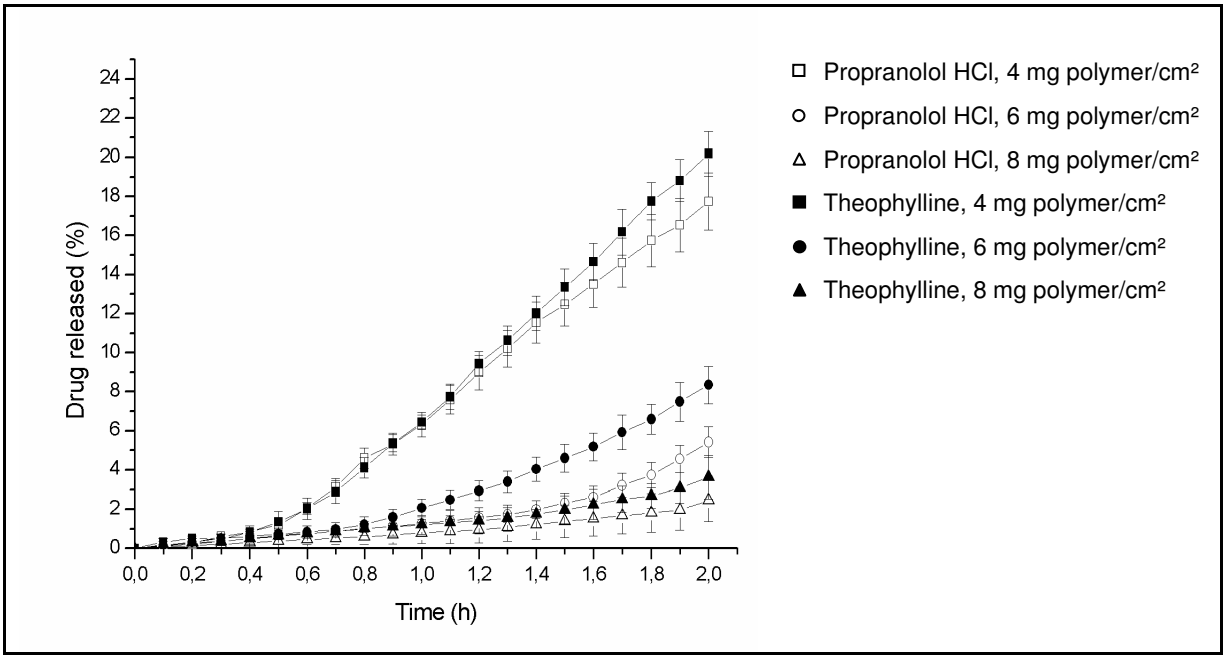


Fig. 3.4 Influence of coating level on lag time in Propranolol HCl and Theophylline release from tablets with coating formulation SR/IR:8/2.

3.4.3 Determination of water uptake behaviour

To study the impact of water diffusion into the tablet on drug release profiles, the water uptake was determined gravimetrically. The findings showed that water penetration was dependent on film coat thickness (Fig. 3.5).

Tablets with a low coating thickness demonstrated fast water penetration behaviour, whereas higher coating film thickness led to initially reduced water permeability with a subsequent rise. Due to the beginning dissolution of the water soluble polymer the diffusibility of the film increases. These results agree with the determined lag times at the beginning of drug release for coating formulation SR/IR:8/2.

The coating composition had only a minor influence on water diffusion into tablets, whereas SR/IR:8/2 coated tablets exhibited a slightly higher water uptake values. Altogether only slight differences in water uptake behaviour were observed for both coating formulations. After five hours absolute water uptake values for all samples were on a comparable level.

Water uptake of 80% is not leading to a macroscopically damaged coating surface demonstrating a high flexibility of the film, which might reduce the danger of dose dumping.

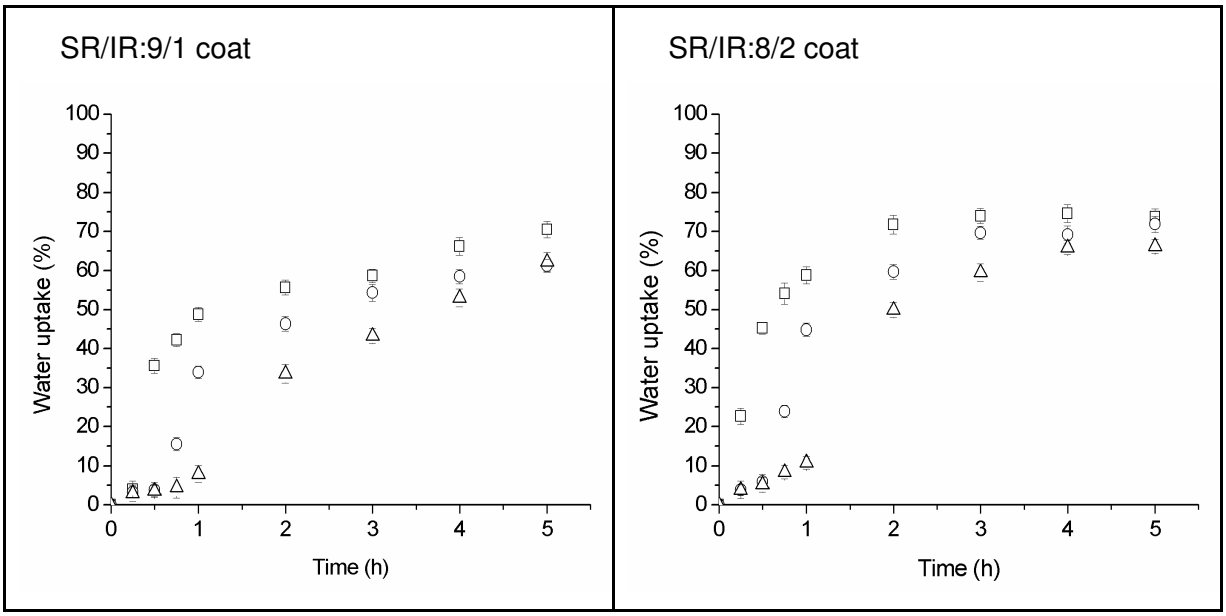


Fig. 3.5 Influence of coating level on water uptake into tablets with different coating formulations (□ 4 mg, ○ 6 mg, Δ 8 mg polymer/cm²).

3.4.4 Monitoring of water diffusion characteristics by means of EPR spectroscopy

EPR spectra of dry tablets showed the immobilization of the spin probe (Fig. 3.6 a-f, 0 min). These are expected for randomly orientated nitroxides in solid samples. Positioning tablets into 0.1 N HCl led in all cases to immediate changes in spectral shape and signal intensity (Fig. 3.6 a-f, 1 min). Only small amounts of water inside the tablet core increase the mobility of the PCM environment. Surprisingly spectra of all tablet samples for measuring point 1 minute showed already a solubilization of spin probe PCM, caused by water penetration into the tablet. At this point neither Theophylline nor Propranolol HCl are released from the tablet core. After contact with dissolution medium the coating polymers are rapidly hydrated and begin to swell, so that water molecules are capable to diffuse through the expanding polymer network. At the beginning diffusion processes are mainly directed into the tablet and are mainly controlled by the one-way water influx. Therefore, drug release processes become more efficient after the tablet core is water saturated. The contribution of the mobile part to the whole spectrum of the nitroxide increased steadily with time, detecting the continuing water diffusion into the tablet.

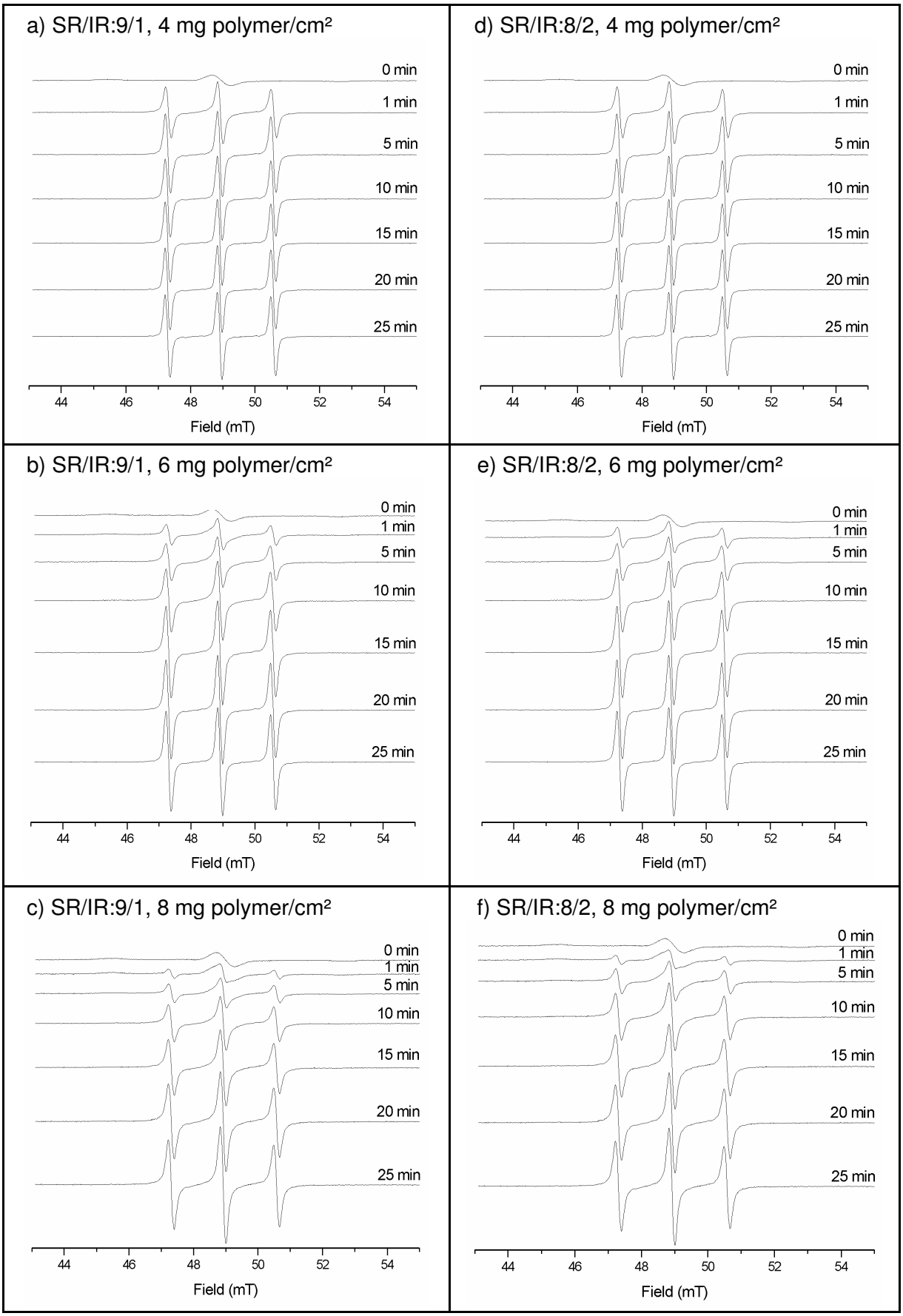


Fig. 3.6 EPR spectra of PCM loaded tablet samples with SR/IR:9/1 and SR/IR:8/2 coat characterized by different coating levels and after different time intervals of exposure to 0.1 N HCl.

After 10 min (4mg polymer/cm²), 20 min (6 mg polymer/cm²) and 25 min (8 mg polymer/cm²) respectively the maximum detectable amount of mobile EPR spin probe is reached. Similar spectral changes were detected for tablets with both coating formulations. As film coating SR/IR:9/1 shows a significantly lower permeability for Theophylline and Propranolol HCl than formulation SR/IR:8/2, it was interesting to see, that water penetration behaviour did almost not change. Only for tablets with a coating application of 8 mg polymer/cm² a slightly decreased contribution of the mobile part to the whole nitroxide spectrum could be detected.

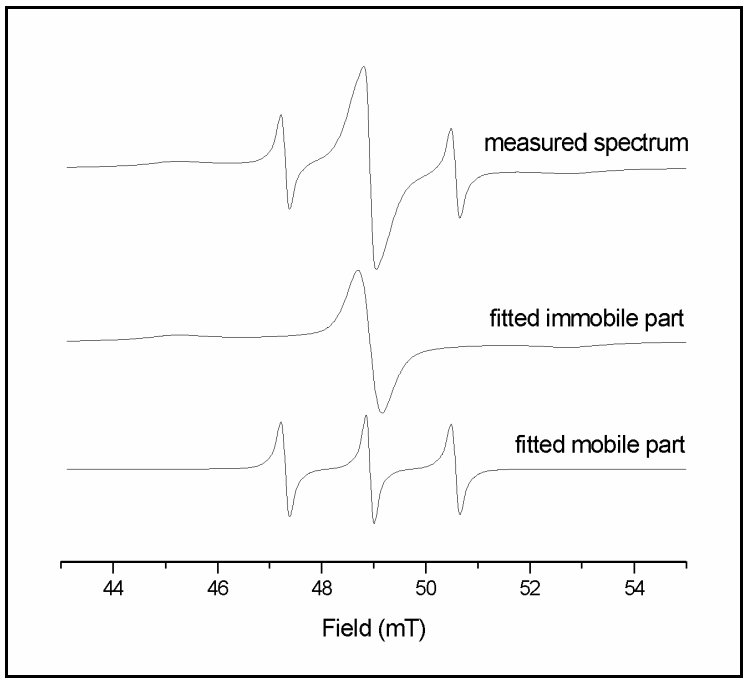


Fig. 3.7 Fitting of mobile and immobile part of spin probe PCM by using EPR simulation software.

For the calculation of mobile and immobile part of PCM respectively the software Nitroxide spectra simulation V. 4.99 from Biophysical laboratory EPR centre (Josef Stefan Institute, Ljubljana, Slovenia) was used (Fig. 3.7). For the immobile part of the spin probe the order parameter was set to 1.00 and the rotational correlation time to 3 ns. Two different optimization steps were used (simplex optimization followed by Monte Carlo optimization). Spectra with an immobile part of nitroxide lower than about 15% could not be fitted with the used program with a high accuracy. Therefore in this study calculated amounts of mobile spin probe yield maximum values of about 80%.
Mobilization characteristics of the spin probe PCM were similar for tablets with both film coat compositions at lower coating levels (Fig. 3.8). Differences became more pronounced for tablets with an increased coating thickness. With an increased

amount of the water soluble PEG-PVA in film coat SR/IR:8/2 the hydration of the polymer film and thus water penetration into the tablet core is improved. Due to a lower diffusion path in tablets with a lower coating level this effect is less distinctive.

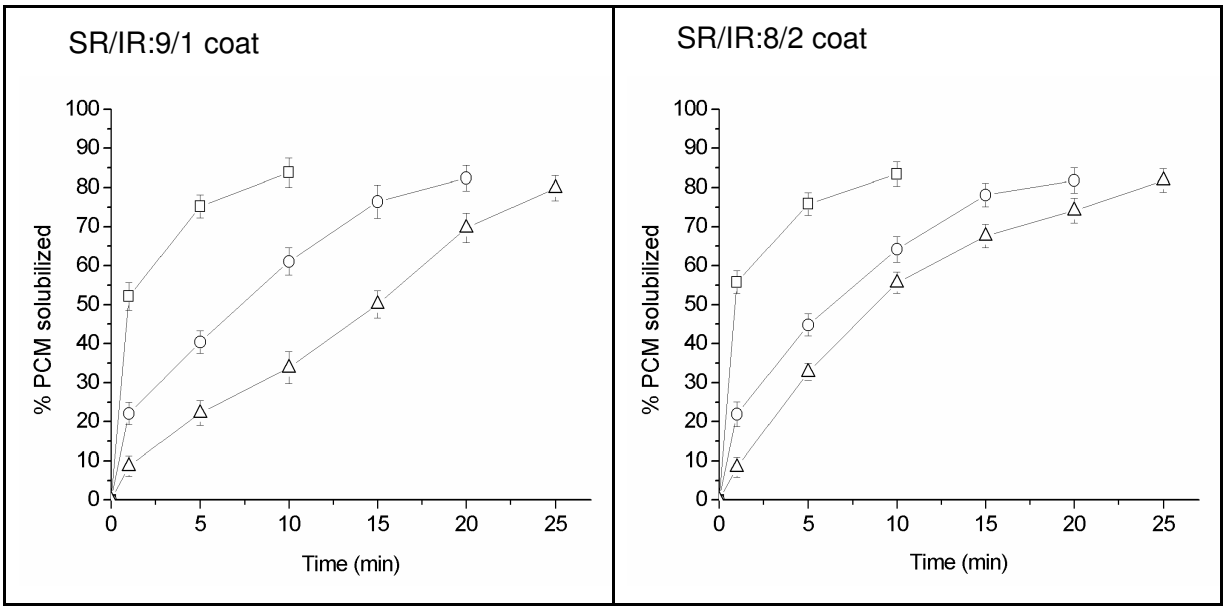


Fig. 3.8 Influence of coating level on water penetration into tablets with different coating formulations leading to mobilization of spin probe PCM (□ 4 mg, ○ 6 mg, Δ 8 mg polymer/cm²).

The results obtained from EPR experiments permit to draw conclusions regarding the drug release characteristics. As PCM and Propranolol HCl exhibit similar physical properties, their behaviour as a model drug in the tablet formulations will be comparable. Therefore, an amount at least 80 % of the spin probe PCM being dissolved within a time interval of 25 minutes for all tabet samples indicate, that approximately the same amount of Propranolol HCl within the tablet core is solubilized. At that time drug release is only marginal with values varying from 0.1 to 1.7 %, whereas the solubilization of the drug was nearly completed. Thus, the drug diffusion through the polymeric film coat represents the dissolution rate limiting step.

3.5 Conclusion

The present work regarding the mechanistic analysis of drug release contributes to a more profound understanding of permeation processes through polymer film coatings using non-invasive methods. The findings demonstrate, that for Propranolol HCl tablets with a coating formulation containing 20% PVA-PEG and 80% PVAc (related to each other as dry mass) a complete and sustained drug delivery is achieved within 24 hours with different release profiles. Water penetration into tablets occurs very rapidly as can be seen in a fast change in molecular mobility of the spin probe PCM for all tablet samples. In contrast to drug release, water permeation is only marginally dependent on PVA-PEG content, as changes in the molecular mobility of the micro environment of the spin probe PCM are detected within one minute for both coating formulations and show similar characteristics in further water permeation process. Differences in coating composition become slightly more pronouced at higher coating levels, as the permeability and hydration of SR/IR:8/2 film coats is increased due to a higher amount of the water soluble polymer Kollicoat® IR. These findings were also underlined by the results of the characterization of water uptake behaviour. For the first time the initial steps of diffusion processes through film coatings were monitored non invasively and continuously by using EPR spectroscopy.

In summary, the release rates depend on drug solubility, coating composition and coating level. Water penetration through the Kollicoat® SR and Kollicoat® IR based films occurs within few minutes. The penetrated water is able to solubilize water soluble molecules inside the tablet core efficiently. Water uptake continues in most cases for 1-2 h at a high rate and slows down thereafter. Drug release rates increase after the water penetration slows down. In conclusion the lag time of drug release does not contradict the observed rapid water uptake, because water transport is one way directed from outside to inside for the first 1-2 h. Drug release becomes only efficient after the tablet core is water saturated and the transport processes through the membrane become diffusion controlled in both directions.

4. Monitoring of dissolution induced changes in film coat composition

4.1 Introduction

As membrane controlled drug delivery coatings are subjected to changes in coating composition, it is necessary to characterize the process of leaching of water-soluble components in relation to drug release pattern for a deeper understanding of drug release mechanisms. The polymers of the coat will start to absorb water and swell after contact with an aqueous medium. Fast water penetration behaviour through polymer coatings with membrane controlled drug delivery were proved in chapter 3. Water permeates through the polymer film dissolving the drug inside the tablet core. Swelling of coating polymers will continue until an equilibrium state is reached between the achievement of hydration that will promote the diffusion and the elastic strength of the polymer on the opposite. As a second process dissolution of hydrophilic polymers occurs [73,84]. For this step a linear polymer or a sufficient hydrophilicity of the polymer is required so it can be solvated by the water in the dissolution medium. Furthermore, plasticizers may dissolve according to their solubility. The leaching of pore-formimg agents from the polymer coat into the dissolution media creates pores which control the release of drug molecules. Due to an osmotic pressure difference water permeation into the tablet will continue until the core is water saturated and the transport processes through the membrane become diffusion controlled in both directions. The water influx induced swelling of the tablet is leading to an expansion of the polymer network and by this to a further increased permeability of the film coat. Questions of interest of this thesis implied release characteristics of water soluble coating polymers in relation to drug release and thereby induced morphological changes of the polymer coating.

Even though coated oral dosage forms play today a very important role on the pharmaceutical market only few investigations have been performed referring to dissolution induced changes in coating composition. Some studies described the monitoring of the plasticizer leaching behaviour using HPLC or DSC [85,86]. Another possibility lies in the quantification of the dry weight loss of isolated films using gravimetrical methods [87,88]. A colorimetric molybdovanadophosphate method has

been applied to detect leaching of dibasic calcium phosphate from films based on aqueous acrylic latex [89]. Leaching of pectin from films consisting of pectin, chitosan and HPMC has been monitored by detecting pectin and its degradation products with a colouring reaction and subsequent measurement of the UV absorption [90].

^{1}H NMR spectroscopy was chosen to quantify the loss of Kollicoat® IR, Kollidon® 30 and triacetin in the film coats as it represents an accurate method for the quantification of organic components. It has already been used to determine the composition of poly(hydroxyethyl-L-asparagine)-coated liposomes, PEG-stabilized lipid nanoparticles and PEG-phosphatidylethanolamine in phospholipids mixtures [91-93]. Surprisingly no studies have been performed concerning the application of ^{1}H NMR spectroscopy in the field of coated oral dosage forms. Advantageous aspects are a simple sample preparation with no need for further isolation of each coating component before measuring and a rapid and easy achievement of results. Characterization of film coat attributes such as mechanical properties or the permeability of polymeric films is often performed by using free films prepared by casting or spraying [94-97]. To receive realistic results regarding the dissolution of soluble film coat components, singly one side of the polymeric film ought to have contact with the dissolution medium. The latter diffuses through the film coat leading initially to a flux into one direction, whereas afterwards the diffusion is directed in both ways. As the experimental set-up to mimic these conditions by using free films is potentially demanding, for ^{1}H-NMR and SEM experiments coated tablets were used, peeling the film coat off the tablet cores for the ^{1}H-NMR trials and analyzing the coated tablet surface by SEM respectively.

4.2 Materials

For ^{1}H-NMR and SEM experiments tablet samples with Propranolol HCl as a model drug and coated with SR/IR:9/1 and SR/IR:8:2 films of 4, 6 and 8 mg polymer/ cm² according to chapter 3.3.2 were used.

4.3 Methods

4.3.1 Monitoring of dissolution induced changes in film coat composition by means of ^{1}H NMR

In preparation for ^{1}H-NMR experiments tablets were placed into an automatic dissolution tester (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) with 0.1 N HCl for the first two hours and subsequently in phosphate buffer pH 6.8 as mentioned above. Tablets were removed after predetermined time intervals and the film coat was peeled off the tablet cores. Adhering particles of tablet core components were carefully removed with 1 ml distilled water and dried in an exsiccator for 24 hours. The dried films were dissolved in DMSO-D_6. ^{1}H NMR spectra were acquired from a 400 MHz ^{1}H-NMR spectrometer (Varian Gemini 2000, Varian GmbH, Darmstadt, Germany). ^{1}H-NMR experiments were performed fivefold according to the USP method [83].

For both water soluble polymer compounds (PVP and PEG-PVA) and plasticizer triacetin calibration curves were plotted by calculating the AUC of appropriate peaks in ^{1}H-NMR spectra of the component dissolved in DMSO-D_6 at different concentrations.

To study the linearity of the method, solutions with different Kollicoat® IR, Kollidon® 30 and triacetin content were analyzed by ^{1}H NMR. Fig 4.1 shows that the amount of each leachable component determined by NMR corresponds linearly with the concentration in the dilution series. Experiments were performed fivefold according to USP method [83].

The regression coefficient for all components was > 0.99. The developed ^{1}H NMR method is therefore suitable to accurately determine and monitor dissolution induced changes in coating composition.

Table 4.1 Regression coefficients regarding the linearity of the recovery rate and limits of detection for the leachable film coat components.

Leachable component	Kollicoat® IR	Kollidon® 30	Triacetin
Coefficient of determination (r^2)	0.9916	0.9975	0.9987
LOD (S/N 3:1)	9 µg/ml	5 µg/ml	6 µg/ml

The LOD for the developed ^{1}H NMR spectrosopic method was determined for a signal to noise ratio of 3:1 (Table 4.1). It was possible to monitor the decay of soluble components in the film coat for up to approximately 1 % of the initial concentration.

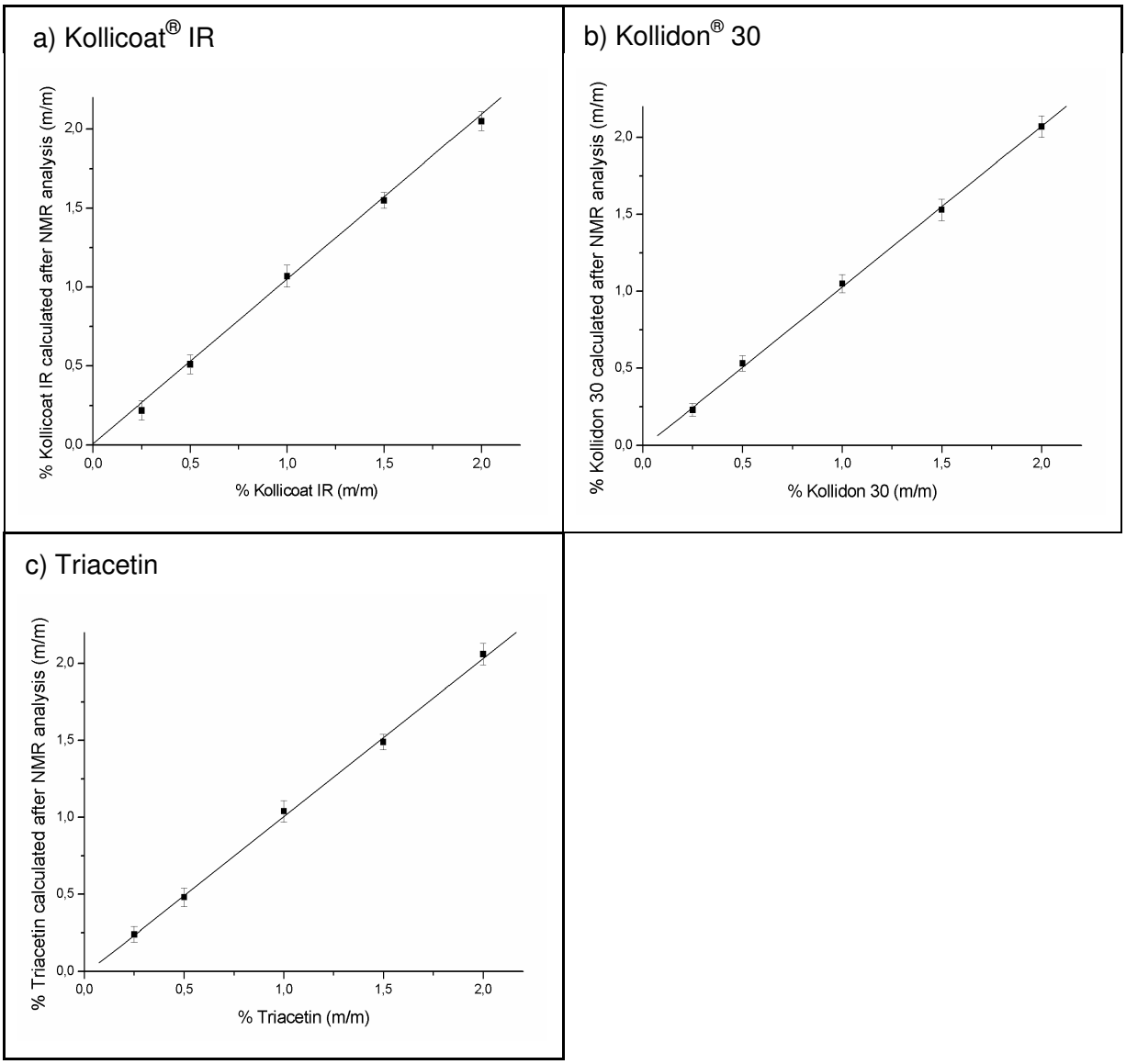


Fig. 4.1 Correlation between the percentage of the leachable film components in a dilution series and the calculated percentage after ^{1}H NMR analysis.

4.3.2 Monitoring of dissolution induced changes in film coat composition by means of SEM

SEM (Philips ESEM XL 30 FEG, Philips Electron Optics) of tablet surfaces was performed before and after exposure to dissolution medium in an automatic dissolution tester (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) and subsequent removal of absorbed water in an exsiccator for 48 hours. SEM micrographs were obtained by using WET-mode (1.7 mbar, acceleration voltage of 12 keV) and by the detecting secondary electron images.

4.4 Results and discussion

4.4.1 Monitoring of dissolution induced changes in film coat composition by means of ^{1}H NMR

^{1}H-NMR spectra of isolated films exhibited characteristic peaks of the polymeric components and the plasticizer triacetin (Fig. 4.2).

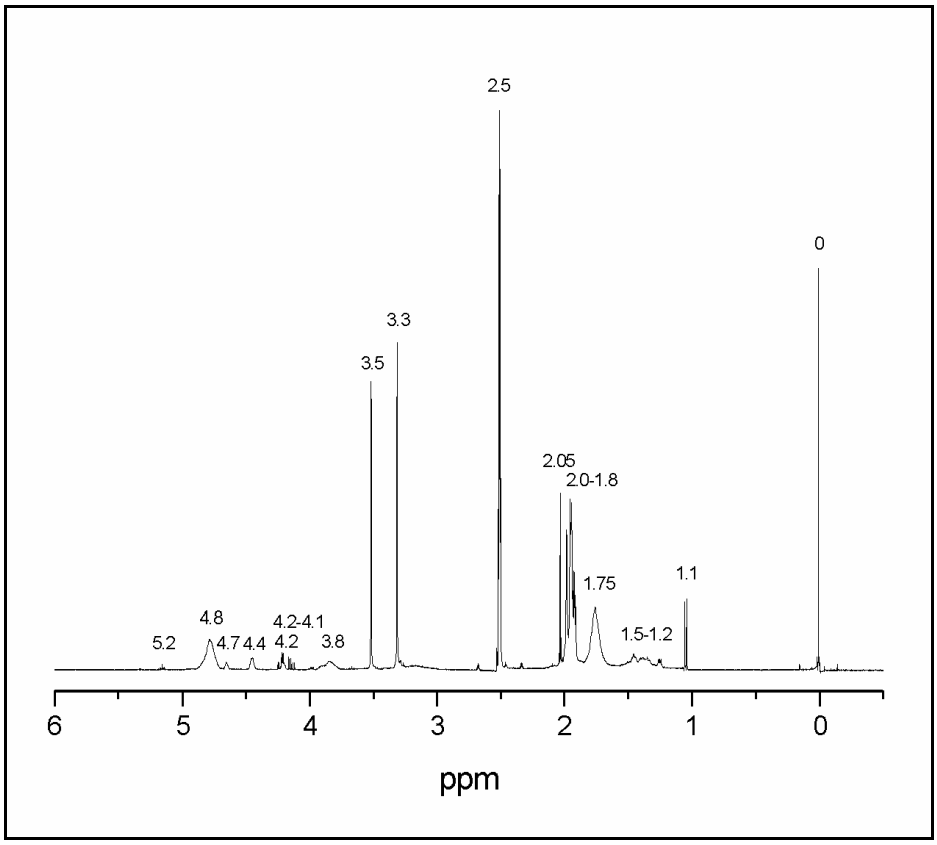


Fig. 4.2 ^{1}H-NMR spectrum of the coat SR/IR:8/2 before exposure to dissolution media.

The assignment of the respective ^{1}H NMR signals for each film component is presented in Fig. 4.3 and Table 4.2.

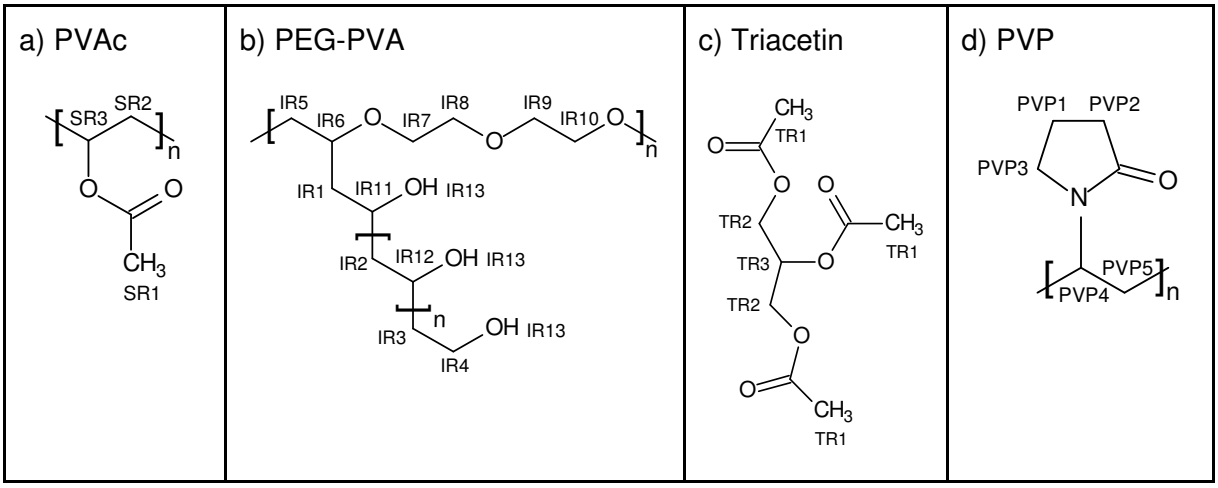


Fig. 4.3 Molecular structures of Kollicoat® SR, Kollicoat® IR, Kollidon® 30 and triacetin. The denominations SR, IR, PVP and TR indicate the type of molecule; the numbers indicate the assignment of the protons in the NMR spectroscopy (Fig. 4.3 and Table 4.2).

^{1}H NMR signals were identified by applying the H NMR predictor software (ACD/Labs, Advanced Chemistry Department Inc., Pegnitz, Germany) on ^{1}H NMR spectra of isolated film components. The complex structure of the film forming polymers hampered in some cases the assignment of the ^{1}H NMR signals. However, it was possible to identify for each leachable component a signal, which was sufficiently resolved and not superimposed by peaks from other coating ingredients or the partially deuterated solvent DMSO-d_6.

Table 4.2 Assignment of the signals in the ^{1}H NMR spectrum of the film coat.

Chemical shift	Assignment
0	TMS
1.1	Kollidon® 30: CH_3 vinyl end
1.2-1.5	Kollicoat® IR: IR1, IR2, IR3
1.75	Kollicoat® SR: CH_3 vinyl end
1.8-2.0	Kollicoat® SR: SR1, SR2
	Kollidon® 30: PVP1, PVP2, PVP5
2.05	Triacetin: TR1
2.5	partially deuterated DMSO
3.3	Kollidon® 30: PVP3
3.3-3.7	Kollicoat® IR: IR5-IR12
3.8	Kollicoat® IR: IR4
4.1-4.2	Triacetin: TR2
4.4-4.7	Kollicoat® IR: IR13
	Kollidon® 30: PVP4
4.8	Kollicoat® SR: SR3
5.2	Triacetin: TR3

For Kollicoat® IR the signal at 3.3 ppm, for triacetin the peak at 2.05 ppm and for Kollidon® 30 the peak at 1.1 ppm were used for calculating the extend of water soluble component leaching (Fig. 4.4).

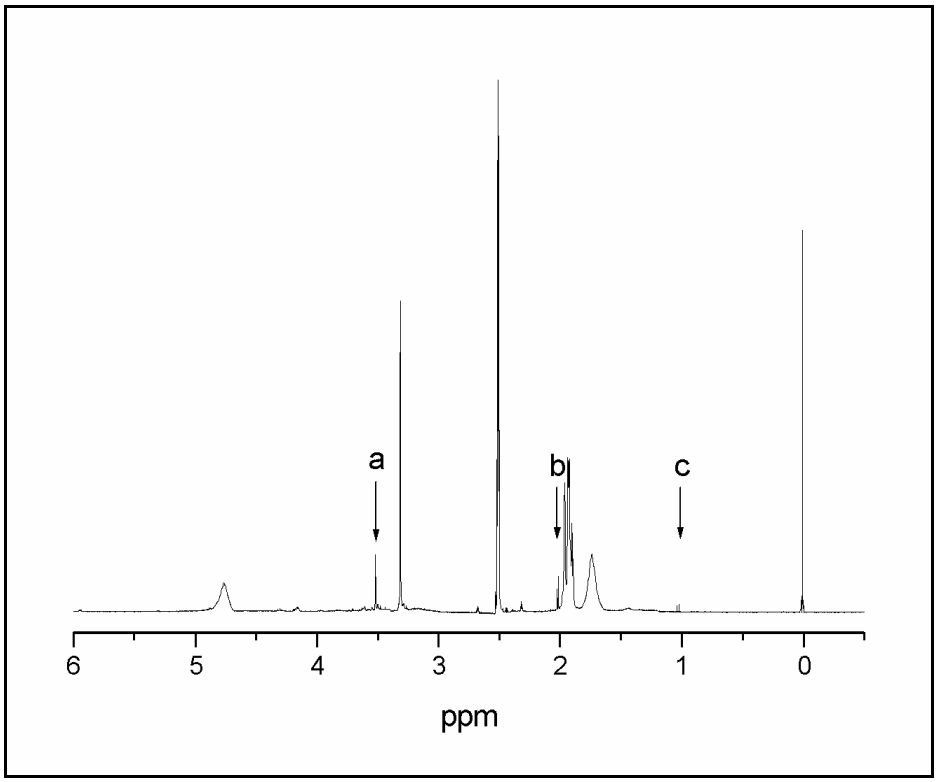


Fig 4.4 Reduction of relevant peaks for monitoring the leaching of a = Kollicoat® IR, b = Kollidon® 30, c = triacetin from film coat SR/IR:8/2 after 2 h of contact with dissolution medium.

The ^{1}H-NMR results indicated that, in contrast to PVAc exhibiting peaks in the range from 1.75 to 2 ppm, the concentration of the water soluble polymers PEG-PVA and PVP as well that of triacetin decreased with time in both coating formulations (Figs. 4.5 and 4.6). After a time interval of 16 h (SR/IR:9/1) and 5 h (SR/IR:8/2) respectively the water soluble coating polymers were no longer detectable. The difference in leaching times is a result of the lower PEG-PVA content in coating formulation SR/IR:9/1. Higher amounts of water soluble polymers lead to a more rapidly increased permeability, so that remaining polymers are leached out faster. In both formulations PVP was unhinged more rapidly. This may be caused by a better solubility due to the linear structure of the polymer compared to PEG-PVA exhibiting the structure of a graft copolymer with a comb-like structure.

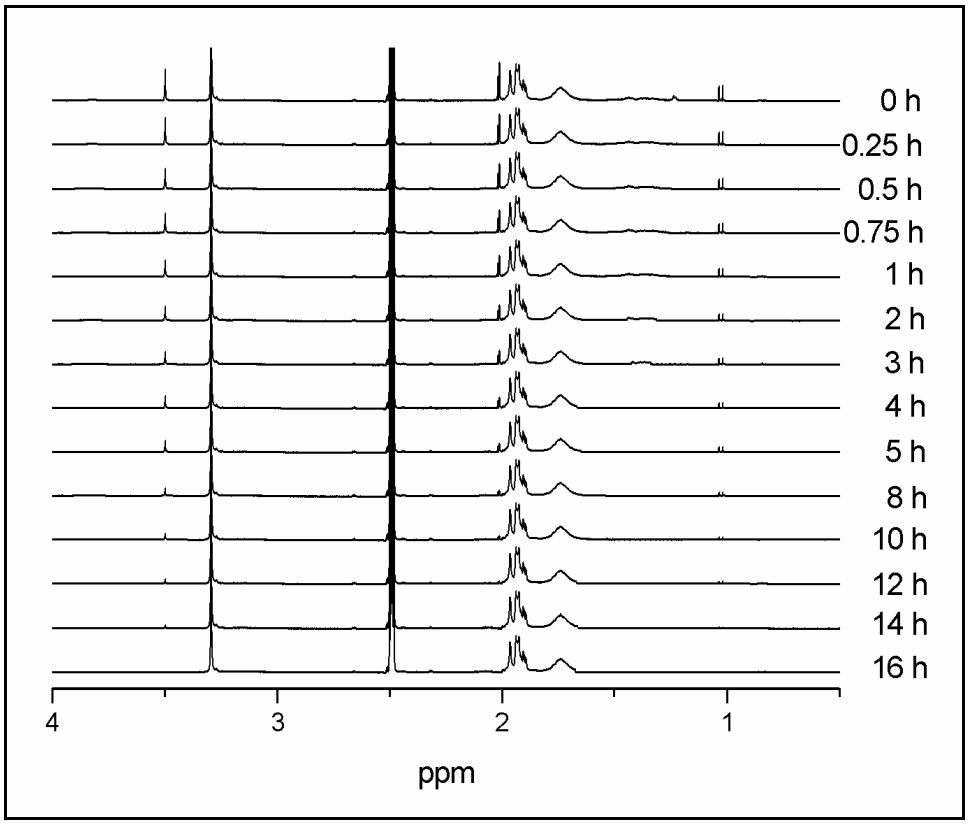


Fig. 4.5 Relevant section of ^{1}H NMR spectra of film coat SR/IR:9/1 after different intervals of contact with dissolution media for monitoring the leaching of water soluble components.

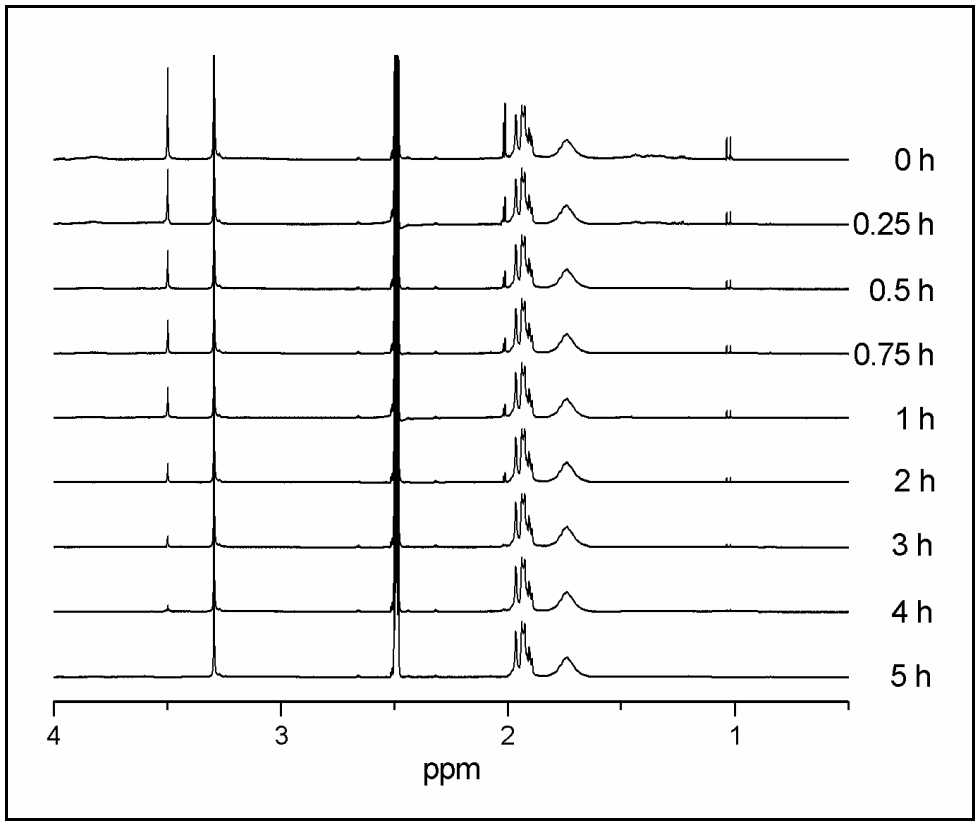


Fig. 4.6 Relevant section of ^{1}H NMR spectra of film coat SR/IR:8/2 after different intervals of contact with dissolution media for monitoring the leaching of water soluble components.

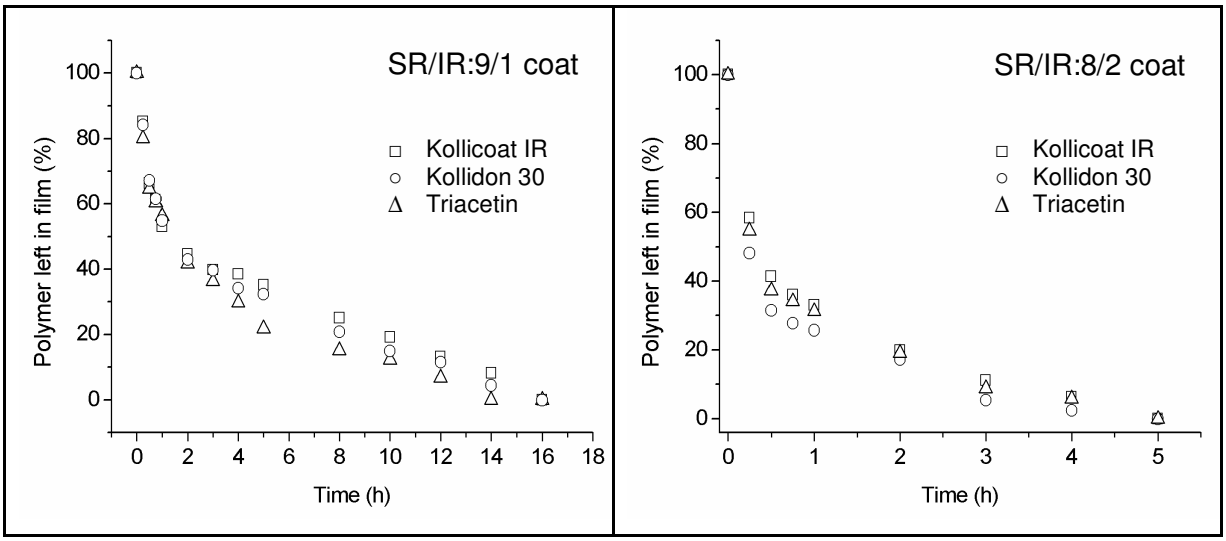


Fig. 4.7 Time dependent decay of Kollicoat® IR, Kollidon® 30 and Triacetin concentration in SR/IR:9/1 and SR/IR:8/2 films.

To quantify the amount of dissolved coating ingredient the AUC of the respective peaks was calculated and plotted against the time (Fig. 4.7). Interestingly, the leaching behaviour of all three substances proved to be very similar. Even though triacetin exhibits a lower hydrophylicity similar leaching characteristics were monitored. This might be a result of the smaller molecular size compared to the polymeric components. In both formulations Kollidon® 30 was released more rapidly, which may be due to the linear structure of the polymer compared to Kollicoat® IR with the structure of a graft copolymer.

Significant differences were found for the absolute time required for the leaching of water soluble film ingredients. Leaching time tripled for the release from films with coating composition SR/IR:9/1 compared to film coats with increased Kollicoat® IR content.

To recieve further information on the leaching characteristics of water soluble film components, results obtained by ^{1}H NMR spectra were fitted to both monoexponential and biexponential decay curves (Fig. 4.8). Obviously, the decay in soluble polymer concentration and plasticizer triacetin were found to be governed by biexponential characteristics with a fast decrease for the first 30 minutes (SR/IR-8/2) and 60 minutes (SR/IR-9/1) respectively, followed by a slight decay over several hours.

The change in leaching characteristics over time may be due local heterogeneities of the local concentrations. Areas with high concentrations of each water soluble polymers and triacetin respectively will dissolve quickly. In contrast, water soluble

Kollidon® 30 and Kollicoat® IR molecules which are entangled within a Kollicoat® SR network will need more time to detangle and to leave the film.

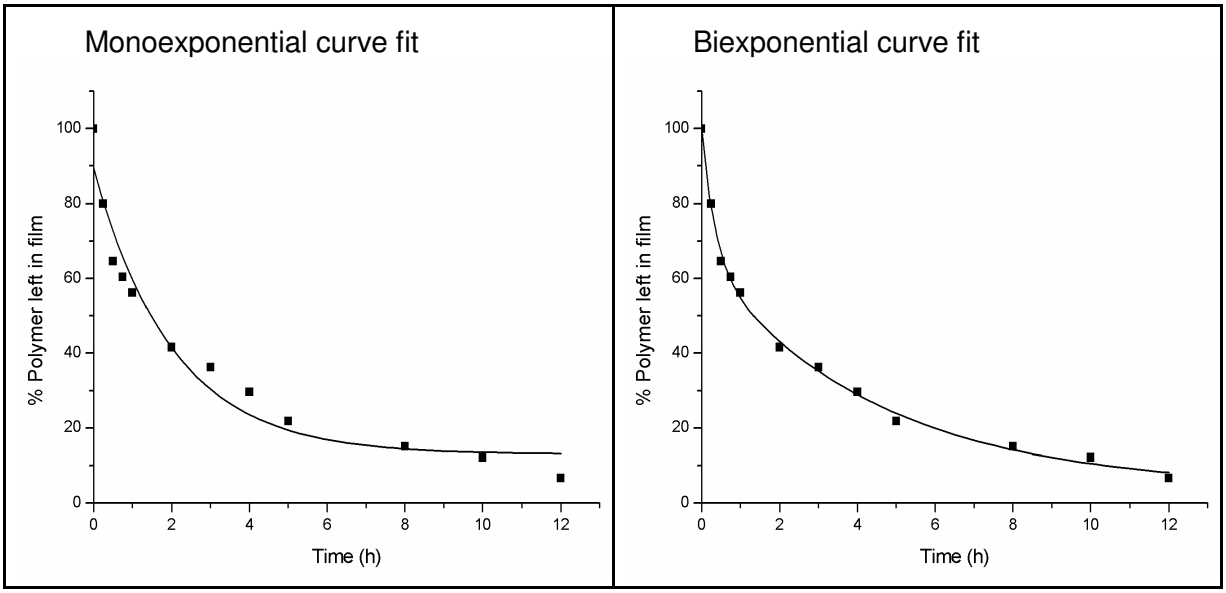


Fig. 4.8 Leaching characteristics of triacetin in SR/IR:9/1 film subjected to monoexponential and biexponential fit as an example .

For a deeper analysis of polymer dissolution characteristics elimination rate constants (k_e) for PEG-PVA, PVP and triacetin were calculated using the feathering method (Fig. 4.9).

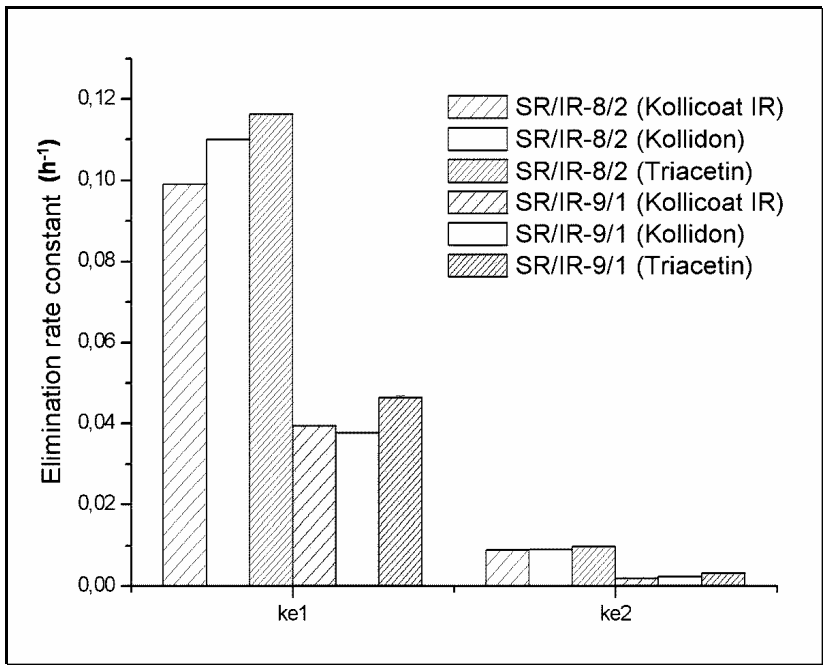


Fig. 4.9 Elimination rate constants of Kollicoat® IR, Kollidon® 30 and triacetin in coating film SR/IR-8/2 and SR/IR-9/1.

Elimination rate constants of Kollicoat® IR and Kollidon® 30 showed among each other similar values in the respective case for fast and slow soluble polymer decay in each coating composition, which might be due to similar solubility characteristics of both water soluble polymers. Only k_{e1} of both polymers in coating composition SR/IR:9/1 showed slight differences. Differences in k_{e1} were for both water soluble polymers in coating composition SR/IR:8/2 related to SR/IR:9/1 about 3:1 and in k_{e2} about 10:1. Obvious differences in polymer concentration decay at the beginning increase even more with continuing dissolution medium contact. PVP and PEG-PVA molecules on or near the tablet surface are solubilized fast and contribute to a fast decay in soluble polymer concentration (k_{e1}). As the distance of PEG-PVA and PVP to the tablet surface increases, dissolution of polymers becomes more and more permeability controlled (k_{e2}).

4.4.2 Monitoring of dissolution induced changes in film coat composition by means of SEM

SEM images showed a relatively rough coating surface, which exhibited a much smoother appearance after exposure to water due to rapid water penetration into the olymer coating and subsequent swelling (Fig 4.10). This effect, caused by the enormous plasticity of poly(vinyl acetate) might be the reason for the stated self-repairing mechanism of Kollicoat® SR, that was reported to ensure an unchanged dissolution profile even after mechanical stress [98,99].

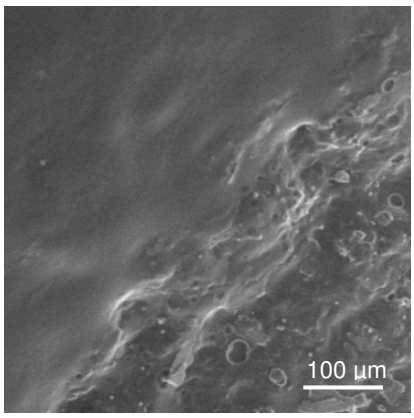


Fig. 4.10 Scanning electron micrograph of SR/IR:8/2 coat before (down right) and after exposure to water (up left).

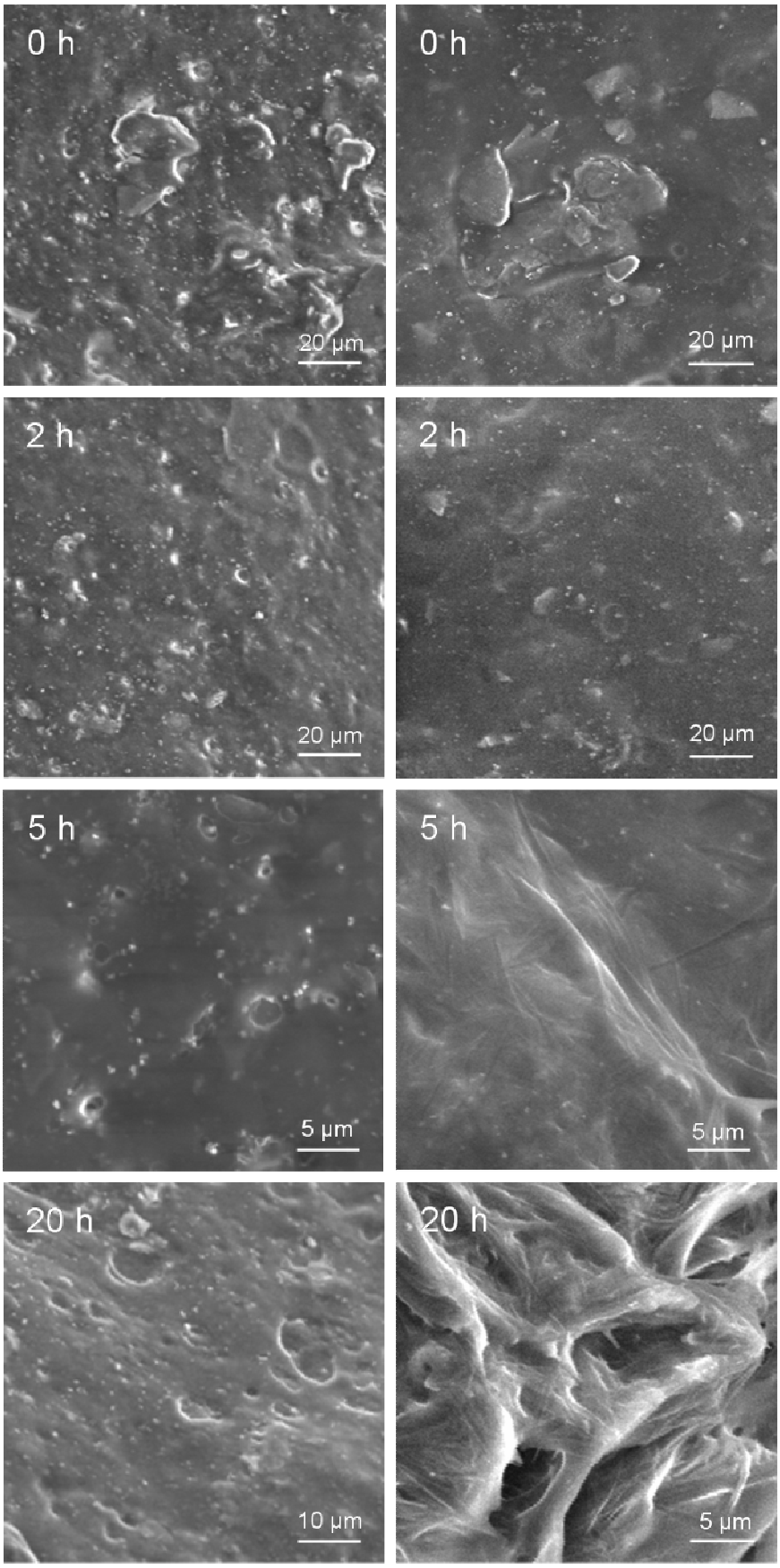


Fig. 4.11 SEM images of tablet surfaces after different time periods of contact with dissolution media.

SEM images of untreated coated tablet surfaces (Fig. 4.11, 0 h) with both coating compositions exhibited a relatively rough coating surface, which was due to water insoluble pigment particles, that are gradually washed off the tablet surface after exposure to dissolution medium (Fig. 4.11, 2 h). Therefore, after two hours of contact with dissolution medium only very slight morphological changes were visible.

Significant differences in coating morphology were monitored after five hours of contact with dissolution media. SEM micrographs of SR/IR:8/2 coated tablets revealed morphological changes in the structure of the coating surface, which were related to an alteration in coating composition (Fig. 4.11, 5 h and 20 h). Due to a leaching out of the water soluble polymers PVP and PEG-PVA the remaining coating polymer PVAc abounds. SEM micrographs exhibited after five hours emerging PVAc polymer strings while in ^{1}H-NMR spectra at that time characteristic peaks for poly(vinyl pyrrolidone) and PEG-PVA were no longer detectable. Surprisingly no pores on the tablet surface caused by leaching of water soluble components were visible. The continuing water diffusion through the polymer coating into the tablet core resulted in a strong swelling of the tablet. SEM images exhibited after twenty hours a strong emerging of the water insoluble polymer PVAc with an expanded polymer network at the end of the dissolution test. Thus the increased permeability of the SR/IR:8/2 coat was visualized. In contrast to this, the tablet surface of SR/IR:9/1 coated tablets was only subjected to minor changes. After 20 hours of contact with dissolution media only some small pore-like structures were observed. Compared to tablet samples with SR/IR:8/2 coat the surface structure exhibits a compact and less permeable appearance. These findings are in good agreement with the drug release profiles discussed in chapter 3.4.1, showing nearly complete Propranolol HCl release for tablet samples with SR/IR:8/2 coat and less than 15 % for those being coated with SR/IR:9/1.

4.5 Conclusion

The dissolution induced changes of the film composition were related to Propranolol HCl release rate, which increased when approximately 80 % (SR/IR:8/2) or 90% (SR/IR:9/1) of both PEG-PVA and PVP as well as triacetin had been released. This divergence was caused by a lower total amount of water soluble polymers in coating composition SR/IR:9/1. Propranolol HCl was not able to permeate through the film coat when PEG-PVA and PVP are leached only in the outer parts of the polymer film as lag times prior to drug release continued after the fast decay of soluble polymer concentration. Water soluble polymers had to dissolve even in the area near the tablet core to create a higher porosity of the film coat. Permeability of the whole coating layer was now high enough to allow increased drug diffusion. It was shown, that the developed ^{1}H-NMR spectroscopy proved to be an appropriate tool for monitoring quantitative changes in coating composition. SEM experiments underlined these findings revealing morphological changes of the coating surface. Drug release kinetics were related to dissolution induced changes in coating composition. Permeability of the film coat increased, when about 90 % of the water soluble polymers and plasticizer triacetin were leached out of the film coat.

5. Development and characterization of poly(vinyl acetate) coated floating tablets

5.1 Introduction

Until now numerous oral controlled drug delivery systems have been developed to prolong drug release. The crucial point in this respect is that the drug has to be absorbed well throughout the whole gastrointestinal tract. Generally, the absorption of active pharmaceutical ingredients from oral drug delivery systems is related to gastrointestinal tract transit time. Physiologically, oral dosage forms exhibit a relatively short transit time in these anatomical segments. The retention of oral dosage forms in the upper gastrointestinal tract causes a prolonged contact time of drugs with the gastrointestinal tract mucosa. This results in a higher bioavailability and therapeutic efficacy, reduced time intervals for drug administration, a potentially reduced dose size and thus an improved patient compliance [100]. Therefore, gastric retentive devices may be used as extended release drug delivery systems as well [101]. Gastroretentive DDSs exhibiting controlled drug release are of particular interest for drugs that are absorbed incompletely due to a relatively narrow region for absorption in the gastrointestinal tract, such as cyclosporin, ciprofloxacin and furosemide [102-105]. Drugs that are less soluble or are degraded in a higher-pH environment such as verapamil HCl and captopril respectively may also benefit from gastric retention [106-109]. Furthermore, the application of gastric retentive devices to drugs acting locally in the stomach (e.g. antibiotics against *Helicobacter Pylori* and misoprostol) are of great interest [110-112]. Drugs exhibiting saturation kinetics regarding their absorption mechanism like cefuroxim axetil may also benefit from gastric retention [113]. In general the group of drugs, that benefits from an oral application using a gastroretentive DDS, includes analgesics except NSAIDs due to their gastric ulcer-causing potential, antibiotics, tranquilizers, diuretics, antidepressants, vitamines, hormones, antacids and antiparkinsonian drugs [6].

Even though gastric retentive systems have been in the focus of interest of many research groups for the last three decades, up to now only a few systems are available on the market: Madopar® HBS, Valrelease®, Gaviscon® Liquid, Topalkan®

and Almagate Flot-Coat® [114-116]. Obviously many obstacles have to be overcome to ensure a reliable function of the gastroretentive device.

In the fasted state the pylorus is closed retaining particles larger than 1-2 mm in the stomach. The gastric retention of a dosage form is related to the physiological conditions and mechanisms affecting the transit times of gastric contents. Gastric emptying may be classified into emptying of liquids, digestible and indigestible solids, whereas solid oral dosage forms are among the latter as they do not possess any significant caloric value [117,118]. The emptying of liquids is governed by muscular contractions of the fundus and follows first order kinetics. Digestible solids are emptied after being thickened to chyme by peristaltic waves of the fundus. The pylorus closes as the muscular contractions approach the antrum, retaining large solid particles as well as indigestible solids until they are further reduced in size. Indegistible solids are emptied from the stomach at regular intervals by the powerful contractions of the IMMC, the so-called housekeeper waves. The cut-off size for particles to be retained in the stomach in this case has been reported as 12.8 ± 7 mm [119,120]. Streubel et al. estimated, that dosage forms should exhibit a minimum size of 13 mm for being retained in the stomach, though even devices with a bigger size were reported to be emptied through the pylorus [121].

Gastric transit times are strongly related to ingestion, whereas the retention of oral dosage forms in the stomach can be correlated with the time period within which the subject remains in the fed state [122]. Regarding the gastric emptying in the fasted state fatty acids such as oleic acid have been reported to significantly contribute to a delay in gastric transit [123,124].

As the retention of a dosage form in the stomach is working against GI tract physiology, some efforts have to be made to ensure that further transport via the pylorus is prevented. Being aware of the physiological conditions in the stomach, various approaches for gastroretentive dosage forms have been proposed including

- mucoadhesive [125,126]
- swelling and/or expanding [127-129]
- and floating systems [130-132].

The development of mucoadhesive gastroretentive devices is based on binding characteristics of various materials such as poly(acrylic acid), chitosan, tragacanth, cholestyramine, sucralfate, polylactic acid and dextran on the mucous membrane

[133-136]. Due to the constant mucus secretion in the stomach and therefore the removal of the mucus from the gastric mucosa, the binding of polymeric components of a DDS to mucin does not always imply gastric retention [122].

Expandable gastroretentive devices have to meet the following standards: a dosage form small enough to be swallowable, an expansion to a size exceeding the aperture of the pylorus and a degradation of the dosage form after completed drug release to avoid an accumulation within the stomach. Systems unfolding in the stomach are mostly fit into gelatin capsules or a gelatin band is used to fix the folded arms of the gastroretentive device [127,137-141]. The increased size of the dosage form is supposed to retain it the stomach. Since the pylorus works as a sphincter, the reported diameter of its aperture of 12.8 ± 7.0 mm is subjected to broad interindividual fluctuations [142]. Due to the strong contractions of the migrating myoelectric complex the ingested dosage form may possibly pass the stomach. Expandable gastroretentive devices imply the risk of unfolding in the esophagus during swallowing and therefore potentially causing serious complications. In contrary, systems expanding too slowly may pass the pylorus before being completely expanded and thus fail gastric retention [122].

Another technological approach for the realization of gastric retentive dosage forms lies in the development of floating devices. Floating dosage forms are floating due to an intrinsic density lower than that of the gastric content, which is reported as 1.004-1.010 g/cm^3, or due to the formation of a gaseous phase inside the system after contact with gastric fluid [143]. This attribute allows them to remain afloat on the surface of the gastric content for a longer period of time without affecting the rate of emptying. A major drawback lies in the fact, that floating DDSs are bound to subjects in the fed state and the administration of sufficient liquid, as a gastric content to float on is required [144]. Up to now the results of in vivo studies regarding the efficacy of floating devices are not consistent. Various authors state that floating of the dosage form does not significantly lead to prolonged gastric retention times or improved bioavailability [122,130,145-147]. Thereby, pharmacokinetic changes were most likely rather attributed to the presence of food than the floating abilities of the dosage form. By contrast, floating devices were shown to offer the advantage of being expelled less likely from the stomach by the MCC compared to sinking devices of the same size [148,149]. Additionally, different authors stated prolonged gastric retention and increased bioavailability for floating DDSs [150-156]. It has to be pointed out,

that up to the present no adverse effects have been reported regarding floating drug delivery systems.

As for a reliable retention behaviour in the stomach food effects and the complex motility of the stomach are of vital importance, only convincing in vivo data can proof the retention efficacy and improved bioavailability of a gastroretentive system, [107,157-162]. As already mentioned, all GRDFs have to withstand the forces excerted by the migrating myoelectric complex. Therefore, the focus of this work lay on the development of a gastrorententive dosage form exhibiting an enhanced mechanical strength.

Regarding the preparation of floating DDSs various approaches can be found in the literature, whereas single unit and multiple unit floating devices are to be distinguished. The hydrodynamically balanced system was the first floating single unit dosage form described by Sheth and Tossounian, consisting of a swellable capsule formulation being composed of drug, hydrocolloids and a mixture of other excipients [163-165]. In general, HBS formulations are characterized by a swellable hydrocolloid forming a device, in which the drug is homogeneously incorporated. As floating and drug release mechanism will often interact, the optimization of floating DDSs was continued by developing bilayer floating formulations consisting of a drug release controlling and a buoyancy supporting layer [112,166-168]. In this case it is possible to adjust both floating characteristics and drug release profiles separately.

Floating of a DDS may also be achieved by the development of matrix tablets or microparticles based on a low density foam powder or hollow spheres exhibiting a lower density compared to gastric contents [132,169-172].

The incorporation of gas generating components in the formulation represents a widely used method for the development of floating drug delivery systems, whereas the gas is entrapped within the device leading to the required lower density of the system compared to gastric contents [131,173-175]. Gas generating excipients often include sodium bicarbonate and sodium carbonate, whereas these components either react with the hydrochloric acid in the stomach or citric acid or tartaric acid being incorporated in the tablet core [106,131,176,177]. Hereby, the developing carbon dioxide may be entrapped in a swelling polymer such as HPMC, methyl cellulose, alginates and chitosan or in a tablet or pellet core surrounded by a polymeric film coat forming a kind of balloon [25,146,153,174,178-181].

In vivo studies reporting increased gastric retention times for floating capsules of size 000 compared to smaller floating and non-floating capsules were seized as suggestions to develop floating tablets, which are additionally gaining size due to carbon dioxide development inside the core [148,149]. In this case, not only the floating characteristics of the developed devices will contribute to the efficiency of gastric retention but the increase in tablet size as well, the latter becoming more important in the phases the stomach is emptied. Therefore, in this chapter a floating oral drug delivery system consisting of a sodium bicarbonate containing tablet core covered by a polymeric film coat to obtain a membrane controlled drug delivery device is described.

The formulation was characterized by a biplanar tablet core with beveled edges consisting of Propranolol HCl as a highly water soluble model drug and sodium bicarbonate as a CO_2 developing agent. Kollidon® SR was chosen as an excipient for direct compression leading to a high tablet hardness at low compression forces while the density of the tablet core was relatively low [38]. HPMC-based CO_2 developing matrix tablets were reported to float less than 6 hours with an accelerated drug release at the end of the floating period due to erosion of the devices [182]. Therefore, the tablet cores were coated to prevent unintentional disintegration and uncontrolled drug release. The coating formulation consisted of Kollicoat® SR as a water insoluble polymer and Kollicoat® IR as a hydrophilic water soluble polymer with two different compositions to receive a drug delivery system with membrane controlled drug release. Most recently, carbon dioxide developing minitablets coated with an acrylic polymer coat consisting of Eudragit© RL 30 D were reported to exhibit an increased drug release after a certain period of time, which was due to the visually observed formation of cracks in the film coat [183]. Obviously, Eudragit© RL 30 D fails to resist the forces emerging from the expansion of the tablet due to the CO_2 development inside the tablet core. Disintegration of Eudragit© RL 30 D coated CO_2 producing tablets was also observed when plasticized with TEC, but could be overcome by blending different amounts of Eudragit© RL 30 D and Eudragit© NE 30 D [129]. As the formation of cracks in polymer films is related to the loss of functionality concerning the floating and the drug retaining abilities, Kollicoat© SR was chosen as the membrane forming excipient due to its exceptional elasticity of the polymer film [25]. PVAc was expected to resist the mechanical stress exerted by the formation of carbon dioxide in the tablet core, as a successful development of

CO_2 producing and poly(vinyl acetate) coated pellets, which were directly compressed into tablets was already reported [24,25,174]. The chosen coating level varied from 10 to 20 mg polymer per cm^2. After contact with an acidic medium comparable to the conditions in the stomach the hydrochloric acid was expected to diffuse through the polymer coat and initialize CO_2 development inside the tablet, leading to a reduced density of the tablet and floatation of the system.

The penetration of hydrochloric acid through the polymer film into the tablet core and subsequent formation of carbon dioxide play a vital role regarding the floating characteristics as well as the hydration of the tablet core being related to the initiation of drug dissolution. Therefore, the monitoring of these processes leads to a deeper understanding of floating and drug release mechanisms. Studies regarding the characterisation of swelling and hydration processes of matrix devices have already been performed [55-57]. Although the application of Magnetic Resonance Imaging to monitor drug delivery processes is widely accepted, the method is scarcely used due to high investment and running costs of superconducting MRI machines. NMR benchtop instruments capable of imaging have been developed very recently. Compared to superconducting standard MRI machines they are much more affordable due to lower price and running costs. In this thesis the benchtop MRI instrument was used to monitor diffusion and swelling processes as well as carbon dioxide development inside the polymer shell.

In terms of floating characteristics of gastroretentive devices not only the onset and duration of flotation plays a major role, but also the ambition of the system to float. Although many studies in the field of floating gastroretentive drug delivery systems have been performed, the characterisation of the floating strength has been neglected in many studies [184-189]. By default, most publications only report the detection of floating period and lag times prior to floating. Up to now, floating strength measurements were only conducted by a small group of scientists [190-194]. As the presence of food in the stomach might increase the viscosity heavily, higher floating forces increase the probability of the tablet to remain afloat, reducing the effects of food viscosity on tablet retention. Therefore the floating strength of the developed systems was monitored using a simplified apparatus according to Timmermans and Moës, measuring the floating strength of a device as the resultant weight [190,192].

5.2 Materials

Propranolol HCl, sodium bicarbonate, magnesium stearate, triacetin and talc were obtained by Sigma Aldrich (Taufkirchen, Germany). Propranolol HCl and sodium bicarbonate were grinded thoroughly in a mortar and passed through a 250 µm sieve. Titanium dioxide was received from Kronos Titan GmbH & Co. OHG, Leverkusen, Germany. Kollidon® 30, Kollidon® SR, Kollicoat® SR 30 D and Kollicoat® IR were supplied by BASF (Ludwigshafen, Germany) and were used as received.

5.3 Methods

5.3.1 Tablet core preparation for preliminary trials

5.3.1.1 Optimization of excipient composition

Preliminary trials regarding the floating characteristics of different excipient blends compressed into tablets were carried out to identify the ideal excipient composition for the development of floating tablets. Therefore, sodium bicarbonate was blended with different amounts of Kollidon© SR to receive powder mixtures with different $NaHCO_3$/Kollidon© SR ratios according to Table 5.1. Magnesium stearate was added as a lubricant. The powder blend was compressed into tablets of 350 mg exhibiting a diameter of 12 mm using an excenter tableting machine (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany). Therefore the powder mixture was manually weighed and hand filled into the die of the tableting machine. Half the tablets of each formulation were subjected to curing conditions of 60 °C in an incubator (Heraeus B6760, Heraeus Instruments GmbH, Hanau, Germany) for 2 h.

Table 5.1 Composition of tablet cores for preliminary floating experiments without model drug.

$NaHCO_3$/Kollidon© SR (m/m)	**1/1**	**1/2**	**1/3**	**1/4**
$NaHCO_3$ (g)	49.5	33	24.75	19.8
Kollidon© SR (g)	49.5	66	74.25	79.2
Magnesium stearate (g)	3.5	3.5	3.5	3.5

Floating behaviour and disintegration characteristics were evaluated visually by positioning tablet samples in a beaker with 100 ml 0.1 N HCl of 37 °C being agitated in a shaking water bath (GFL 1083, Gesellschaft für Labortechnik GmbH, Burgwedel, Germany) working at 45 movements per minute. All experiments were performed in triplicate.

5.3.1.2 Optimization of drug content and crushing forces

To evaluate the appropriate drug amount of the floating tablet, further trials were performed with varying Propranolol HCl amounts blended with the optimized excipient premix. The powder mixture for the manufacturing of the tablets was prepared according to Table 5.2 by blending Propranolol HCl, sodium bicarbonate and Kollidon® SR for 10 minutes in a z-arm mixer (AR 400, Erweka GmbH, Heusenstamm, Germany). Powder mixtures with a Propranolol HCl content of 33 % (A), 25 % (B), 20 % (C) and 10 % (D) were obtained. After adding magnesium stearate the mixture was blended for another 2 minutes. Biplanar tablets measuring 11 mm in diameter were prepared by direct compression using a single punch tableting machine (Korsch EK0/DMS, Korsch Pressen GmbH; Berlin, Germany). The compression force was adjusted to receive tablets with a crushing force of 75 N, 100 N and 150 N respectively. Radial crushing forces were determined as an average of 10 tablets using the crushing force tester TBH 30 (Erweka GmbH, Heusenstamm, Germany). Temperature treatment and floating experiments were performed as described above.

Table 5.2 Composition of tablet cores for preliminary floating experiments with model drug Propranolol HCl.

Formulation (Propranolol HCl content)	**A (33 %)**	**B (25 %)**	**C (20 %)**	**D (10 %)**
Propranolol HCl (g)	116.5	87.5	70	35
$NaHCO_3$ (g)	46	51.8	55.3	62.3
Kollidon© SR (g)	184	207.2	221.2	249.2
Magnesium stearate (g)	3.5	3.5	3.5	3.5

5.3.2 Preparation of optimized tablet cores

The powder mixture for the manufacturing of the tablets was prepared according to Table 5.3 using the same procedure as described in chapter 5.3.1.2. Tablets with beveled edges measuring 11 mm in diameter were prepared by direct compression using a single punch tableting machine (Korsch EK0/DMS, Korsch Pressen GmbH, Berlin, Germany). Compression force was set to 6 kN to receive tablets characterized by a crushing force of 75 N ± 4 N. The crushing force was determined using an Erweka TBA 30 crushing force tester (Erweka GmbH, Heusenstamm, Germany). Tablets were then stable enough to resist the mechanical forces in the drum coater and showed a low friability of 0.1 %. The friability was determined as an average of 5 tablets being weighed before and after 100 rotations of the friability tester (Abriebtester, Arzneimittelwerk Dresden, Germany) according to the Ph. Eur. [195].

Table 5.3 Composition of tablet cores.

Tablet components	Amount (mg)
Propranolol HCl	35.0
Kollidon® SR	249.2
Sodium bicarbonate	62.3
Magnesium stearate	3.5

5.3.3 Coating of tablet cores

To investigate the influence of Kollicoat® IR content on drug release and floating characteristics coating formulations with different Kollicoat® SR / Kollicoat® IR ratios (SR/IR:9/1, SR/IR:8.5/1.5 and SR/IR:8/2), related to each other as dry mass, were produced. Coating dispersions were prepared according to the compositions shown in Table 5.4. The preparation of the coating suspensions was carried out according to chapter 3.3.2.

The coating process was carried out in a drum coater (Lab-Coater GC 300, Glatt Maschinen- und Apparatebau AG, Pratteln, Switzerland). Process parameters adjusted for the coating of the tablet cores are given in Table 5.5. Tablet samples were taken at 10, 12, 14, 16, 18 and 20 mg polymer/cm² coating level respectively.

Table 5.4 Coating compositions with different Kollicoat® SR/Kollicoat® IR ratios.

Kollicoat®SR / Kollicoat®IR ratio	**9/1**	**8.5/1.5**	**8/2**
Kollicoat® SR 30 D	496.0	496.0	422.0
Kollicoat® IR	16.5	22.3	26.0
Triacetin	7.0	7.0	7.0
Kollidon® 30	5.0	5.0	5.0
Titanium dioxide	5.0	5.0	5.0
Talc	35.0	35.0	35.0
Distilled water	435.5	429.7	475.0

Table 5.5 Coating process parameters.

Coating parameter	**Adjustment**
Inlet temperature	50 ° C
Process air	100 m³/h
Atomizing air pressure	2 bar
Spray rate	7.5 g/min
Pan speed	7 rpm

5.3.4 Monitoring of the floating strength

To monitor in vitro the total vertical force *F* working on an immersed object an experimental setup using an apparatus simplified according to Timmermans and Moës was used (190,192). As the force *F* determines the resultant weight of the floating tablet, it may be used to quantify and thus to further characterize floating behaviour. The magnitude and direction of force *F* and thus the resultant weight of the floating object is determined by the vectorial sum of the gravity (F_{grav}) and buoyancy (F_{buoy}) forces acting on the tablet,

$$F = F_{buoy} - F_{grav} \qquad (2)$$

$$F = d_f \cdot g \cdot V - d_s \cdot g \cdot V = (d_f - d_s) \cdot g \cdot V$$

$$F = \left(\frac{d_f - m}{V} \right) \cdot g \cdot V$$

where F is the total vertical force, g the acceleration of gravity, d_f the density of the fluid, d_s the density of the tablet, m the tablet mass and V the tablet volume. For positive values of F the resultant force is directed upwards and thus leads to floatation of the system.

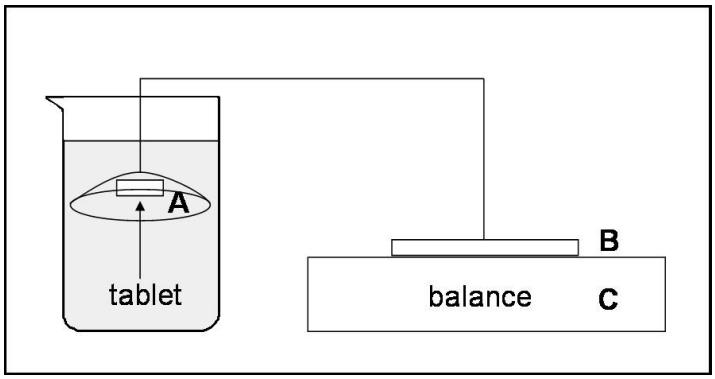


Fig. 5.1 Experimental setup for the determination of the floating strength (A = sample holder, B = metal base, C = analytical balance).

The instrument used to determine the floating strength of the tablet samples measured the force equivalent to F required to maintain the tablet totally submerged into the dissolution medium (Fig 5.1).

A sample holder (A) was connected to a metal base (B) placed on an analytical balance (C) via a metal pole. For the performance of floating strength experiments the tablets were placed in a beaker with 0.1 N HCl of 37 °C, so that the sample holding device was covered with dissolution medium. After the positioning of the tablet in the dissolution medium and subsequent taring of the analytical balance the sample was shifted under the sample holder. The floating strength was then determined as the weight diminution on the analytical balance over time. Floating experiments were performed in triplicate.

Furthermore, the floating lag time was measured in conjunction with the dissolution experiments. FLT is defined as the time taken by the tablet to reach the top from the bottom of the vessel. Regarding safety issues of the dosage form it is necessary ensure the removal of the DDS from the stomach after drug release is completed to avoid accumulation. Therefore, studies regarding the total floating duration (FD) were performed. Therefore, the time period for which the tablet constantly floats on the surface of the medium was measured by placing the tablets in a paddle equipped

automatic dissolution apparatus (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) working with 900 ml 0.1 N HCl of 37 °C and a stirring speed of 50 rpm. Floating lag time and floating duration were determined in triplicate in conjunction with the dissolution experiments.

5.3.5 Determination of dissolved drug amount

Propranolol HCl dissolution studies were carried out with an automatic dissolution tester (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) in 900 ml 0.1 N HCl of 37 °C at 50 rpm. Released Propranolol HCl amounts were determined by measuring the UV absorption at 290 nm and calculated using calibration curves of the drug. Dissolution experiments were carried out over 24 hours and performed in triplicate.

After extrapolating the linear part of the dissolution curve to the abscissa it was possible to calculate the lag times at the initial phase of the drug dissolution profiles. Errors were a function of the correlation coefficient of the best fit straight line and reached maximum values of 1.7 %.

5.3.6 Monitoring of hydration and gas development characteristics by means of ^{1}H NMR benchtop imaging

^{1}H NMR imaging experiments were performed on a benchtop MRI spectrometer working at a frequency of 20 MHz and having a static magnetic field of strength (B_0) of 0.5 T (Oxford Instruments, UK). Tablets were placed in a USP paddle dissolution apparatus with 900 ml 0.1 N HCl of 37 °C, stirred at 50 rpm and removed for MRI measurements after predefined time intervals. The sample holder was filled with 2 ml 0.1 N HCl and glass beads on the bottom to allow three-dimensional water penetration even in case of sinking tablets. A slice of 10 mm thickness was selected parallel to the magnetic field (axial axis). A standard spin-echo sequence was used with an echo time (TE) of 9.8 s and a repetition time (TR) of 300 ms leading to an acquisition time of about 10 min for each image. Sixteen scans were accumulated to obtain 128 x 128 pixel images with a field of view of 4 cm, which led to an in-plane resolution of 312.5 µm. The MRI images were taken after 10 min, 1 hour and then in 1 hour intervals up to 8 hours. The last image was obtained after 24 hours of

hydration and swelling in 0.1 N HCl. MRI experiments were performed in triplicate for each tablet composition.

5.3.7 Impinging light microscopy

Impinging light microscopy of axial cut tablets after predefined time intervals of contact with 0.1 N HCl of 37 °C was performed using an Olympus SZX 9 stereozoom microscope (Olympus Deutschland GmbH, Hamburg, Germany).

5.4 Results and Discussion

5.4.1 Preliminary trials regarding the composition of the tablet core

5.4.1.1 Optimization of excipient composition

Lag times prior to floating and disintegration times are given in Table 5.6. Due to the swelling of Kollidon© SR after contact with aqueous media, this polymer offers the ability to entrap the air being incorporated during the compression step or the carbon dioxide developing due to the neutralization reaction between $NaHCO_3$ and HCl. Both tablet formulations with a high $NaHCO_3$/ Kollidon© SR ratio were initially sinking, whereas an increased PVAc percentage of 75 % and 80 % respectively led to floating tablets ab initio. A higher $NaHCO_3$ content did not lead to improved floating characteristics, as the developing carbon dioxide was not efficiently entrapped by the low of amount of stabilizing polymer Kollidon© SR.

Table 5.6 Disintegration and floating lag times of preliminary tablet samples with and without curing.

$NaHCO_3$/Kollidon© SR (m/m)	**1/1**	**1/2**	**1/3**	**1/4**
Floating lag time without curing (min)	9±2	4±2	0	0
Floating lag time with curing (min)	3±1	0	0	0
Disintegration time without curing (min)	12±2	34±3	56±4	71±3
Disintegration time with curing (min)	76±4	122±3	306±6	*

*no complete disintegration within 24 hours

Curing of the tablet samples was associated with a decrease in floating lag times. Heating the tablet samples above the T_g of the polymer PVAc leads to an increased mobility of the polymer chains, whereas imperfections in the structure of the polymer matrix are equalized, leading to a hardening of the tablet. Additionally, adhering humidity is removed by the temperature treatment decreasing the weight and therefore the density of the systems. The stronger cohesion of the tablet matrix reduced (50 % Kollidon© SR content) or eliminated (33 % Kollidon© SR content) the lag times prior to floating onset as developing carbon dioxide was entrapped more efficiently by the polymer network.

Regarding the disintegration characteristics higher amounts of sodium bicarbonate were, as expected, related to a strong CO_2 development and a disintegration of the tablet. As already mentioned before, the PVAc content was to low to entrap the carbon dioxide efficiently, leading to a complete disintegration within 12 ± 2 min and 34 ± 3 min respectively of tablet samples with 50 % and 33 % $NaHCO_3$. An increased Kollidon© SR content prolonged the disintegration time to approximately one hour, as the influence of polymer network interfering salt sodium bicarbonate was reduced. Curing of tablet samples led to a strong and non-linear increase in disintegration time related to Kollidon© SR content. The strongest effects were observed for the tablet formulation with the lowest $NaHCO_3$/ Kollidon© SR ratio. Even though the contact with hydrochloric acid caused an expansion in tablet dimensions and a fractional disintegration of the cores, the tablets exhibiting an expanded fibrous structure were floating for more than 24 hours. As the lag times prior to floating were not existent or relatively short, the impact of tablet curing on floating onset was determined to be only marginal, whereas the disintegration kinetics revealed to be strongly influenced by temperature treatment. Therefore, the $NaHCO_3$/Kollidon© SR ratio of this formulation was chosen for further experiments.

5.4.1.2 Optimization of drug content and crushing forces

Tablets exhibiting a radial crushing force of 150 ± 5 N did neither float nor disintegrate within a time slice of 24 hours. Even temperature treatment did not improve the floating characteristics of these tablet samples and they were therefore not further examined.

A decreased crushing force of 100 ± 4 N led to improved floating and disintegration behaviour, whereas all tablet samples were initially sinking and therefore exhibited

lag times prior to floating onset (Table 5.7). Floating lag times varied from 8 to 22 minutes on average and were further decreased after the tablet samples were subjected to temperature treatment. Tablets with formulation A 100 N and B 100 N disintegrated completely whereas higher PVAc contents in formulation C 100 N and D 100 N inhibited disintegration. Only a slight increase in tablet dimensions was observed as the carbon dioxide development inside the tablet caused the formation of a sponge-like structure exhibiting nearly the same shape compared to the beginning of the experiment.

Table 5.7 Disintegration and floating lag times of preliminary tablet samples containing Propranolol HCl and exhibiting a crushing force of 100 N with and without curing.

Formulation	**A 100 N**	**B 100 N**	**C 100 N**	**D 100 N**
Floating lag time without curing (min)	22±3	18±3	12±2	8±2
Floating lag time with curing (min)	18±2	13±2	9±1	6±2
Disintegration time without curing (min)	46±3	81±4	*	*
Disintegration time with curing (min)	85±4	155±6	*	*

*no complete disintegration within 24 hours

A further decrease in crushing force values to 75 ± 5 N led to initially floating devices (formulation D 75 N) and tablets with floating lag times between 5 and 11 minutes (formulations A 75 N, B 75 N and C 75 N) on average, caused by a lower compression force excerted on the powder mixture during compression (Table 5.8).

Table 5.8 Disintegration and floating lag times of preliminary tablet samples containing Propranolol HCl and exhibiting a crushing force of 75 N with and without curing.

Formulation	**A 75 N**	**B 75 N**	**C 75 N**	**D 75 N**
Floating lag time without curing (min)	11±2	7±2	5±1	0
Floating lag time with curing (min)	7±2	5±2	3±1	0
Disintegration time without curing (min)	35±3	59±3	78±5	87±5
Disintegration time with curing (min)	57±5	97±5	143±4	294±7

The instant floating characteristics of the tablet samples with the highest PVAc content were due to the relatively low apparent density of the system at the beginning

of the floating experiment. Tablets being subjected to the temperature treatment exhibited decreased floating lag times as well as already observed in the previous experiments.
The disintegration of the devices was accelerated compared to tablet samples characterized by a crushing force of 100 N. Due to the lower compression forces the cohesion forces within the tablet core are not able to resist the expansion of the device caused by the carbon dioxide development. Surprisingly, cured tablets with formulation D 75 N were observed to float approximately 5 hours before being completely disintegrated. Though the density of the systems was low due to the formation of a voluminous sponge-like structure, the gas entrapment efficiency was sufficient to maintain the disintegrating structure afloat.

Due to their initial floating characteristics tablet samples with formulation D 75 N were chosen for the further development of a floating device. The application of a tablet coat on these cores was expected to result in an increased floating duration as the polymer film will prevent the carbon dioxide from fast escaping from the tablet core. Additionally, the application of a film coat reduces the disintegration of the tablet samples. As the formulations manufactured with the lowest compression forces exhibited the strongest disintegration behaviour, the drug release characteristics from a coated tablet with a D 75 N core were, compared to the formulations exhibiting a higher crushing force of 100 N or 150 N, expected to be more influenced by the surrounding polymer film than by the tablet core.

5.4.2 Monitoring of floating characteristics

All examined tablet samples were initially sinking. After a lag time the tablets began to move to the surface of the medium. Tablets with coat SR/IR:8.5/1.5 and coat SR/IR:9/1 remained afloat until the end of the monitored 24 h time interval, whereas SR/IR:8/2 coated tablets exhibited small cracks in the tablet coat releasing CO_2. As SR/IR:8/2 coated tablet samples were sinking after 8 to 10.5 hours, depending on their coating level (Fig. 5.2), these systems were not further investigated.

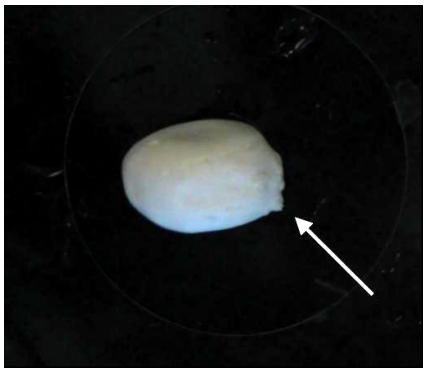
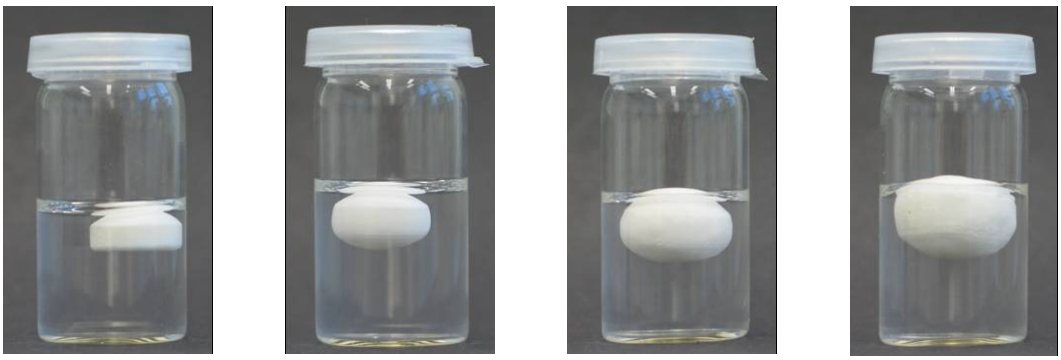


Fig. 5.2 Crack formation in the polymeric film coat of a tablet sample with 10 mg polymer/cm² SR/IR:8/2 coat after 8 hours of contact with 0.1 N HCl.

Positioning of the samples in 0.1 N HCl led to immediate water and thus hydrochloric acid penetration through the polymer coat. After contact with the sodium bicarbonate of the tablet core carbon dioxide development was initiated leading to an expansion and a reduced density of the system, initializing floatation (Fig. 5.3 a-c). In contrast to tablet samples with an SR/IR:8/2 coat tablets with a reduced content of PEG-PVA of 10-15 % did not exhibit cracks in the polymeric film and thus were still floating after 24 hours (Fig 5.3 d).



a) 15 min b) 1 h c) 4 h d) 24 h

Fig. 5.3 a-d Photographs of floating tablet samples with SR/IR:8.5/1.5 coat after different time intervals of contact with 0.1 N HCl.

After varying lag times for the different tablet samples the devices began to float (Fig. 5.4). Floating characteristics were strongly related to coating level and composition of the polymer film. Increased Kollicoat® IR amounts and lower coating levels led to shortened lag times, a stronger increase in floating strength and higher maximum floating strength values.

These characteristics may be explained by different mechanisms. Since water penetration through the polymer film is related to coating thickness as already

described in chapters 3.4.3 and 3.4.4, hydrochloric acid diffusion and thus gas development within the floating devices will act similarly.

Another aspect includes the leaching of water soluble compounds out of the polymer shell. The leaching characteristics of water soluble film components such as Kollicoat® IR, PVP and triacetin have been monitored with MCC-based tablet cores and were described in chapters 4.4.1 and 4.4.2.

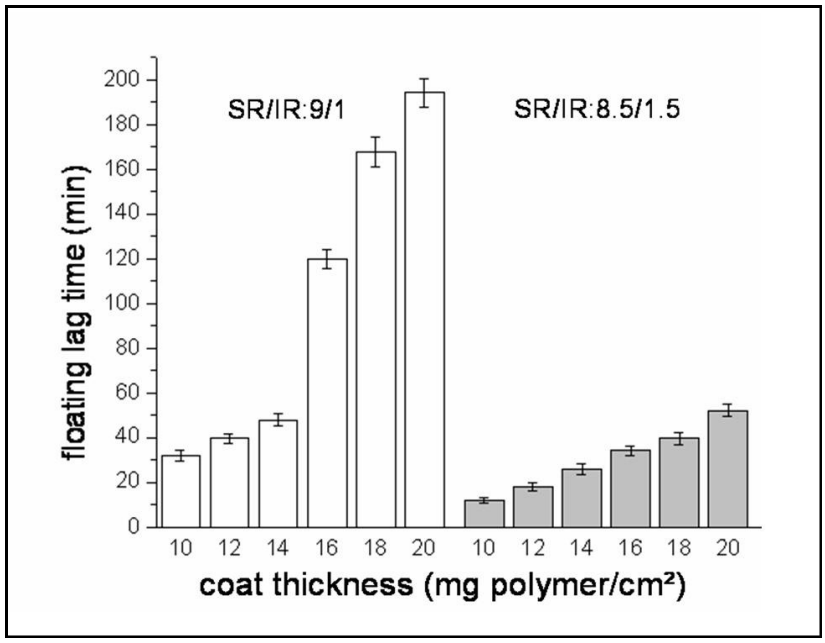


Fig. 5.4 Floating lag times of tablets coated with different Kollicoat® SR/IR ratios in relation to coating thickness.

An increased amount of the water soluble Kollicoat® IR leads to a faster dissolution of other leachable components and a higher porosity of the polymer film coat. As the total amount of the remaining polymer Kollicoat® SR is reduced in samples with coating formulation SR/IR:8.5/1.5, the required force exerted by the gas to expand the polymer network is lower than for tablet samples with 10 % Kollicoat® IR content. This might explain the differences in floating lag time increase, exhibiting approximately linear characteristics for tablet samples with coat SR/IR:8.5/1.5 and almost exponential behaviour for tablets with coat SR/IR:9/1 (Fig. 5.4). For SR/IR:9/1 coated tablets the influence of the higher PVAc content in the polymeric film coat becomes more pronounced at higher coating levels. An increased Kollicoat® SR / Kollicoat® IR ratio led for all tablet samples to higher lag times compared to tablets with coat SR/IR:8.5/1.5. The shortest lag time was observed for floating devices with an SR/IR:8.5/1.5 coat of 10 mg polymer/cm² and was found to be 12 min ± 1 min.

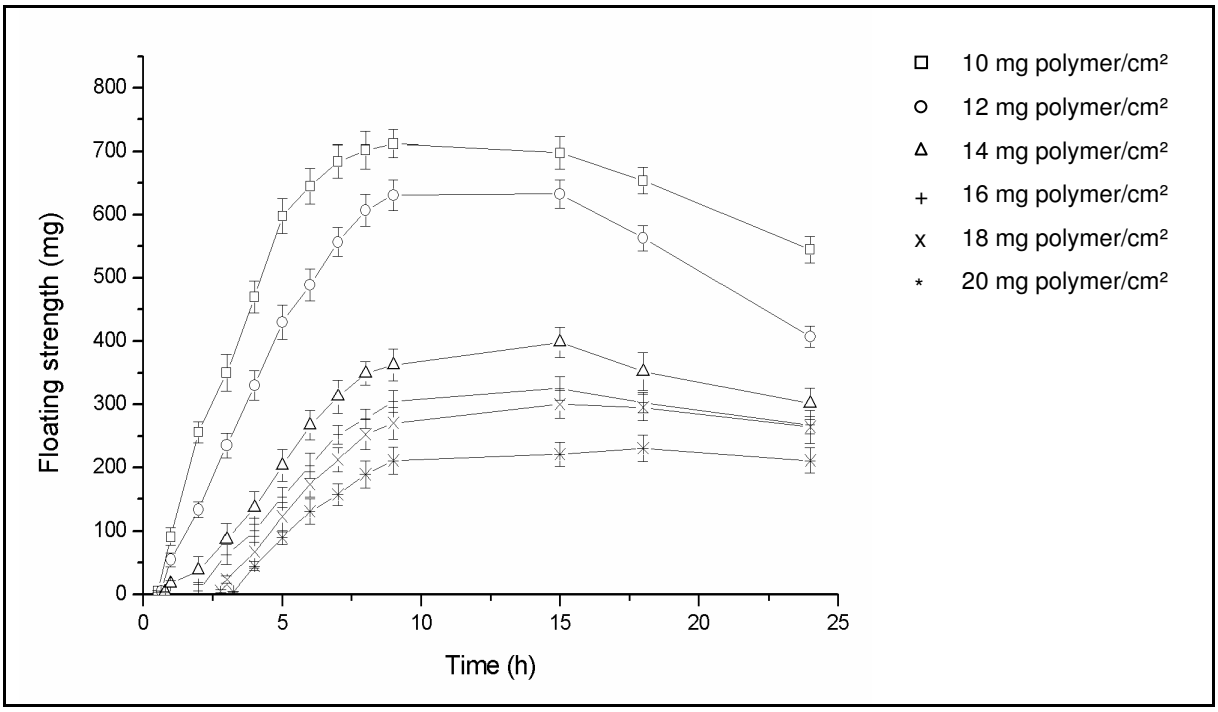


Fig. 5.5 Floating strength of tablet samples with coating formulation SR/IR:9/1.

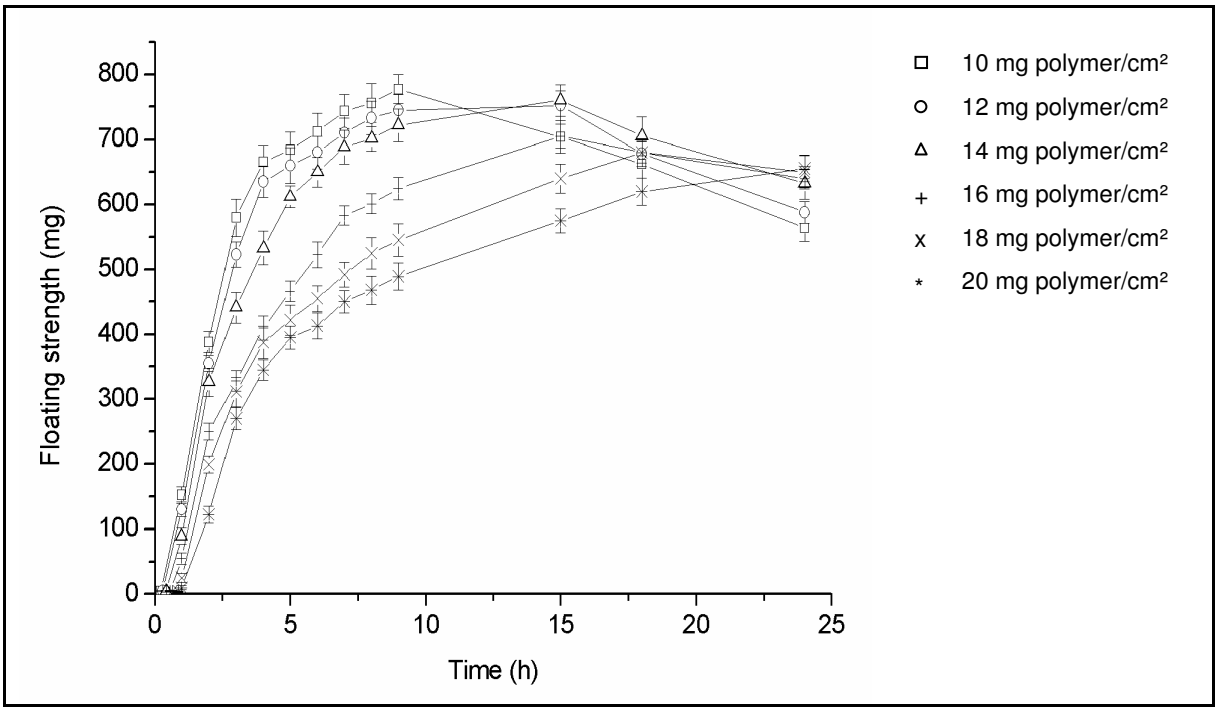


Fig. 5.6 Floating strength of tablet samples with coating formulation SR/IR:8.5/1.5.

The increase in floating strength of the monitored tablet samples was strong within the first phase of the floating process and slowed down to reach a maximum value after about 9 to 15 hours (Figs. 5.5 and 5.6). Maximum floating strength values were higher and reached earlier for tablets with SR/IR:8.5/1.5 coat as well as for floating

devices with a thinner polymer film layer. Additionally, these samples exhibited a faster increase in floating strength at the beginning.

A subsequent plateau phase was more pronounced for SR/IR:9/1 tablet samples. After 10 to 15 hours the floating strength of these tablets remained constant or decreased. Constant floating strength values over a certain time period indicate an equilibrium state between the carbon dioxide development and swelling of the device to keep the tablet afloat and the dissolution of carbon dioxide in the penetrating aqueous medium as well as water penetration through the polymer film itself leading to a sinking of the tablet.

Tablets with coat SR/IR:8.5/1.5 and a coating level of 20 mg polymer/cm² exhibited within the monitored time interval of 24 hours only an increase in floating strength. In this case the gas development dominates all effects contributing to the total floating strength of the DDS. A plateau phase, following for most tablet samples, is not reached with these systems, which is most likely due to a decreased permeability of the polymer film caused by the higher coating level.

The carbon dioxide development, due to the reaction of sodium bicarbonate with penetrating hydrochloric acid, occuring more rapidly than the removal of the gas through the polymeric coat, will result in an initial increase in floating strength.

The origin of reduced floating strength values lies in the removal of carbon dioxide from the inside of the polymer shell. Combining Fick's law of diffusion with Henry's law the volume of a gas diffusing through a membrane is given by equation (3):

$$\frac{\delta M}{\delta t} = \frac{D_G \cdot K_G \cdot A_F \cdot (\rho_1 - \rho_2)}{d} \tag{3}$$

where $\delta M/\delta t$ is the diffusing gas amount per time unit, D_G diffusion coefficient of the gas, K_G the solubility coefficient of the gas in the liquid, A_F the real flow-through area, ρ_1 the pressure of the gas above the liquid film, ρ_2 the pressure of the gas below the liquid film and d the thickness of the liquid layer. Thus, an increased porosity and a reduced thickness of the film coat will lead to higher permeating gas amounts. As the thinner polymer films on the tablets exhibit a higher porosity due to a more intensive expansion of the polymer network, the reduction in floating strength occurs earlier than for samples with a higher coating thickness. Another aspect lies in an increased tablet surface. As SR/IR:8.5/1.5 tablet samples exhibit a stronger expansion of the polymer film, an increased tablet surface as well as a reduced diffusion path will

increase the net mass transport through the membrane. Therefore, both lower PVAc and higher PEG-PVA content in the film coat of SR/IR:8.5/1.5 coated tablets will contribute to improved diffusion through the polymer coat in both directions leading to less pronounced plateau phases in floating strength values for these tablet samples, as the increased permeability of the film coat is reducing the ability to entrap the carbon dioxide within the polymer shell.

Floating of the tablets continued until the deformation of the tablet coat due to the carbon dioxide formation, the leaching of water soluble film components and the disintegration of the tablet core become to strong and the formation of cracks occurred.

The determined floating duration for all tablet formulations is given in Table 5.9. Even though tablet samples with an increased Kollicoat® SR/Kollicoat® IR ratio as well as those exhibiting an increased coating level exhibit an increased lag time prior to floating onset, the total floating duration is increased compared to tablets with an SR/IR:8.5/1.5 coat or tablets with a thinner polymer coat. Thus, the lower permeability of the polymeric films is entrapping the carbon dioxide more efficiently.

Table 5.9 Floating duration of tablets with SR/IR:9/1 and S/IR:8.5/1.5 coat.

Tablet samples	**FD (days)**	**Tablet samples**	**FD (days)**
SR/IR:9/1		***SR/IR:8.5/1.5***	
10 mg polymer/cm²	1.45	10 mg polymer/cm²	1.25
12 mg polymer/cm²	1.63	12 mg polymer/cm²	1.33
14 mg polymer/cm²	1.87	14 mg polymer/cm²	1.50
16 mg polymer/cm²	2.08	16 mg polymer/cm²	1.67
18 mg polymer/cm²	2.17	18 mg polymer/cm²	1.71
20 mg polymer/cm²	2.33	20 mg polymer/cm²	1.75

The removal of the floating drug delivery device from the stomach after drug release is important to avoid an accumulation in vivo. Even though only in vivo studies regarding the gastric retention properties can supply evidence of a potential accumulation risk, a total in vitro floating duration of two or more days is not

applicable for this purpose. Therefore, tablet samples with a SR/IR:8.5/1.5 coat of a low coating level seem to be a more appropriate possibility to ensure the safety of the system.

5.4.3 Characterization of Propranolol HCl release behaviour

The developed floating drug delivery systems were able to efficiently control Propranolol HCl release over a time period of 24 hours (Figs. 5.6 and 5.7). The drug release profiles exhibited linear zero order release kinetics with different total amounts of liberated drug within 24 hours. Propranolol HCl release rates increased with a higher Kollicoat® IR concentration in the coating formulation. A complete drug delivery within the monitored time interval was only registered for tablet samples with coat SR/IR:8.5/1.5 of 10 mg polymer/cm². In contrast maximum drug release values for tablets with coating formulation SR/IR:9/1 reached only about 15 to 35 %.

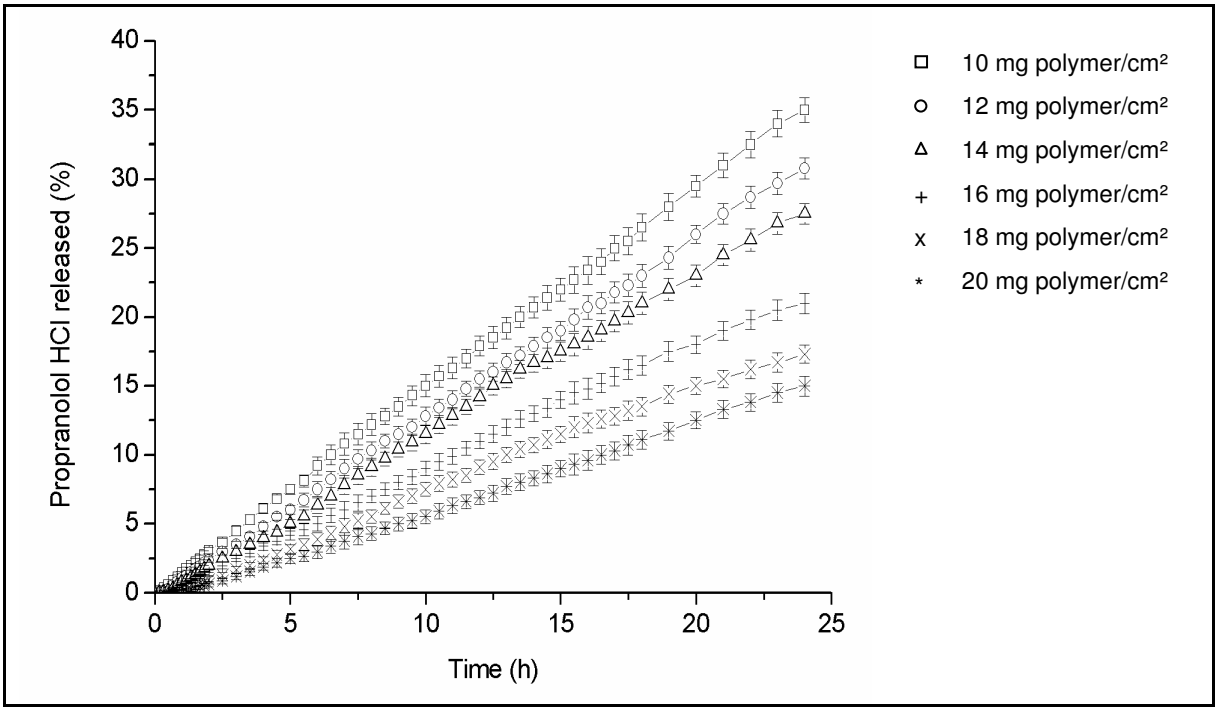


Fig. 5.6 Propranolol HCl release from tablet samples with coating formulation SR/IR:9/1.

Drug release rates were a function of the coating thickness, the porosity and the surface area of the film coat. Thus, drug release as well as floating characteristics is affected by similar mechanisms. Therefore, samples with increased permeability for carbon dioxide will exhibit increased Propranolol HCl release rates as well.

Zero order drug release kinetics are related to a reservoir with undissolved drug amounts within a controlled drug release device. As long as drug release curves showed linear characteristics, the tablet core remained Propranolol HCl saturated. Only tablets with a 10 mg polymer/cm² coat of SR/IR:8.5/1.5 exhibited the emptying of this reservoir as the dissolution curve flattened at the end of the monitored drug release interval.

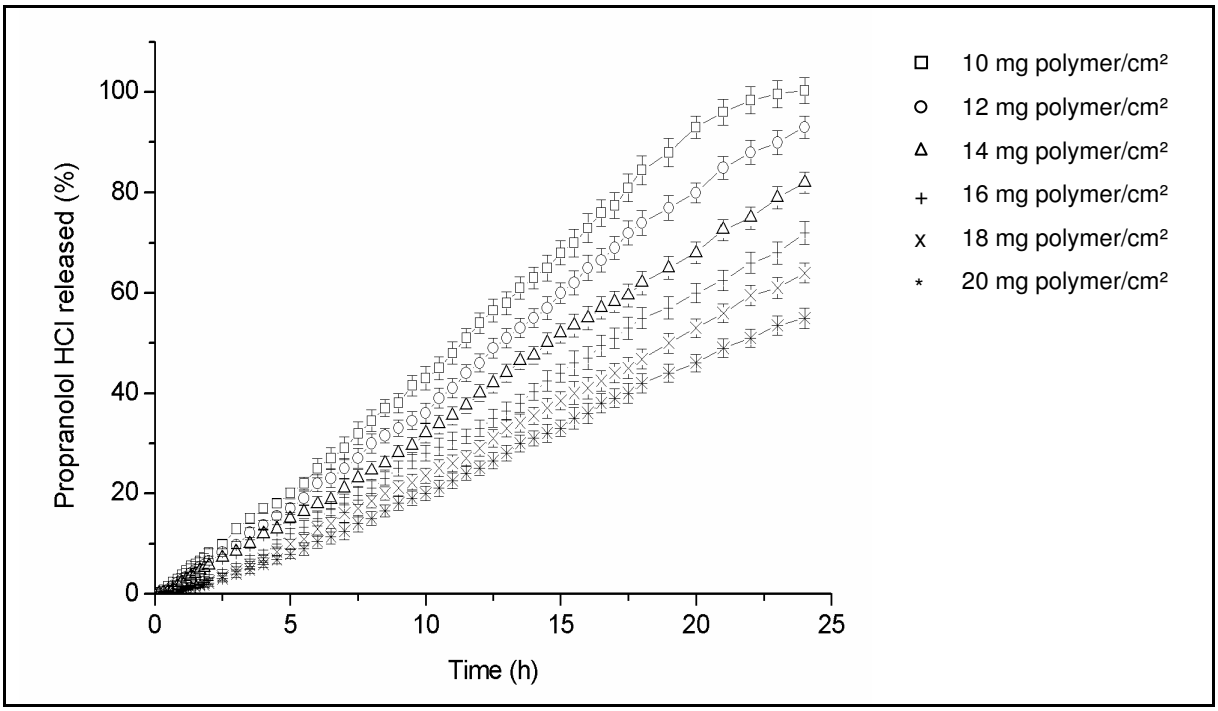


Fig. 5.7 Propranolol HCl release from tablet samples with coating formulation SR/IR:8.5/1.5.

5.4.4 Determination of lag times prior to drug release

Lag times prior to drug release were related to the thickness of the polymer film, as tablets with a higher coating level showed decreased Propranolol HCl release rates. Comparing both coating formulations, an increased Kollicoat® IR content in the polymer film tended to decrease the lag times. Figure 5.8 gives a more detailed description of the initial drug release characteristics within the first two hours of contact with dissolution medium. It is obvious, that the lag times do not represent time intervals without any drug release but with at least marginal Propranolol HCl liberation. Drug release rates remained low for a short period of time and increased afterwards.

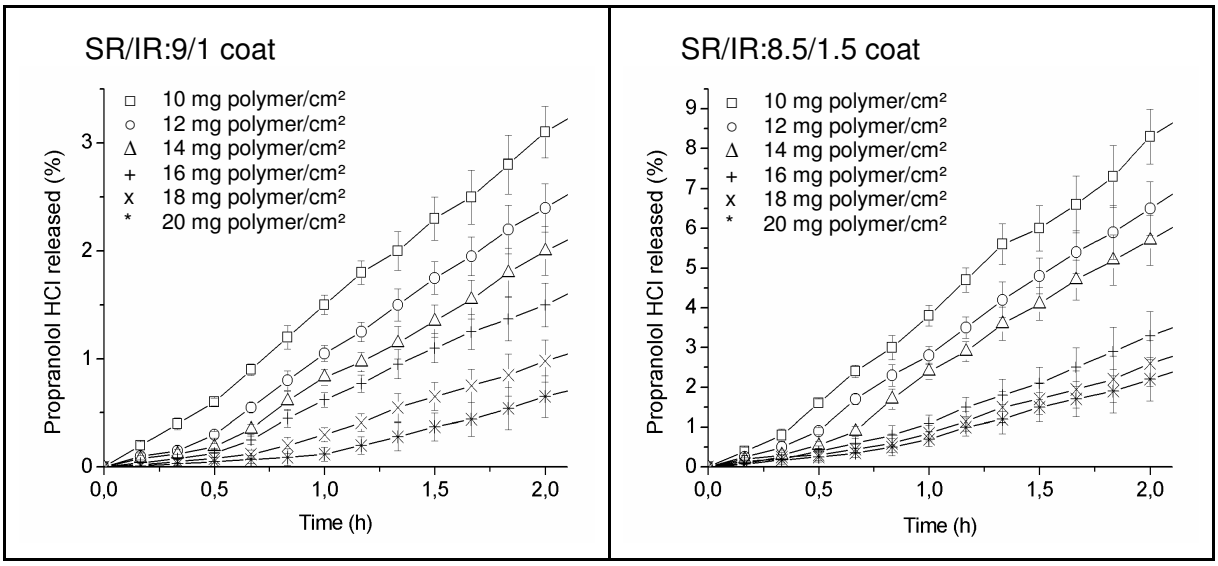


Fig. 5.8 Propranolol HCl release within the first two hours from SR/IR:9/1 and SR/IR:8.5/1.5 coated tablets.

For both tablet formulations characterized by a coating level of 10 mg polymer/cm² a lag phase prior to drug release was not determinable due to the instant increase in drug release rates at the beginning of the dissolution experiment. For these tablet samples the permeability of the film coat was sufficiently high to ensure linear drug release behaviour from the beginning.

Table 5.10 Drug release lag times of the floating tablets in relation coat thickness and coat composition.

Tablet samples	Lag times prior to drug release (min)	Tablet samples	Lag times prior to drug release (min)
SR/IR:9/1		***SR/IR:8.5/1.5***	
10 mg polymer/cm²	0	10 mg polymer/cm²	0
12 mg polymer/cm²	17	12 mg polymer/cm²	15
14 mg polymer/cm²	24	14 mg polymer/cm²	21
16 mg polymer/cm²	28	16 mg polymer/cm²	28
18 mg polymer/cm²	34	18 mg polymer/cm²	30
20 mg polymer/cm²	49	20 mg polymer/cm²	31

The determined lag times prior to drug release are shown in Table 5.10. Surprisingly, lag time values of tablet samples with the same coating thickness but different

coating composition differ only marginally, whereas the absolute amount of Propranolol HCl released from SR/IR:8.5/1.5 coated reached approximately twice to threefold the values of those from tablets with an SR/IR:9/1 coat within the same time interval.

The influence of the higher Kollicoat® SR content in SR/IR:9/1 coated tablets regarding lag times prior to drug release became more pronounced at higher coating levels, as the increase in drug release lag times increased stronger for these tablet samples.

5.4.5 Monitoring of hydration and gas development characteristics by means of ^{1}H NMR benchtop imaging

Benchtop ^{1}H NMR Imaging was used to monitor tablet and film coat hydration and swelling characteristics of selected tablet samples. Figure 5.9 gives a schematic sequence of different main phases regarding swelling and carbon dioxide development taking place inside the tablet, which can be monitored using the benchtop MRI instrument.

Swelling processes started with an initially hydrated polymer film and a dry unswollen tablet core, whereas in this phase the device was not yet afloat. Carbon dioxide development started on the on the surface of the tablet core. At the beginning of this process CO_2 accumulated on the top side of the tablet leading to an expansion of the film coat. Thus, a dome shaped, floating tablet could be observed. Additionally, the swelling of outer parts of the tablet core occured, whereas the inner part was still dry and unhydrated. Continuing diffusion of hydrochloric acid inside the tablet lead to a biconvex and swollen tablet with gas accumulation within the tablet coat on the top side as well as on the bottom side of the tablet core. The carbon dioxide inside the floating device expanded the tablet coat intensively, leading to a strong volume increase with time and formation of a balloon shaped floating tablet. The swelling layer of the tablet core increased, whereas a part of the inner core was still unhydrated. Ongoing diffusion processes increased the development of carbon dioxide and thus the volume of the floating device. A completely hydrated tablet core with beginning CO_2 development inside the tablet core was observed. The former shape of the core was still visible though now intensively swollen. The final phase was represented by a tablet, which was often slightly reduced in size exhibiting a disintegrated core entrapping several smaller gas bubbles.

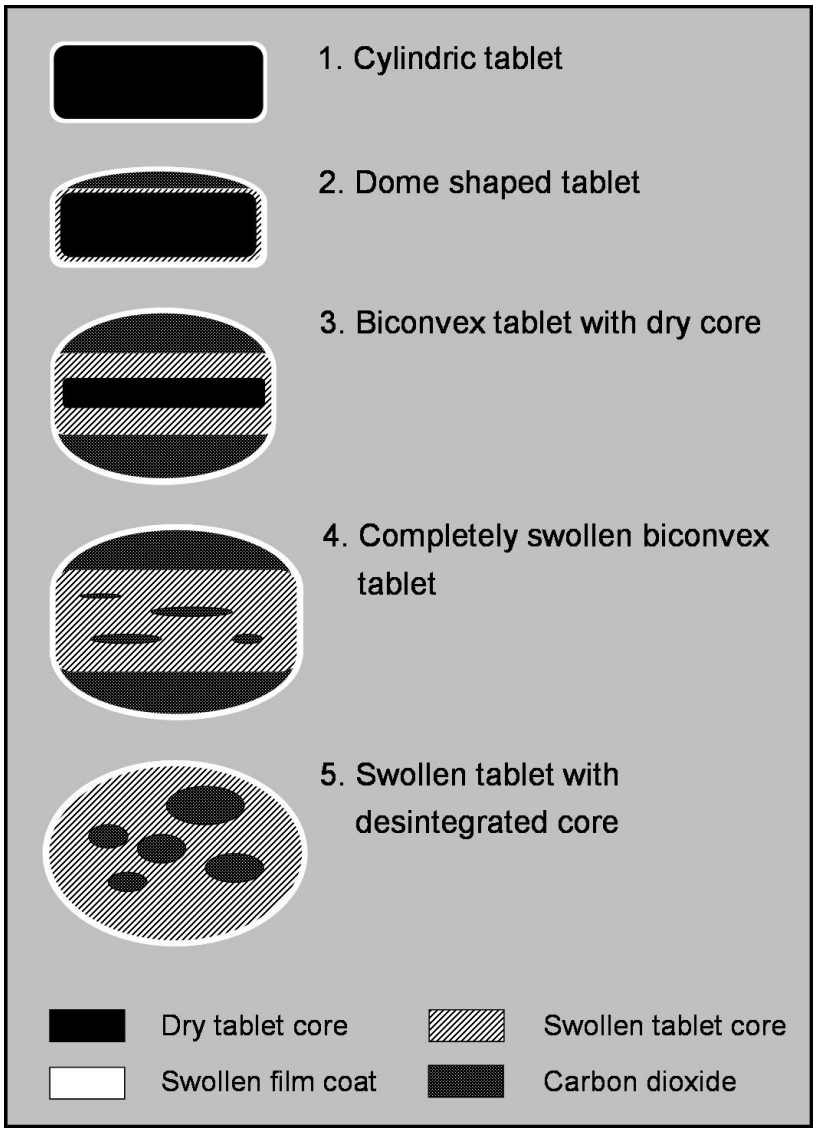


Fig 5.9 Schematic process of tablet swelling and carbon dioxide development inside the floating devices.

The figures obtained by using ^{1}H NMR benchtop MRI represent axial side images of tablet samples characterized by a coating level of 10 mg and 14 mg polymer/cm² with coating formulation SR/IR:9/1 (Figs. 5.10 and 5.11) and SR/IR:8.5/1.5 respectively (Figs. 5.12 and 5.13). Dark areas in the ^{1}H NMR images refer to low spin densities or short T_1 relaxation times, which are related to dry parts of the tablet or carbon dioxide development inside the tablet core. Brighter areas of the tablets compared to the 0.1 N HCl surrounding the device may lead to the conclusion that the spin density in this area is higher than in the dissolution medium, but this contrast was obtained by measuring with a repetition time, which was shorter than the T_1 of the free water in the medium but much longer than the T_1 of water in the matrix tablets. As the magnetization of the free water in the medium, in contrast to the water in the tablet, was not able to return to equilibrium, the signal intensity for water inside the tablet

increased although its spin density was lower. Thus it was possible to follow hydration characteristics and carbon dioxide formation of the developed systems more easily.

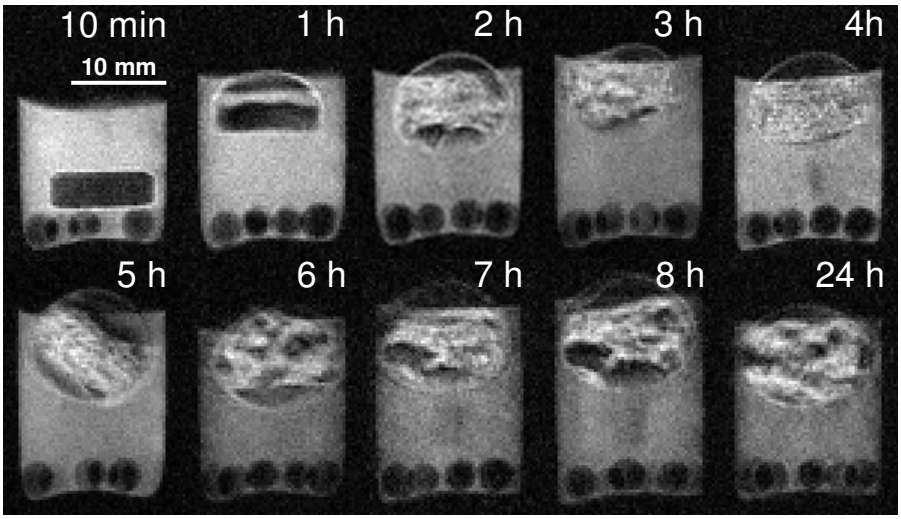


Fig. 5.10 ^{1}H NMR benchtop magnetic resonance images of tablets with a 10 mg polymer/cm² SR/IR:9/1 coat after different time intervals of contact with 0.1 N HCl.

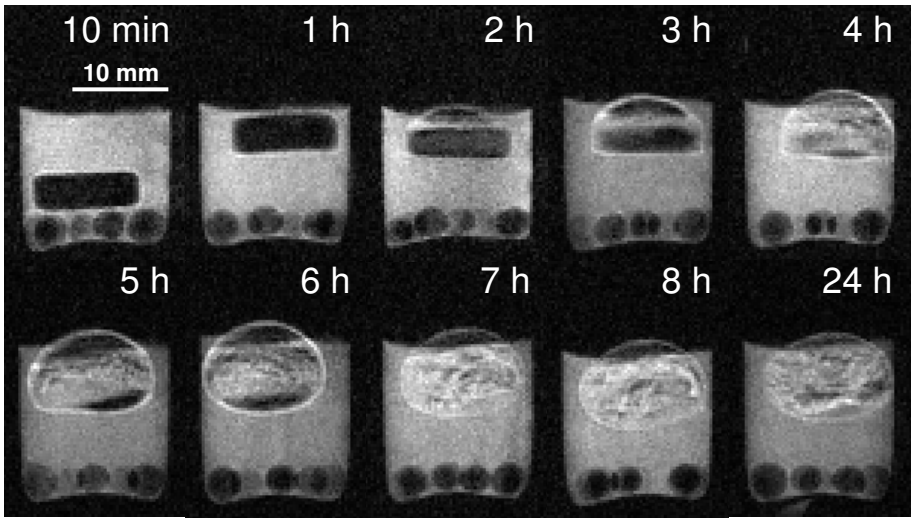


Fig. 5.11 ^{1}H NMR benchtop magnetic resonance images of tablets with a 14 mg polymer/cm² SR/IR:9/1 coat after different time intervals of contact with 0.1 N HCl.

Benchtop magnetic resonance images revealed that positioning tablets into 0.1 N HCl led in all cases to an initial sinking of the tablets. Only magnetic resonance images for samples with 10 mg polymer/cm² SR/IR:8.5/1.5 coat were floating after 12 min. The swollen polymer film was visible as a bright edge surrounding the core due to the immediate water diffusion into the tablet. For the tablet core a signal with a short T_1 relaxation time was detected, which leads to the conclusion that the

hydration of the inner part of the tablet had not yet begun. It was possible to monitor the continuing water diffusion into the tablet over time appearing as an increasing water diffusion layer.

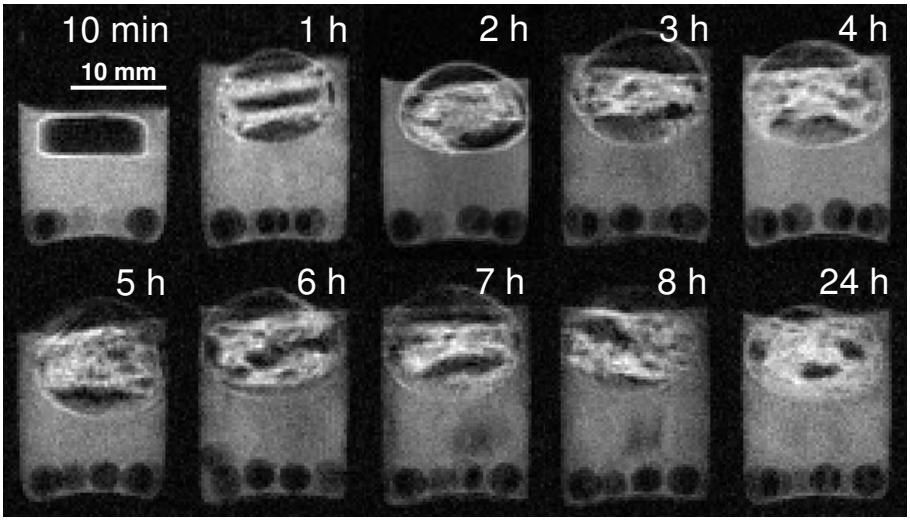


Fig. 5.12 ^{1}H NMR benchtop magnetic resonance images of tablets with a 10 mg polymer/cm² SR/IR:8.5/1.5 coat after different time intervals of contact with 0.1 N HCl.

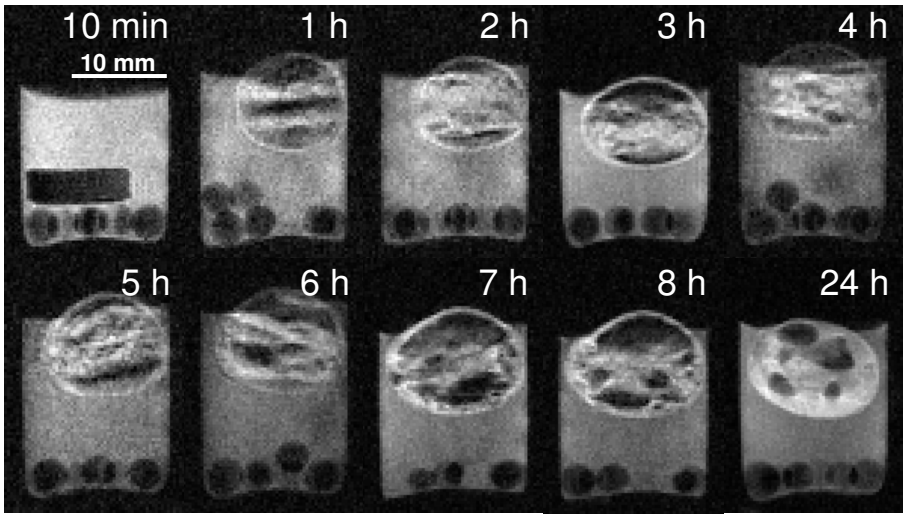


Fig. 5.13 ^{1}H NMR benchtop magnetic resonance images of tablets with a 14 mg polymer/cm² SR/IR:8.5/1.5 coat after different time intervals of contact with 0.1 N HCl.

The process of tablet swelling and gas development was accelerated for samples with a lower Kollicoat® SR / Kollicoat® IR ratio and a lower coating level. Therefore, magnetic resonance images of tablets with coat SR/IR:8.5/1.5 exhibited a faster initial increase in tablet size compared to samples with a higher Kollicoat® SR / Kollicoat® IR rate. Carbon dioxide development due to the neutralization reaction between hydrochloric acid diffusing from the dissolution medium and sodium

bicarbonate in the tablet core led for tablet samples with 10 % Kollicoat® IR content in the film coat to the formation of a dome shaped tablet. Due to an intense carbon dioxide formation inside the tablet samples with a SR/IR:8.5/1.5 coat, causing a fast expansion of the device, a phase with a dome shaped tablet was not observed. The increased permeability and flexibility of the SR/IR:8.5/1.5 coat caused a strong increase in tablet size, forming a kind of balloon. Thus, after one hour an expanded, biconvex tablet was detected, while this phase was attained by SR/IR:9/1 samples not until 2 hours (10 mg polymer/cm² coat) and 6 hours (14 mg polymer/cm² coat) respectively. The tablet size increased primarily in axial direction and only slightly in tangential direction.

Furthermore, an increased Kollicoat® IR rate led to an earlier disintegration of the tablet core. Differences in swelling and CO_2 development characteristics were more pronounced for SR/IR:9/1 samples with different coating levels than for SR/IR:8.5/1.5 tablets with varying film thicknesses. For SR/IR:9/1 tablets, the tablet core of samples with 14 mg polymer/cm² started to disintegrate only marginally after 7 hours, while tablets with a decreased polymer film exhibited a strong core disintegration after the 6 hours. In contrast to this both MRI monitored SR/IR:8.5/1.5 samples exhibit quite similar swelling and gas formation behaviour.

In most magnetic resonance images the swollen and expanded polymeric film coat was visible as a bright edge surrounding the tablet core. The last images of each MRI series detected a floating device, where tablet coat and tablet core were no longer distinguishable. The increased signal intensity inside the tablet core may be caused by a high amount of aqueous dissolution medium bound by the polymer network. Even if the shape of the tablet core is no longer visible, the poly(vinyl acetate) structure of the disintegrated tablet core is still strong enough to entrap gas bubbles inside the polymeric shell. The reduced volume of the floating device, which was observed for some formulations, is caused by the diffusion of carbon dioxide and Propranolol HCl from the tablet core.

5.4.6 Impinging light microscopy

Impinging light micrographs underlined the findings of the benchtop MRI study, as most stadiums of carbon dioxide formation observed before were retrieved (Fig. 5.14). A cylindrical shaped tablet with undisintegrated core and only slight CO_2 formation was observed after 15 min of contact with hydrochloric acid. Gas

development started in the outer parts of the tablet core, which showed no tendency of disintegration. After two hours the floating device forms a biconvex tablet due to the strong expansion of the polymeric film.

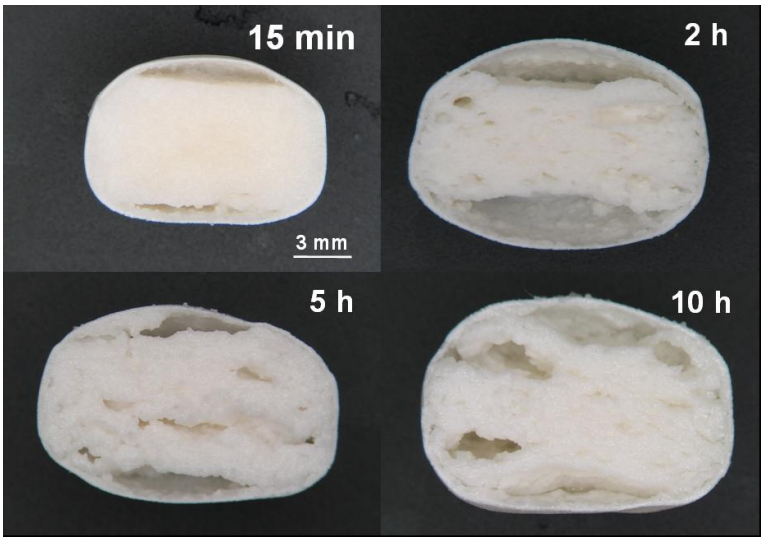


Fig. 5.14 Impinging light micrographs of axial cut tablet samples with coat SR/IR:8.5/1.5 of 10 mg polymer/cm² after different time intervals of contact with 0.1 N HCl.

Small cavities within the tablet core become visible and increase over time leading to a disintegration of the tablet after ten hours. The 10 h micrograph shows clearly the cavities, where the carbon dioxide is entrapped. Additionally, an all in all increase in tablet size was observed as well.

5.5 Conclusion

The present chapter demonstrates the exceptional attributes of poly(vinyl acetate) as an excipient for floating devices showing controlled drug delivery. Kollidon® SR is able to ensure a low initial density of the floating system and to overcompensate the sinking characteristics of the model drug Propranolol HCl. The high elasticity of Kollicoat® SR films reduces the risk of dose dumping even for expanding, carbon dioxide developing systems. The high flexibility of poly(vinyl acetate) films is further increased after contact with dissolution medium due to water acting as a plasticizer. The Kollicoat® SR film simultaneously provides a controlled release of the drug and ensures an effective capture of the CO_2 within the tablet. Hereby, the Kollicoat® SR/Kollicoat® IR ratio represent an important factor, as Kollicoat® IR contents in the film coat of 20 % led to a destabilization of the polymeric film and the formation of cracks. As the dimensions of the floating DDS increased during the interval of drug release, both floating ability and size will contribute to the gastroretentive characteristics of the dosage form, whereas the latter will become more pronounced when stomach contents are emptied. Although a variety of gastroretentive systems has been developed until now, most of the published studies neglect floating strength studies and focus only on the monitoring of floating lag time and floating duration. Applying floating strength measurements to the developed floating tablets it was possible to quantify and to compare floating characteristics of different systems. Tablets with a 10 mg/cm² SR/IR:8.5/1.5 coat proved to exhibit optimized characteristics for an application as a gastroretentive DDS, showing a floating onset of 12 minutes on average, the strongest and fastest increase in floating strength at the beginning, a reliable floating within a time interval of 24 hours and a complete drug release governed by zero order kinetics. As all devices exhibit an initially high density leading to a sinking of the tablets at the beginning they imply the risk of premature emptying. The performance of MRI experiments led to a more profound understanding not only of swelling poly(vinyl acetate)-based drug delivery systems but of carbon dioxide developing floating devices in a non-invasive and continuous manner.

6. Development and characterization of poly(vinyl acetate) floating matrix tablets

6.1. Introduction

In this chapter a second option for the realization of a floating oral dosage form is described by the development of a floating matrix tablet. Compared to coated floating tablets, matrix devices offer several advantages. The dosage form may be prepared with a single manufacturing step, reducing costs and expenditure of time. As the drug is dispersed homogeneously throughout a polymeric matrix they do not exhibit the risk of dose dumping due to drug leakage. A disadvantage lies in the fact, that the empty matrix has to be removed from the body. Furthermore, in the continuing dissolution process an increase in diffusion path as well as a decreased effective diffusion area will result in drug release rates varying with square roots of time and thus continuously diminishing drug liberation.

For the development of a floating matrix drug delivery system selecting a suitable polymer with a bulk density of less than 1 g/cm^3, forming a cohesive gel barrier and the ability to dissolve slowly enough to retain the drug over a longer period of time is representing a challenge [163].

Hydrocolloids of natural or semisynthetic origin are commonly used for the development of so called hydrodynamically balanced systems. HPMC is most widely used as a matrix forming excipient in gastroretentive systems as it is available in various qualities, differing in molecular weight and viscosity [196-199]. Other approaches include the use of Carbopol, HPC, EC, agar, alginic acid, carragenans or natural gums as matrix forming excipients [129,130,200-203]. The functional principle of these devices is based on the fact, that the matrix begins to swell and forms a gel layer with entrapped air around the tablet core after contact with gastric fluid, whereas this gel layer controls the drug release. After the outer gel layer is eroded, the swelling boundary is moving towards the dry core, maintaining hydration and buoyancy of the system [117,204].

Addition of fatty acids to these formulations leads to devices exhibiting a low density, whereas the diffusion of aqueous medium into the device is decreased reducing the erosion of the system [163-165,205]. A drawback lies in the passivity of these systems, depending on the air entrapped in the device during the compression step

[206]. An approach to avoid this issue lies in the increase in floating strength by incorporating sodium bicarbonate as gas forming agent dispersed in a HPMC hydrogel matrix [207,208].

The use of synthetic polymers such as methacrylic acid-methylmethacrylate (Eudragit®) copolymers or poly(vinyl acetate) leads to the formation of inert matrices. Apart from the addition of common tableting excipients such as lactose or dicalcium phosphate, drug release profiles from polymeric matrices may be adjusted by blending polymers with different hydrophilicity [209-211]. Furthermore, polymer blends have been reported to improve the tablet hardness and the ability to retard drug release [212]. These systems swell only to a limited extent. In this connection Kollidon® SR has already been reported to control the release of various drugs such as Propranolol HCl, Diphenhydramine HCl and Diltiazem HCl when used as a matrix forming excipient [38,213-219]. It shows excellent flowability and can be used as an excipient for direct compression, whereas these tablets are characterized by a low friability and high crushing forces at low compression forces during the tableting process [220].

Furthermore, drug release characteristics may be adjusted by adding swellable or water soluble excipients such as pectin and methyl hydroxyethylcellulose [221]. For the floating matrix systems described in this chapter again Propranolol HCl was used as a model drug. It was expected that the good floating properties of Kollidon® SR would be able to compensate the deficient floating properties of Propranolol HCl, as it has already been used as a matrix forming excipient in floating formulations [222]. Poly(vinyl acetate) forms a non-disintegrating matrix which will only swell to a limited amount when placed in an aqueous environment. Propranolol HCl release from Kollidon® SR matrices will be governed by the diffusion of dissolution medium into the matrix, swelling of the polymer matrix, dissolution of poly(vinyl pyrrolidone) and the drug and the diffusion of these two dissolved substances out of the matrix.

Kollidon® SR formulations have been reported to show sensitivity to exposure to different temperature treatments [223]. Therefore, curing experiments were performed to detect the extent of temperature influences on drug release profiles.

As polymer swelling plays an important role in pattern and amount of drug release and floatation behaviour, monitoring water penetration into the tablet core leads to a deeper understanding of drug release mechanisms. To maintain flotation of the tablets the balance between swelling and water diffusion into the tablet has to be

preserved. In this regard the gravimetric quantification of water uptake characteristics to monitor swelling behaviour is often used due to its simple practicability [199,224]. Liquid boundary movements in tablets have already been monitored invasively by axially cutting tablets after quick-freezing and freeze-drying [225]. By contrast, magnetic resonance imaging offers the possibility to characterize swelling and water diffusion characteristics of matrix tablets in a non-invasive manner [55-57,226]. Therefore, the ^{1}H NMR benchtop MRI instrument was applied on systems of interest described in this chapter.

Additionally, floating strength experiments were performed using a simplified apparatus according to Timmermanns and Moës [190,192] to allow a better evaluation and comparison of the floating ability of the developed matrix tablets.

6.2 Materials

Kollidon® SR was used as a plastic matrix former (BASF Ludwigshafen, Germany). Propranolol HCl was obtained by Sigma Aldrich, Taufkirchen, Germany. Magnesium stearate was used as a lubricant (Caelo GmbH, Hilden, Germany).

6.3 Methods

6.3.1 Preparation of floating matrix tablets

The composition of the matrix tablet was selected according to the preliminary trials regarding the tablet core mixture of the coated floating DDSs (chapter 5.3.1.2), whereas the sodium bicarbonate fraction was replaced by Kollidon® SR to receive a higher PVAc content for a system floating independently of carbon dioxide development. Kollidon® SR and Propranolol HCl were blended in a z-arm mixer (AR 400, Erweka GmbH, Heusenstamm, Germany) for 10 minutes. After adding magnesium stearate the powder mixture was blended for another 2 minutes. Biplanar tablets characterized by a diameter of 11 mm with different Propranolol HCl amounts (E = 33%, F = 25%, G = 20%, H = 10%) according to Table 6.1 were prepared by direct compression on a single punch tableting machine (Korsch EK0/DMS, Korsch Pressen GmbH, Berlin Germany).

Table 6.1 Composition of floating Propranolol HCl matrix tablets.

Composition (mg)	E	F	G	H
Propranolol HCl	116.5	87.5	70.0	35.0
Kollidon® SR	230.0	259.0	276.5	311.5
Mg stearate	3.5	3.5	3.5	3.5

The tablet weight was kept constant at 350 mg. Tableting parameters were adjusted to receive a crushing force of 75 N (±4 N), which was determined using an Erweka TBA 30 crushing force tester (Erweka GmbH, Heusenstamm, Germany). Compression forces varied between 3.3 and 4.6 kN.

6.3.2 Curing experiments

For the characterization of curing influences on drug release behaviour and possible matrix erosion half of the tablets were subjected to a temperature regimen of 1 or 3 hours respectively at 60 °C in an incubator (Heraeus B6760, Heraeus Instruments GmbH, Hanau, Germany).

6.3.3 Determination of tablet density

For calculating the apparent densities of the tablet samples their volumes and masses were determined. The height and the diameter of the prepared tablets were measured using a micrometer gauge and then used for the calculation of the volume of the cylindrical devices. Measurements were performed fivefold. The true density of the matrix devices was determined using a helium pycnometer (Accupyc 1330, Micrometrics, Mönchengladbach, Germany) and by averaging 3 measurements. The porosity ε of the samples was then calculated using equation (4):

$$\varepsilon = 1 - \frac{\rho_a}{\rho_t} \tag{4}$$

where ρ_a represents the apparent density and ρ_t the true density of the samples.

6.3.4 Quantification of insoluble tablet matrix erosion

For analyzing the extent of erosion of the insoluble polymer matrix tablets were positioned in an automatic dissolution tester (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) with 900 ml 0.1 N HCl of 37 °C and working at 50 rpm paddle speed. The sampling was performed after 24 hours. After filtrating the dissolution medium and subsequent 12 hours of drying of the filter residue in an incubator (Heraeus B6760, Heraeus Instruments GmbH, Hanau, Germany) working at 60° C the samples were weighed. Experiments were performed in triplicate.

6.3.5 Propranolol HCl release studies

Dissolution tests were performed in triplicate in a dissolution rate test apparatus according to the method 2 in the USP [83]. For this purpose an automatic dissolution tester (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) was used,

operating with 900 ml 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C and 50 rpm. The formulations prepared were subjected to dissolution tests for 24 hours. The amount of dissolved Propranolol HCl was determined by measuring the UV absorption at 290 nm and calculated using a calibration equation for the drug.

6.3.6 Monitoring of floating behaviour

Floating strength measurements were performed using the same experimental setup and procedure described in chapter 5.3.4. All floating experiments were performed in triplicate.

6.3.7 Determination of swelling parameters

As tablet swelling represents a vital factor to maintain buoyancy of the floating devices the increase in radial and axial tablet extensions was measured as tablet diameter and tablet height. Therefore photographs of the tablets after predetermined time intervals of contact with 0.1 N HCl of 37 °C were taken and evaluated using an image analysing software (AnalySis auto, Olympus Deutschland GmbH, Hamburg, Germany).

6.3.8 ^{1}H NMR benchtop imaging experiments

^{1}H NMR benchtop imaging experiments were carried out using the same experimental conditions and parameters described in chapter 5.3.6 for the characterization of the coated floating tablets. Experiments were performed in triplicate.

6.4 Results and discussion

6.4.1 Determination of tablet density

Apparent tablet density of all samples was lower than 1.004 mg/cm^{3} and related to Propranolol HCl: Kollidon® SR ratio, whereas higher Kollidon® SR contents led to a decreased tablet density as well as an increased porosity (Table 6.2). The polymeric structure of Kollidon® SR possesses an enhanced ability to entrap air during the compression process compared to the crystalline structure of the salt Propranolol

HCl. Additionally Propranolol HCl exhibits a slightly higher density (1.233 g/cm³) compared to Kollidon® SR (1.211 g/cm³). The porosity increased linearly (r = 0.989 for uncured and r = 0.993 for cured tablet samples) with decreasing drug contents in the matrix tablets. The determined values of the apparent density as well as the porosity changed for cured tablets compared to tablets without temperature treatment. The spontaneous densification of poly(vinyl acetate) due to subjection to curing conditions have been modelled by measuring volume and enthalpy recovery [227]. Interestingly, the values remained constant after three hours of curing compared to those obtained from tablets being subjected to an increased temperature for only one hour. These results provide an indication that the temperature induced changes might have been completed after one hour of curing. Therefore, the values determined after curing of one hour and three hours are not given separately in Table 6.2.

Table 6.2 Apparent density, true density and porosity of Propranolol HCl matrix tablets before and after being subjected to curing conditions.

Formulation	**Apparent density (mg/cm³)**		**True density (mg/cm³)**		**Porosity**	
Curing	before	after	before	after	before	after
E (33 % drug)	0.92	0.91	1.216	1.216	0.24	0.25
F (25 % drug)	0.89	0.86	1.216	1.216	0.27	0.29
G (20 % drug)	0.85	0.83	1.215	1.215	0.30	0.32
H (10 % drug)	0.82	0.79	1.214	1.214	0.33	0.35

The increase of the apparent density due to the temperature treatment manifests in an all in all increase in tablet height and diameter, which might be caused by the higher mobility and flexibility of the polymer chains in presence of temperatures above the glass transition temperature, leading to a slight extension of the tablet dimensions. Additionally, a slight weight loss after the curing process, which might be due to the loss of in the tablet remaining humidity, contributed to the decrease in tablet density.

In summary, the reduction in tablet density and thus the increase in tablet porosity were only marginal for all tablet formulations.

6.4.2 Quantification of insoluble tablet matrix erosion

Disintegration of the tablet samples did not occur, indicating the formation of true matrices. Within the first hour of contact with dissolution medium tablet samples with formulation E (cured and uncured) and formulation F (uncured) began to show a slight erosion of the insoluble matrix on the edges of the tablet, which was visible due to sedimenting particles on the bottom of the vessel.

Table 6.3 Quantification of insoluble tablet matrix erosion of uncured and cured tablet samples (n.d. = not determinable).

Formulation	Erosion of uncured tablets (%)	Erosion of cured tablets (%)
E (33 % drug)	3.4 ± 0.2	2.6 ± 0.1
F (25 % drug)	1.6 ± 0.1	n.d.
G (20 % drug)	n.d.	n.d.
H (10 % drug)	n.d.	n.d.

The curing process led to a solidification of the tablet as the temperature exceeding the glass transition temperature caused an increased mobility of the polymer chains reducing imperfections in the matrix structure. On the other hand Propranolol HCl contributes to defects in the matrix structure due to its crystalline nonpolymeric structure. Therefore, higher Propranolol HCl contents as well as tablet samples in the uncured state increased the probability of matrix instability at exposed areas like the edge of the tablet. However, erosion of the unsoluble tablet matrix occurred only marginally and can therefore be seen as negligible.

6.4.3 Characterization of Propranolol HCl release

Kollidon® SR efficiently sustained the Propranolol HCl release from the matrix devices. In the literature an amount of at least 20 – 30 % Kollidon® SR is required to extend drug liberation [35,213]. The drug release profiles of all tablet formulations exhibited a decrease in dissolution rate after being cured (Fig. 6.1), which is usually related to a relaxation in polymer structure or reorganization of defects emerging from the compression process [228]. Subjecting the tablet samples to the curing conditions for three hours did not further change the dissolution profile compared to

samples being cured for only one hour, indicating a stabilization of the dissolution profile after one hour of temperature treatment. These findings comply with the results obtained by Shao et al., who stated a stabilization of the dissolution rate of PVAc-based matrix tablets after being subjected to a temperature treatment of 1 hour at 60 °C [218]. This group did not detect significant changes in the drug release profile by extending the curing up to 18 hours, which is in accordance with the curing conditions reported for EC-based matrix tablets and coated beads ranging from 60 °C to 90 °C of a few hours up to one day [229,230].

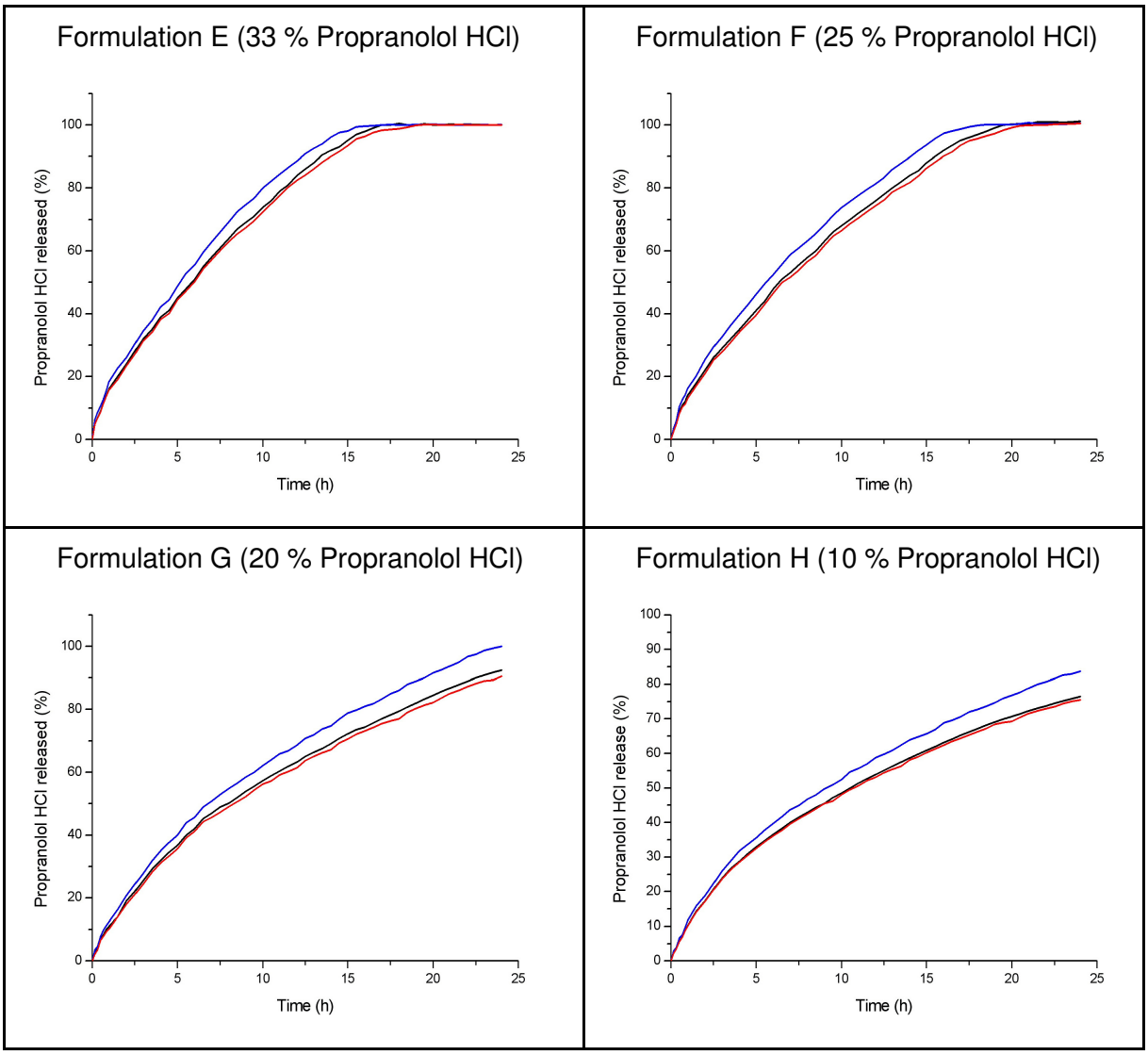


Fig. 6.1 Propranolol HCl release profiles of uncured (blue), 1 h cured (black) and 3 h cured (red) tablet samples.

As a stabilization of the physical tablet properties after one hour of curing was assumed, these samples were used for all further experiments.

Kollidon® SR controlled the release of the hydrophilic model drug Propranolol HCl efficiently over a time period of at least 17 hours (Fig. 6.2). Complete drug release within 24 hours was achieved for formulation E and F. Higher polymer contents led to decreased drug release rates as well as a lower total amount of released drug. Furthermore, no lag times prior to drug release were observed.

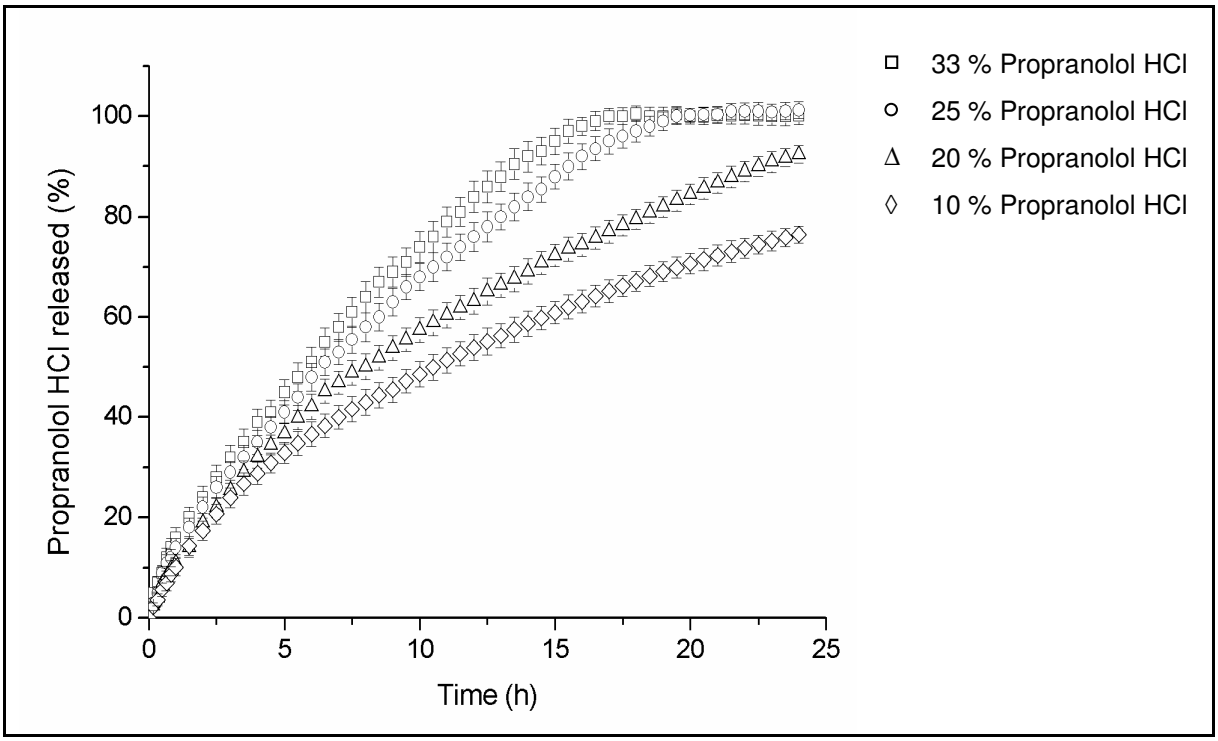


Fig. 6.2 Release of Propranolol HCl from Kollidon® SR matrix tablets into 0.1 N HCl.

The most important mechanisms controlling the drug release from matrix tablets are diffusion, swelling and erosion. After contact with aqueous dissolution medium water concentration gradients form at the water/polymer interface leading to a beginning water diffusion into the matrix system. As water acts as a plasticizer, the glass transition temperature of the polymer is decreased. In case the temperature of the surrounding dissolution medium exceeds the T_g the polymer matrix changes from the glassy to the rubbery state. Continuing water diffusion into the matrix device will result in a limited swelling of the polymeric device. In contrast to HPMC, PVAc as an inert water insoluble matrix former will neither form a hydrogel-based diffusion layer nor strongly erode.

In general, drug release from matrix devices may be controlled by the diffusion of the drug out of the matrix device or the polymer relaxation resulting in some cases in the dissolution of the matrix releasing the drug. Often a combination of both mechanisms

can be found. Swelling of the polymeric matrix will additionally contribute to the drug release characteristics.

For inert and non-eroding matrix systems with a completely dissolved drug incorporated within the device the drug release is given by Fick's second law of diffusion:

$$\frac{\delta \mathrm{c}\,(\mathrm{x,t})}{\delta \mathrm{t}} = -\frac{\delta J(x)}{\delta x} = +D\,\frac{\delta^2 c(x)}{\delta x^2} \tag{5}$$

where *c* represents the concentration of the drug, *x* the coordinate of the path, *t* the time, *J* the mass flow and *D* the diffusion coefficient.

The drug release from non-erodible matrix systems characterized by a drug which is suspended within the polymeric matrix is described by the Higuchi equation:

$$\frac{M_t}{A} = \sqrt{D\,(2c_0 - c_s)c_s\,t} \tag{6}$$

where M_t represents the absolute amount of the drug released at time *t*, *A* the surface area of the matrix device with contact to the surrounding dissolution medium, c_0 the initial drug concentration in the polymer matrix and c_s the solubility of the drug within the polymer. The equation describes the concentration gradient driven diffusion through an extending diffusion barrier, whereas the concentration gradient has to be kept constant with $c_0 >> c_s$. In case c_s falls below c_0 the drug release characteristics are no longer governed by Higuchi kinetics. This is also true for matrix systems containing poorly water soluble drugs as the drug dissolution will represent the rate-determining step. Swelling and erosion of the polymer matrix will change the value of the diffusion constant *K* and thus lead to deviations from the Higuchi kinetics as well. Further assumptions for the validity of the Higuchi equation are the maintenance of perfect sink conditions, a constant diffusivity of the drug, a one-dimensional diffusion, no interactions occurring between the matrix and the drug and the drug particle size being much smaller than the thickness of the system. Beyond that, the formation of pores within the polymeric matrix due to the dissolution of the drug or water soluble matrix components is neglected in the Higuchi equation.

The Higuchi equation is valid for a thin matrix layer with an incorporated drug substance, i.e. the area of the upside and underside of the investigated tablet has to be much greater than the height of the tablet. This means that the validity of the Higuchi equation in case of tablets is limited to thin discs. Nevertheless drug release

from matrix tablets which do not conform to these requirements is often fitted to Higuchi kinetics due to its simplicity. This offers the possibility to receive a rough idea of the drug release mechanism of the investigated matrix system.
Equation (6) may be simplified to the following term:

$$\frac{M_t}{M_\infty} = K\sqrt{t} \tag{7}$$

with M_∞ representing the absolute drug amount released cumulatively from the matrix and K as a constant comprising the characteristics of the respective dosage form. Clearly, drug release is related to square root of time kinetics and bound to the initial drug concentration incorporated in the matrix, the composition of the matrix system, the porosity, the tortuosity of the pores within the matrix and finally the solubility of the drug.

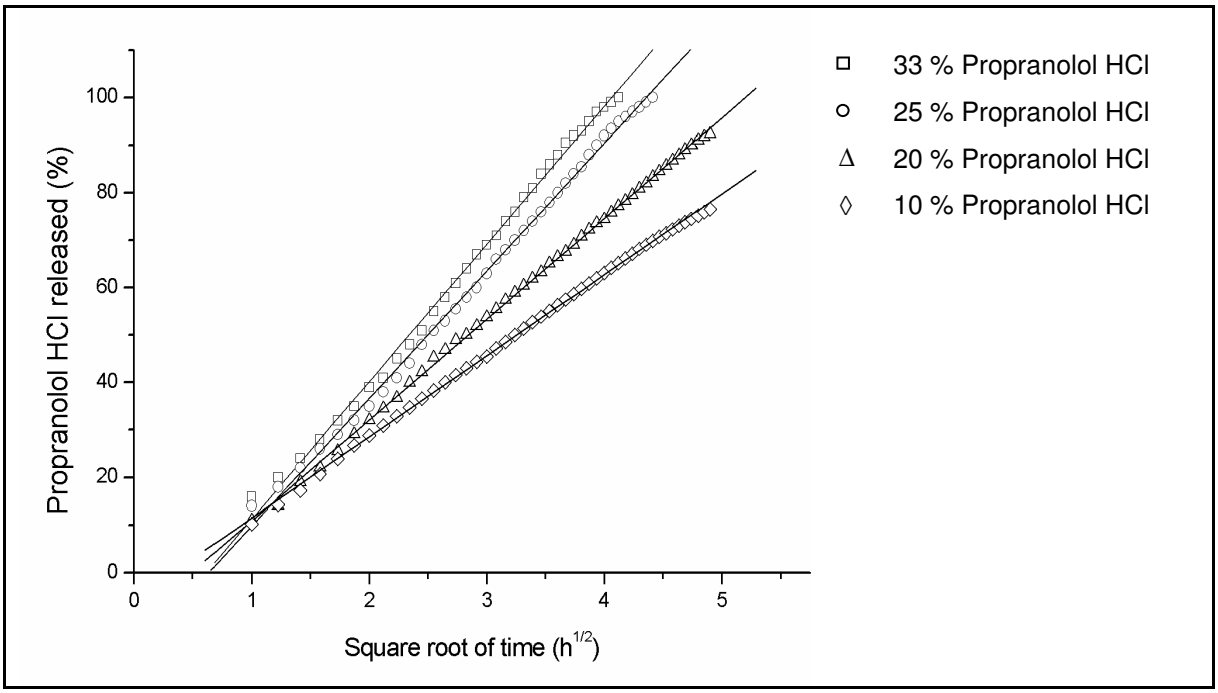


Fig. 6.3 Propranolol HCl release profiles from Kollidon® SR matrix tablets into 0.1 N HCl after fitting to Higuchi kinetics.

For the analysis of drug release characteristics the cumulative amount of released drug was plotted against the square root of time (Fig. 6.3). The coefficient of determination r^2 represents the squared correlation coefficient and was used as an indicator for the fitting of the considered model (Table 6.4). Propranolol HCl release from Kollidon® SR-based matrix tablets follows approximately square root time of kinetics. It has to be pointed out, that drug release kinetics also depend on the

physicochemical properties of the model drugs as the literature is divided as to which kinetical model describes the drug release from poly(vinyl acetate)-based tablets. Various groups detected drug release with square root time of kinetics as well as non-square root time of kinetics for different drugs [231,232].

Table 6.4 Coefficients of determination (r^2) for fitting the Propranolol HCl release from the floating PVAc matrices to square root time of kinetics.

Formulation	r^2
E (33 % Propranolol HCl)	0.9962
F (25 % Propranolol HCl)	0.9976
G (20 % Propranolol HCl)	0.9994
H (10 % Propranolol HCl)	0.9994

To receive more detailed information about the drug release mechanism the data obtained from the dissolution studies were analyzed according to equation (8) related to the Korsmeyer-Peppas model [233,234]:

$$f_t = a\, t^n \tag{8}$$

where f_t represents the percentage of drug released at time t (M_t/M_∞), a is a constant incorporating geometric and structural characteristics and n is an exponent which indicates the drug release mechanism. For $n = 0.5$ the drug release from the matrix is diffusion controlled, whereas n values of 1.0 indicate a drug release independent of time and therefore corresponds to zero-order release kinetics being related to a swelling controlled drug release. As these values are only valid for the interpretation of the drug release mechanism from slabs, variations in matrix geometry lead to deviations in n values for the different drug release mechanisms. In the case of cylindrical devices the value of the variable n corresponds to different diffusion mechanisms given in Table 6.5 [235].

Fickian diffusion is related to $n = 0.45$, whereas $n = 0.89$ indicates case II transport (zero order release) and $n > 0.89$ super case II transport. Values of n between 0.45 and 0.89 identify anomalous (non-Fickian) diffusion, corresponding to coupled diffusion and polymer relaxation. In practice, drug release from polymeric matrices will not solely be either diffusion-controlled or dissolution controlled but be characterized by a predominant drug release mechanism superpositioning competing

processes. Therefore, the application of the Korsmeyer-Peppas model on DDSs of interest provides information regarding the prevalent mechanism of drug liberation.

Table 6.5 Corresponding drug release mechanisms for different values of *n.*

Values of *n*	**Drug release mechanism**
0.45	Fickian diffusion
0.45 – 0.89	Non-Fickian diffusion
0.89	Case II transport (zero order release)
> 0.89	Super case II transport

As the Korsmeyer-Peppas model is often valid for cumulative released drug amounts up to ~ 60 %, the data used for the analysis were limited to this range. To identify the drug release mechanism, *n* values for the different formulations were calculated using equation (8) and by linearly fitting the part of the drug release curve where $M_t/M_\infty < 0.6$ in a log-log coordinate plane.

This simple, semi-empirical model for drug release kinetics has already been used for Kollidon® SR, starch acetate/ethyl cellulose and HPMC-based matrix drug delivery systems [131,236,237]. Nevertheless, the fact has to be taken into account, that this so-called “power-law” assumes constant diffusivities as well as constant dimensions of the studied system [238]. As swelling is limited in Kollidon® SR-based matrix systems, the application of the Korsmeyer-Peppas model on these systems can be considered.

The coefficient of determination r^2 was used as an indicator for the fitting of the considered model. Apparently the release of Propranolol HCl from the PVAc floating tablets follows the Korsmeyer-Peppas model. Table 6.6 shows the hereby assessed *n* values. As for all of all formulations the release exponent *n* exhibits values close to 0.45, a drug release mechanism which is governed by Fickian diffusion for the water-soluble drug Propranolol HCl can be affirmed. These findings are in accordance with those of Reza et al. who stated a drug release which was predominated by Fickian diffusion for Kollidon® SR matrix systems as well [35]. The release rate constant *a* decreased with higher Kollidon® SR levels. An analogous effect has already been reported by Shah et al. concerning HPMC-based matrix devices [239].

Table 6.6 Kinetic parameters based on equation (8) for Propranolol HCl matrix tablets (*a* – release kinetic constant; *n* – release exponent; r^2 – coefficient of determination; $T_{50\%}$ - the time for 50 % of the drug to be released).

Formulation	*a* (h^{-n})	*n*	r^2	$T_{50\%}$ (h)
E (33 % Propranolol HCl)	0.267	0.426	0.986	5.7
F (25 % Propranolol HCl)	0.264	0.448	0.986	6.2
G (20 % Propranolol HCl)	0.255	0.456	0.988	8.1
H (10 % Propranolol HCl)	0.250	0.465	0.996	11.0

Increased Kollidon® SR/drug ratios resulted in decreased release kinetic constant. These findings are in accordance with the results obtained by Shao et al. regarding the drug release from Kollidon® SR-based matrices.

Referring to matrix drug delivery systems containing a polymer blend with water soluble and water insoluble compounds like Kollidon® SR, a hydrophilic drug will be released due to dissolution and diffusion of the drug through water filled capillaries. As polyvinyl pyrrolidone dissolves from the matrix system as well, this effect will lead to an increase in pore size and quantity and thus enhanced drug release. Higher levels of a hydrophilic drug contributed strongly to this effect as can be seen in a faster drug release for the samples E and F compared to G and H.

6.4.4 Monitoring of floating behaviour

All tablet samples were floating immediately due to their low apparent densities (Table 6.2). The floating strength was related to Kollidon® SR and Propranolol HCl content (Fig. 6.2). Higher excipient levels were related to a slightly lower density and thus improved floating behaviour. These results indicate that the incorporation of Propranolol HCl has a negative effect on the floating properties of the tablets. During the dissolution process Propranolol HCl will start to dissolve, whereas the water insoluble matrix former Kollidon® SR will begin to swell. Therefore the ability to efficiently entrap the air present in the matrix tablet will improve with increased Kollidon® SR contents.

Floating of all PVAc-based matrices continued over 24 hours with terminal resultant weight values for samples E to H of 11.5 mg, 12.7 mg, 17.2 mg and 33.5 mg respectively.

Referring to equation (2) in chapter 5.3.4 it is obvious that the total floating force of the tablets is related to their density and their volume being associated with the water uptake and the swelling characteristics of the system.

Positioning of the samples in dissolution medium led to immediate water penetration into the tablets without a significant swelling and thus volume increase of the device, causing initially reduced floating strength values. This effect can be observed with the examined samples due to a stronger initial decrease in floating strength. To ensure the matrix tablets to remain afloat, the balance between water uptake and swelling of the device has to be maintained. After about 2 or 3 hours the floating strength remains almost constant and decreases only marginally. At this point water diffusion into the tablets was compensated by the swelling of the device. The penetrated water was also capable of solving and withdrawing entrapped air from the matrix, leading to a step-wise loss in floating strength as well.

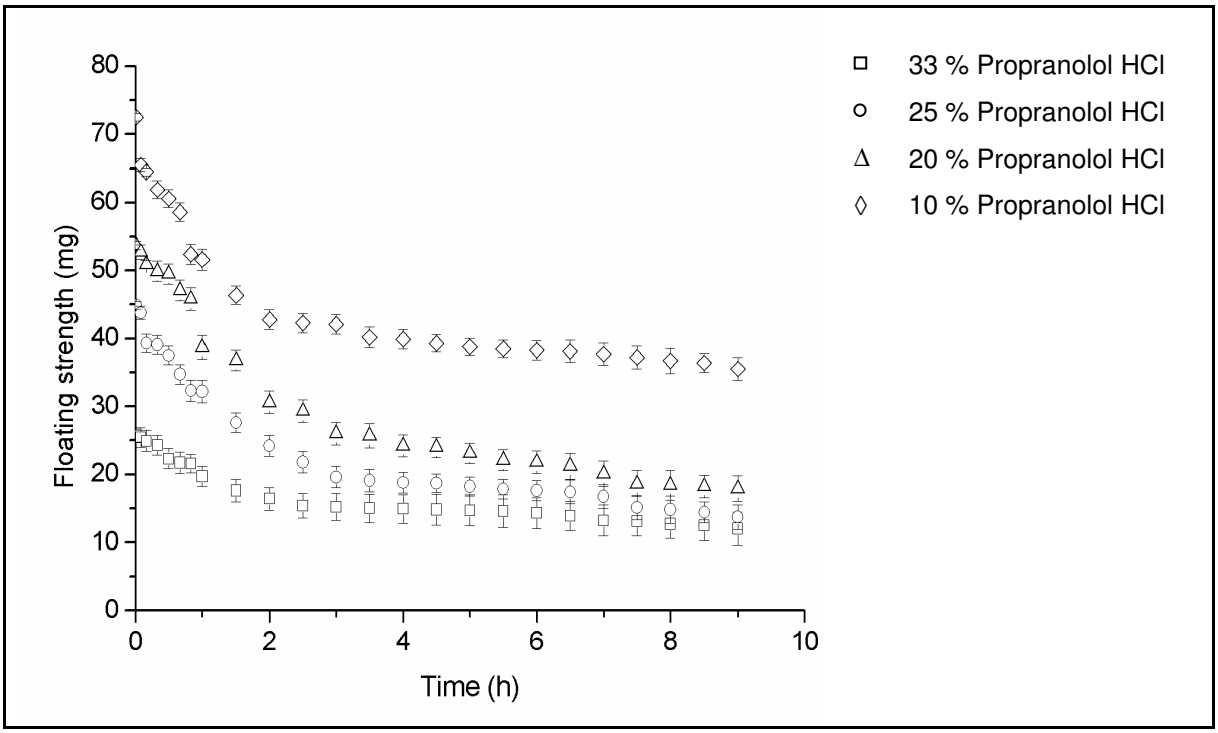


Fig. 6.4 Floating strength of Propranolol HCl matrix tablets in 0.1 N HCl.

Interestingly, the curve progression of the floating strength values deviates from the ones described for HPMC matrix tablets, which show an initially strong increase in resultant weight values due to the intense swelling after contact with aqueous medium [240]. In contrast to PVAc-based matrix tablets, swelling effects initially overcompensate the water imbition into the tablets until a maximum floating strength

value was reached. Afterwards resultant weight values declined caused by more pronounced water uptake to reach equilibrium. As swelling was obviously limited for Kollidon SR matrices only a decrease in floating strength values was observed.

6.4.5 Characterization of swelling behaviour

To reveal differences in swelling behaviour photographs of swollen tablets with the lowest (formulation E) and the highest (formulation H) polymer content are shown in Figs. 6.5 and 6.6. Slightly uneven tablet surfaces that occur after 1 h (E) and 3.5 h (H) are due to entrapped air inside the tablet.

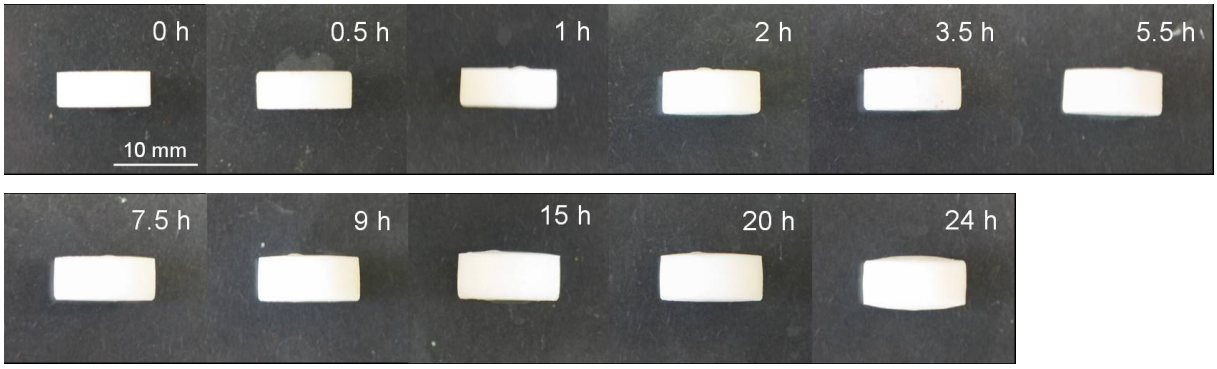


Fig. 6.5 Swelling characteristics of matrix tablets with 33 % Propranolol HCl (E) in 0.1 N HCl as a function of time.

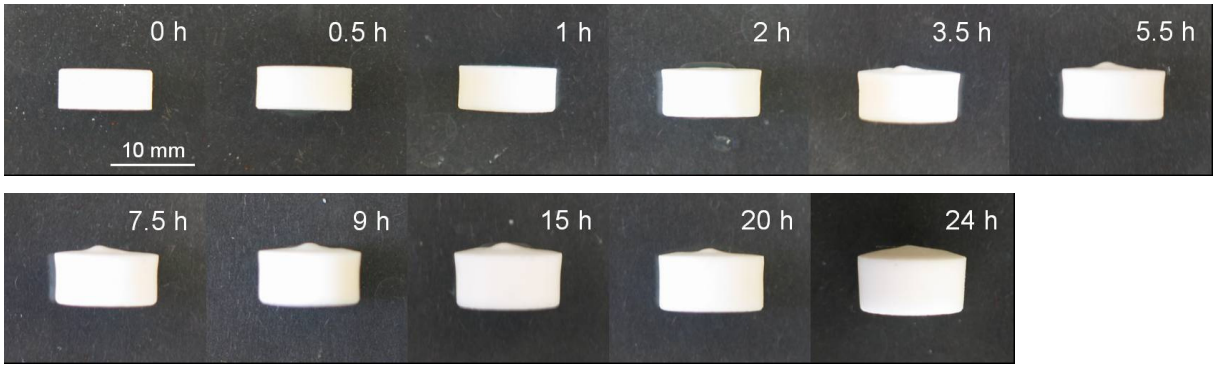


Fig. 6.6 Swelling characteristics of matrix tablets with 10 % Propranolol HCl (H) in 0.1 N HCl as a function of time.

To expose differences in swelling behaviour caused by increased polymer/drug ratios of the different tablet compositions, tablet swelling data i.e. increases in tablet height and diameter were fitted by applying the equation according to Therien-Aubin et al. [57]:

$$S = S_{max} (1 - e^{-kt}) \quad (9)$$

where S represents the swelling at time t, S_{max} the maximum swelling value and k the swelling rate.

The respective values of S_{max} and k for the examined tablet samples are listed in Table 6.7. Changes in polymer concentration affected swelling characteristics only marginally, as only slight differences of S_{max} and k values were observed.

Swelling characteristics were anisotropic, i.e. were more pronounced in axial direction than in radial direction, which is probably due to the same effect already described for starch and HPMC-based matrix tablets [57,241,242,243,244].

Table 6.7 Swelling data of Propranolol HCl matrix tablets according to equation (9).

Formulation	***radial***		***axial***	
	k_s (h^{-1})	S_{max} (%)	k_s (h^{-1})	S_{max} (%)
E (33 % Propranolol HCl)	0.18	9.7	0.18	31.7
F (25 % Propranolol HCl)	0.18	10	0.20	32.2
G (20 % Propranolol HCl)	0.18	10.2	0.21	32.7
H (10 % Propranolol HCl)	0.19	10.6	0.23	33.3

As compression is applied on the systems in axial direction, granules are deformed into irregular spheres. After contact with water and subsequent swelling these granules regain their spherical shape which is associated with a stronger increase in tablet height than in tablet diameter. Higher polymer concentrations were related to slightly increased swelling, which is explicable due to the fact that the fraction of the model drug does not contribute to the swelling process. As only the concentration but not the type of polymer in our formulations was changed, the marginally occurring changes in swelling characteristics were already expected.

Axial cuts of matrix tablets subjected to dissolution test conditions exhibited a slightly porous structure caused by the release of Propranolol HCl and the water soluble polymer PVP (Fig. 6.7). Furthermore, isolated cavities featuring larger dimensions were observed.

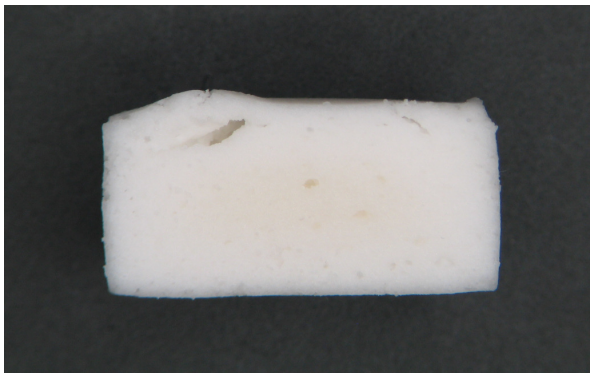


Fig. 6.7 Axial cut tablet with composition H after 9 hours of contact with 0.1 N HCl of 37 °C.

6.4.6 ^{1}H NMR benchtop imaging experiments

^{1}H NMR benchtop imaging was used to monitor matrix hydration and swelling characteristics of the tablet samples with the highest (formulation E) and the lowest (formulation H) Propranolol HCl content. Figures represent axial side images of the chosen matrix tablets. Selected images for both samples are shown in Fig. 6.8 and 6.9 respectively.

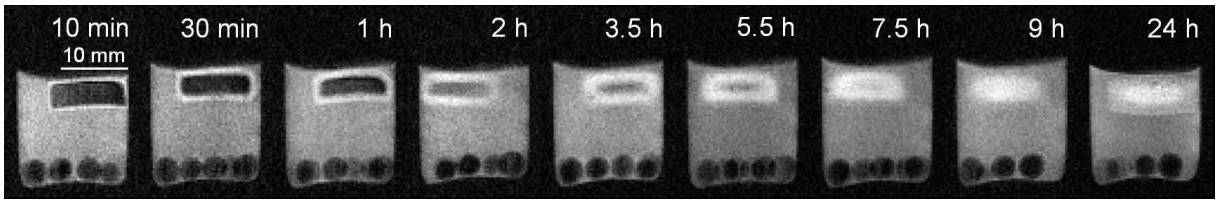


Fig. 6.8 Water penetration into matrix tablets with 33 % Propranolol HCl (E) in 0.1 N HCl as a function of time.

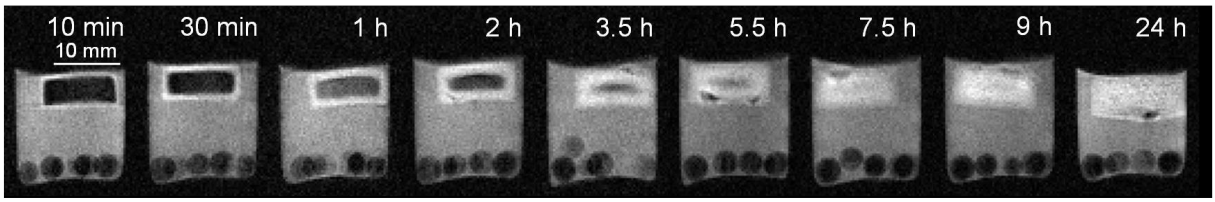


Fig. 6.9 Water penetration into matrix tablets with 10 % Propranolol HCl (H) in 0.1 N HCl as a function of time.

The ^{1}H signal intensity is a function of proton density, relaxation times and imaging sequences. Dark areas in the ^{1}H NMR images refer to low spin densities or short T_1 relaxation times, which are related to dry parts of the tablet. Protons in the swollen polymer layer are stimulated repeatedly, whereas the signal of the protons in the surrounding medium is suppressed by choosing an appropriate imaging sequence. This fact explains the higher signal intensity in the gel layer compared to the signal of

the dissolution medium, where the spin density is higher and relaxation times are longer. Measurements were conducted T_1 related to shorten measurement periods. Thus it was possible to follow hydration characteristics of the developed systems more easily.

^{1}H NMR images exhibited axial sights of floating matrix tablets. Glass beads, which were added to allow three-dimensional water diffusion even in case of sinking tablets were visible as dark spots on the bottom of the test tube. For both samples the beginning water diffusion into the tablets was visible after 10 minutes due to a bright edge representing the hydrated polymer layer surrounding the dry tablet core. It was possible to monitor the continuing water diffusion into the tablet over time as can be seen in an increase in thickness of the water diffusion layer. Benchtop ^{1}H NMR images revealed isotropic water diffusion for both tablet samples. After 9 hours the matrices were completely hydrated. The water diffusion front clearly separates regions in the tablet matrix being characterized by a polymer in the glassy and in the swollen rubbery state. Initially the solubilzation of the drug is required to enable drug diffusion and thus liberation. Swollen areas of the tablet matrices indicate regions where the drug is directly exposed to the aqueous dissolution medium. Therefore, drug release is only possible from hydrated tablet regions. The hydration of tablet samples with higher drug content was expected to be faster due to rapid leaching of the hydrophilic model drug and a lower amount of matrix forming polymer hampering drug and water diffusion. Interestingly no significant difference in hydration velocity for both formulations was observed. For tablets with a higher drug content after several hours of contact with dissolution medium the visualization of the outer parts of the tablet matrix was decreased, so that only the inner core of the matrix tablet was visible. This might be due to a higher porosity and slight erosion in these areas of the matrix and thus resulting sponge-like structure with high amounts of dissolution medium inside the matrix. The increased relaxation times reduced then the contrast to the free water in the medium.

Magnetic resonance images of samples with formulation H exhibited cavities with entrapped air inside the matrix, which were visible as dark spots. The origin of this air lies in the leaching of Propranolol and Kollidon® 30 as well as in the increased initial porosity of the tablet leading to the lowest density of all samples. The swelling of the tablet, which was visible due to an all in all increase in radial and axial tablet extensions, additionally contributed to the formation of pores. The proceeding

leaching process increases the probability for the formation of larger cavities. The fact, that these increased pores almost exclusively form in the outer regions of the matrix devices further indicates the involvement of leaching and swelling processes, which are terminated earlier in these areas compared to the inner core of the matrix.

6.5 Conclusion

Drug release can be approximately modelled by the application of square root of time kinetics, which allows the prediction of drug release profiles from Kollidon® SR based matrix tablets with varying polymer/drug ratios.

In this chapter floating oral drug delivery devices were developed by using direct compression without any time consuming granulation processes. Drug release was delayed efficiently by Kollidon® SR as a matrix forming excipient and was found to be governed by Fickian diffusion.

In contrast to HPMC matrix tablets, which were found to exhibit increased drug release rates with more pronounced swelling characteristics, for Kollidon® SR based matrix devices the drug release was reduced in tablet samples with stronger polymer swelling [207]. HPMC is characterized by strong swelling upon contact with aqueous medium leading to the relaxation of the polymer chains and thus volume expansion. The incorporated drug is then able to diffuse out of the tablet matrix. For inert poly(vinyl acetate) based matrices two different mechanisms mainly governing the drug release are competing with each other. PVAc matrices swell only to a limited amount due to the water insolubility of the polymer, whereas the swelling of the device facilitates the drug diffusion out of the tablet matrix. On the other hand, decreased polymer contents and thus higher drug amounts in the DDS result in an increased formation of pores caused by the leaching of the drug. Propranolol HCl as a water soluble drug will contribute to this mechanism to a higher extent compared to a poor water soluble drug. Therefore, increased drug/polymer ratios resulted in increased drug release rates. The effect of pore formation due to drug dissolution was found to overcompensate the swelling effects on drug release.

For estimating food effects on application of floating oral drug delivery effects it is of great importance to study floating performance not only regarding floating duration but floating strength as well. All formulations remained afloat for a time interval of 24 hours and showed an increased floating strength for samples with a higher polymer/drug ratio. In addition Benchtop Magnetic Resonance Imaging proved to be a valuable method to monitor water diffusion and swelling processes of the developed matrix tablets non-invasively and continuously.

7. Summary and perspectives

7.1 English version

Sustained release oral dosage forms play a very important role at the pharmaceutical market [245,246]. Principles for drug retardation include coating of tablets, capsules and pellets, matrix or hydrocolloid embedding, osmotic controlled release systems and multiparticulate dosage forms. Since many drugs like e.g. antihypertensives demand constant plasma levels, controlled drug delivery systems are used to avoid high fluctuations of drug plasma levels and decrease the frequency of administration. This leads to reduced side effects and a better compliance.

The focus of this thesis was on the development and characterization of solid oral dosage forms based on poly(vinyl acetate). For this purpose two different ready to use excipient preparations were utilized, namely Kollicoat® SR and Kollidon® SR. The former represents an aqueous polymer dispersion consisting of 27 % poly(vinyl acetate), 2.7 % PVP and 0.3 % silica. In combination with the water soluble coating polymer Kollicoat® IR film coats allowing membrane controlled drug delivery are obtained. In this thesis polymer coats with different Kollicoat® SR/IR ratios and coating thicknesses were used to adjust the desired drug release pattern. Additionally the impact of drug solubility on drug release pattern was studied by incorporating Theophylline and Propranolol HCl respectively as model drugs.

Thermal analysis the polymer films by means of DSC and TMA revealed an efficient plastization by the addition of triacetin. Interestingly a further decrease in glass transition temperature was found for polymer films with an increased Kollicoat® IR content. This effect can be explained by the chemical structure of Kollicoat® IR being a water soluble film forming polymer with a covalently bound plasticizer.

Drug release from tablets coated with polymer films characterized by Kollicoat® SR/IR ratios of 9/1 and 8/2 was related to the content of water-soluble PEG-PVA, coating level and drug solubility. In this connection the blend of both coating polymers proved to efficiently extend drug release. Despite the long history of coated oral dosage forms, many aspects regarding a deeper analysis of the drug release mechanism have been neglected. As for an initialization of the drug release the drug has to be solubilzed within the tablet core the monitoring of water diffusion processes through the polymer coat leads to a deeper understanding of mechanisms governing drug

liberation. Therefore EPR spectroscopy was applied on systems ot interest. As both model drugs are EPR silent, the EPR spin probe 3-Carbamoyl proxyl was incorporated into tablets. EPR studies indicated an immediate water penetration through the coating layer into the tablet core. It was shown, that water is able to solubilize the majority of water soluble compounds within minutes. Thus EPR spectroscopy proved to be a powerfol method to monitor the first steps of diffusion processes and the physicochemical state of coated dosage forms.

Another aspect affecting drug release patterns lies in the dissolution induced change in film coat composition. Film coats of tablets with membrane controlled drug delivery are subjected to changes in film composition due to a leaching out of water soluble compounds, whereas this process determines the permeability of the polymer film. The leaching of Kollicoat® IR, Kollidon® 30 and plasticizer triacetin were monitored by means of ^{1}H NMR spectroscopy and SEM. Drug release kinetics was found to be related to dissolution induced changes in coating composition. The permeability of the film coat for the incorporated drug Propranolol HCl increased, when about 80 % (coat SR/IR:8/2) and 90 % (coat SR/IR:9/1) respectively of the water soluble compounds were leached out of the film coat. The developed ^{1}H NMR method allowed the monitoring of leaching kinetics without time consuming sample preparation. SEM micrographs revealed morphological changes of the polymer coat on the tablet surface that were also related to an alteration of film coat composition.

As a further step the previously analyzed polymer coats were applied on Kollidon® SR-based tablet cores to receive gastroretentive drug delivery systems. Kollidon® SR represents a freely flowable physical mixture of 80 % poly(vinyl acetate) and 20 % poly(vinyl pyrrolidone). Due to its strong dry binding properties Kollidon® SR is used as matrix forming excipient. Furthermore, Kollidon® SR-based tablets exhibit a low density and a high crushing strength even when being compressed at lower compression forces. By the addition of sodium bicarbonate to the tablet core, a coated floating tablet was obtained. As water penetration through the polymeric film coat was shown to occur within minutes, the hydrochloric acid of the dissolution medium was expected to rapidly diffuse into the tablet, leading to a floatation of the system due to the CO_2 development. In these systems coatings based on Kollicoat® SR/IR polymer blends proved to strongly extend drug release. The exceptional elasticity of the coating formulations was able to withstand the forces excerted by the formation of carbon dioxide inside the tablet. Thus the risk of dose

dumping by the use of poly(vinyl acetate) as a coating polymer was reduced. Regarding the floating characteristics floating lag time, floating duration as well as floating strength were determined. The latter plays an important role regarding the in vivo performance of the gastroretentive tablet as the system has to float in the presence of food. By performing floating strength measurements it was possible to evaluate and compare the floating abilities of the developed systems more accurately. Floating properties were dependent on coating level and film composition. Though the application of MRI is widely accepted to study drug release mechanisms, until now no studies regarding the monitoring of floating drug delivery systems are available. Benchtop magnetic resonance imaging allowed the monitoring of water diffusion, swelling and carbon dioxide formation inside the tablet. Thus it was possible not only to receive deeper insights into the drug release mechanism but also into processes determining the floating ability of the system.

To compare floating DDSs characterized by different mechanisms resulting in the floatation of the tablet, Kollidon® SR based floating matrix devices were developed and characterized applying the same techniques used for the coated floating tablets. Floating abilities and drug release pattern were related to drug:polymer ratio, leading to a decreased drug release rate and improved floating behaviour at a higher poly(vinyl acetate) content. Furthermore drug release kinetics and swelling characteristics were determined.

Table 7.1 Overview regarding advantages and disadvantages of the developed floating DDSs.

Coated floating tablets	**Floating matrix tablets**
Advantages	*Advantages*
- linear drug release profile	- no lag times prior to floating onset
- high floating strength values	- pH-independent floating mechanism
Disadvantages	*Disadvantages*
- lag times prior to floating onset	- drug release following Higuchi kinetics
- pH-dependent floating mechanism	- initially low and continiously decreasing floating strength values

Comparing finally both developed floating drug delivery systems, it has to be pointed out, that none of the floating DDS developed in this thesis is implying only advantageous characteristics (Table 7.1). However, an essential advantage of the developed systems described in this work compared to systems already on the market lies in the short lag time prior to flotation as well as the strong floating strength characteristics. Based on the findings of this thesis further optimization may be taken into account.

Future perspectives

Despite promising approches concerning the development of floating tablets only reliable in vivo data can proof the efficacy of the system. Regarding the design of in vivo studies, tests in the fed state as well as in the fasted state have to be taken into account to ensure whether optimized drug plasma profiles are based on the gastroretention of the system or on food effects. Therefore not only the determination of drug plasma levels is of importance but also the monitoring of the gastroretentive properties of the system for example by applying γ-scintigraphy or MRI.
Although a review of the corresponding literature revealed controversial opinions regarding the in vivo behaviour and thus the benefits of single-unit and multiple-unit dosage forms, the use of monolithic devices is in general no longer seen as a state of the art technology in the development of oral drug delivery systems [247]. In contrast to this, small floating and non-floating capsules, were reported to be emptied fastest from the stomach, compared to capsules with an increased size, due to their small dimension [148]. This clearly reduces the transit time through the GI tract and thus the time period to provide extended drug release action and will be more pronounced for even smaller DDS such as minitablets, pellets and microspheres. Nevertheless, a clear advantage comparing these systems with monolithic devices lies in avoiding an “all or nothing” principle. Therefore, the application of some findings presented in this thesis to develop extended release multiparticulate DDSs based on poly(vinyl acetate) may be beneficial.

7.2 German version

Retardarzneiformen spielen auf dem pharmazeutischen Markt eine wichtige Rolle [245,246]. Zu den Prinzipien der verzögerten Wirkstofffreisetzung zählen überzogene Tabletten, Kapseln und Pellets, Matrix- oder Hydrokolloideinbettungen, osmotisch kontrollierte Freigabesysteme und multipartikuläre Arzneiformen. Da viele Arzneistoffe wie zum Beispiel Antihypertensiva konstante Plasmaspiegel erfordern, werden Systeme mit kontrollierter Wirkstofffreisetzung verwendet, um starke Schwankungen im Plasmaspiegel zu verhindern und damit die Einnahmehäufigkeit zu verringen. Die führt zu verringerten Nebenwirkungen und einer besseren Compliance.

Im Mittelpunkt dieser Arbeit stand die Entwicklung und Charakterisierung fester, oraler Darreichungsformen auf Polyvinylacetatbasis. Mit dieser Zielsetzung wurden zwei verschiedene gebrauchsfertige Hilfstoffzubereitungen, namentlich Kollicoat® SR und Kollidon® SR, verwendet. Erstere stellt eine wässrige Polymerdispersion, bestehend aus 27 % Polyvinylacetat, 2.7 % PVP und 0.3 % Siliziumdioxid dar. In Kombination mit dem wasserlöslichen Überzugspolymer Kollicoat® IR werden Filmüberzüge mit membrankontrollierter Freisetzung erhalten. In dieser Arbeit wurden Polymerüberzüge in unterschiedlichen Kollicoat® SR/IR Verhältnissen und Schichtdicken verwendet, um das gewünschte Freisetzungsprofil anzupassen. Zusätzlich wurde durch die Verwendung von Theophyllin und Propranolol HCl als Modellarzneistoffe der Einfluss der Arzneistofflöslichkeit auf das Freigabeprofil analysiert.

Die Thermoanalyse der Polymerfilme mittels DSC and TMA zeigte eine effektive Wirkung des Weichmachers Triacetin. Interessanterweise wurde für Polymerfilme mit einem erhöhten Kollicoat® IR-Anteil eine weitere Absenkung der Glasübergangstemperatur beobachtet. Dieser Effekt ist durch die chemische Struktur von Kollicoat® IR zu erklären, welche einen an einen wasserlöslichen Filmbildner gebundenen Weichmacher darstellt.

Die Arzneistofffreigabe aus Tabletten, überzogen mit Polymerfilmen unterschiedlicher Zusammensetzung (SR/IR:9/1 und SR/IR:8/2), war an den Anteil an wasserlöslichem PEG-PVA, an die Schichtdicke des Überzugs und die Arzneistofflöslichkeit gebunden. Trotz der weitreichenden Historie überzogener, oraler Arzneiformen wurden viele Aspekte bezüglich eines tieferen Verständnisses von Freisetzungsmechanismen bis heute vernachlässigt. Da für die beginnende

Arzneistofffreigabe der Arzneistoff im Tablettenkern gelöst vorliegen muss, führt die Beobachtung des Wasserdiffusionsprozesses durch den Polymerfilm zu einem tieferen Verständnis der Wirkstofffreisetzungsmechanismen. Hierfür kam die ESR-Spektroskopie an ausgewählten Systemen zum Einsatz. Da beide Modellarzneistoffe „ESR-stumm“ sind, wurde die ESR-Spinsonde 3-Carbamoylproxyl in die Tabletten inkorporiert. Die ESR-Untersuchungen zeigten eine sofortige Wasserpenetration durch die Überzugsschicht in den Tablettenkern. Es konnte gezeigt werden, dass das Wasser in der Lage war, innerhalb weniger Minuten einen großen Anteil der wasserlöslichen Komponenten zu lösen. Somit konnte belegt werde, dass die ESR-Spektroskopie eine leistungsstarke Methode darstellt, um die initialen Schritte von Diffusionsprozessen und den physiko-chemischen Zustand überzogener Arzneiformen zu beobachten.

Ein weiterer, die Freisetzungsprofile beeinflussender Faktor ist die auflösungsbedingte Veränderung der Zusammensetzung des Filmüberzugs. Filmüberzüge von Tabletten mit membrankontrollierter Freisetzung unterliegen durch das Auswaschen von wasserlöslichen Komponenten Veränderungen in der Filmzusammensetzung, wobei dieser Prozess die Durchlässigkeit des Polymerfilms bestimmt. Das Herauslösen von Kollicoat® IR, Kollidon® 30 und dem Weichmacher Triacetin wurde mit Hilfe der ^{1}H NMR Spektroskopie und der Rasterelektronenmikroskopie verfolgt. Die Freistzungskinetik war abhängig von freisetzungsbedingten Veränderungen in der Filmzusammensetzung. Die Durchlässigkeit des Filmüberzugs für den inkorporierten Arzneistoff Propranolol HCl erhöhte sich, als ca. 80 % (SR/IR:8/2) bzw. 90 % (SR/IR:9/1) der wasserlöslichen Komponenten aus dem Film herausgewaschen waren. Die entwickelte ^{1}H NMR-Methode erlaubte das Verfolgen der Auswaschungskinetik ohne aufwendige Probenvorbereitung. Die SEM-Aufnahmen zeigten morphologische Veränderungen der Oberfläche des Polymerüberzugs, welche ebenfalls auf eine freisetzungsbedingte Veränderung der Filmzusammensetzung zurückzuführen sind.

Als ein weiterer Schritt wurden die zuvor analysierten Polymerüberzüge auf Kollidon® SR enthaltende Tablettenkerne aufgebracht, um gastroretentive Arzneistofffreigabesysteme zu erhalten. Kollidon® SR stellt eine frei fließende physikalische Mischung aus 80 % Polyvinylacetat und 20 % Polyvinylpyrrolidon dar. Durch seine starken Trockenbindeeigenschaften wird Kollidon® SR als Hilfstoff für Matrices verwendet. Weiterhin weisen Tabletten auf Basis von Kollidon® SR eine

geringe Dichte und selbst bei geringen Presskräften eine hohe Bruchfestigkeit auf. Durch die Zugabe von Natriumhydrogencarbonat zum Tablettenkern wurde eine überzogene Schwimmtablette erhalten. Da eine Wasserdiffusion durch den Polymerfilm innerhalb weniger Minuten bereits nachgewiesen wurde, gab es die Erwartung, dass auch die Salzsäure aus dem Freisetzungsmedium schnell permeieren und zu einem CO_2 bedingten Aufschwimmen des Systems führen würde. In diesen Systemen zeigten Überzüge bestehend aus Kollicoat® SR/IR Polymermischungen eine stark verzögerte Arzneistofffreisetzung. Die außergewöhnliche Elastizität der Überzugsformulierungen war in der Lage, den in der Tablette durch die CO_2-Entwicklung wirkenden Kräften zu widerstehen. Somit wurde durch die Verwendung von Polyvinylacetat das Risiko einer ungewollten, schlagartigen Arzneistofffreisetzung reduziert. Im Hinblick auf die Schwimmeigenschaften wurden die Lag-Zeit vor dem Aufschwimmen, die Schwimmdauer sowie die Auftriebsstärke bestimmt. Letztere spielt eine wichtige Rolle in Bezug auf das Verhalten der gastroretentiven Tablette in vivo, da die Tablette in Gegenwart von Nahrungsbestandteilen schwimmen muss. Durch die Durchführung von Auftriebsstärkemessungen war es möglich, das Aufschwimmvermögen der entwickelten Systeme genauer zu bewerten und zu vergleichen. Die Auftriebseigenschaften waren bei diesen Systemen von der Schichtdicke des Überzuges und der Filmzusammensetzung abhängig.

Obwohl die Anwendung der Magnetresonanztomographie weithin zur Charakterisierung von Arzneistofffreisetzungsmechanismen anerkannt ist, sind bis heute keine Studien bezüglich der Erfassung schwimmender Arzneistofffreigabesysteme verfügbar. Benchtop MRI erlaubte das Verfolgen von Wasserdiffusion, Quellung und CO_2-Bildung innerhalb der Tablette. Daher war es nicht nur möglich, tiefere Einblicke in Arzneistofffreigabemechanismen, sondern auch in solche Prozesse zu erhalten, welche die Aufschwimmeigenschaften des Systems bestimmen.

Um schwimmende Arzneistofffreigabesysteme mit unterschiedlichen Aufschwimmmechanismen vergleichen zu können, wurden floatierende Matrices auf Kollidon® SR-Basis hergestellt und mit denselben Methoden wie zuvor untersucht. Die Aufschwimmeigenschaften und das Azneistofffreigabeprofil waren abhängig vom Arzneistoff:Polymer-Verhältnis mit verringerter Arzneistofffreisetzung und

verbesserten Schwimmeigenschaften bei höherem Polymeranteil. Weiterhin wurden die Freisetzungskinetik sowie die Quellungseigenschaften bestimmt.
Bei einem abschließenden Vergleich der beiden entwickelten, schwimmenden Arzneistofffreigabesysteme muss darauf hingewiesen werden, dass keines der in dieser Arbeit beschriebenen Systeme ausschließlich vorteilhafte Eigenschaften in sich vereint (Tabelle 7.2). Dennoch liegt ein entscheidender Vorteil der im Rahmen dieser Arbeit entwickelten Systeme im Vergleich zu den sich bereits auf dem Markt befindlichen in der kurzen Auftriebs-lag-Phase sowie der hohen Auftriebsstärke. Deshalb kann, basierend auf den Erkenntnissen dieser Arbeit, eine weitere Optimierung in Betracht gezogen werden.

Tabelle 7.2 Überblick über die Vor- und Nachteile der entwickelten Schwimmarzneiformen.

Überzogene Schwimmtabletten	**Matrix-Schwimmtabletten**
Vorteile	*Vorteile*
- lineares Arzneistofffreisetzungsprofil - starkes Auftriebsvermögen	- keine Lag-Zeiten vor dem Aufschwimmen - pH-unabhängiger Auftriebsmechanismus
Nachteile	*Nachteile*
- Lag-Zeiten vor dem Aufschwimmen - pH-abhängiger Auftriebsmechanismus	- Arzneistofffreisetzung folgt der Higuchi-Kinetik - anfänglich geringes und kontinuierlich abnehmendes Auftriebsvermögen

Ausblick

Trotz vielversprechender Lösungsansätze im Hinblick auf die Entwicklung von Schwimmtabletten können nur verlässliche in vivo-Daten die Effizienz eines solchen Systems nachweisen. Hinsichtlich des Designs von in vivo-Studien sollte sowohl eine Prüfung nach Nahrungsaufnahme als auch eine im nüchternen Zustand in Betracht

gezogen werden um sicherzustellen, ob die optimierten Blutspiegelkurven auf der Gastroretention des Systems oder auf Nahrungsmitteleffekten beruhen. Hierfür ist nicht nur die Erhebung von Blutspiegelkurven, sondern auch die Kontrolle der gastroretentiven Eigenschaften des Systems zum Beispiel mittels γ-Scintigraphie oder MRI von Bedeutung.

Obwohl eine Durchsicht der entsprechenden Literatur kontroverse Meinungen bezüglich des in vivo-Verhaltens und der damit verbundenen Vorteile von einzeldosierten und multipartikulären Arzneiformen aufzeigte, kann allgemein die Verwendung monolithischer Arzneiformen nicht mehr als Technologie gemäß dem aktuellen Stand von Forschung und Wissenschaft angesehen werden [247]. Im Gegensatz dazu wurde für kleine schwimmende und nicht schwimmende Kapseln eine schnellere Magenpassage im Vergleich zu größeren Kapseln berichtet [148]. Dies reduziert eindeutig die Transitzeit durch den Gastrointestinaltrakt und damit das Zeitfenster für eine retardierte Wirkstofffreisetzung und wird für noch kleinere Arzneiformen wie zum Beispiel Minitabletten, Pellets und Microspheren noch eine stärkere Ausprägung aufweisen. Dennoch liegt beim Vergleich dieser Systeme mit monolithischen Arzneiformen ein klarer Vorteil darin, das „alles oder nichts“-Prinzip zu umgehen. Somit könnte die Anwendung einiger Erkenntnisse, die in dieser Arbeit aufgezeigt wurden, der Entwicklung multipartikulärer Arzneistofffreigabesysteme mit verzögerter Freisetzung auf Basis von Polyvinylacetat dienlich sein.

List of publications

1. Reviewed papers

S. Strübing, H. Metz, K. Mäder
Mechanistic analysis of drug release from tablets with membrane controlled drug delivery, Eur. J. Pharm. Biopharm., 66 (2007) 113-119.

S. Strübing, H. Metz, F. Syrowatka, K. Mäder
Monitoring of dissolution induced changes in film coat composition by ^{1}H NMR spectroscopy and SEM, J. Control. Release, 119(2) (2007) 190-196.

S. Strübing, H. Metz, K. Mäder
Characterization of poly(vinyl acetate) based floating matrix tablets, J. Control. Release, 126(2) (2008) 149-155.

S. Strübing, T. Abboud, R.V. Contri, H. Metz, K. Mäder
New insights on poly(vinyl acetate)-based coated floating tablets: Characterization of hydration and CO_2 generation by benchtop MRI and its relation to drug release and floating strength, Eur. J. Pharm. Biopharm., 69(2) (2008) 708-717.

2. Conferences

S. Strübing, K. Mäder
Characterisation of drug and water penetration behaviour of film coated tablets with diffusion controlled drug delivery, Controlled Release Society, German Chapter Annual Meeting, Jena, Germany, 2006 (Podium presentation).

S. Strübing, H. Metz, K. Mäder
A deeper insight into the mechanism of drug release from Kollicoat® SR/IR coated tablets, 33rd Annual Meeting of the Controlled Release Society, Vienna, Austria, 2006 (Podium presentation).

S. Strübing, H. Metz, K. Mäder
Characterization of release processes from Kollicoat® SR/IR coated tablets, Part 1: Drug release and ESR studies, Polypharma, Halle/Saale, Germany, 2006 (Poster presentation).

S. Strübing, F. Syrowatka, K. Mäder
Characterization of drug release processes from Kollicoat® SR/IR coated tablets, Part 2: ESEM and NMR spectroscopy study, Polypharma, Halle/Saale, Germany, 2006 (Poster presentation).

S. Strübing, K. Mäder
New insights in dissolution induced changes of coated dosage forms by NMR spectroscopy and ESEM, Joint Meeting of the Czech, German and Hungarian Pharmaceutical Societies, Marburg, Germany, 2006 (Poster presentation).

S. Strübing, H. Metz, K. Mäder
Characterization of permeation processes of coated dosage forms with novel polymers, 34th Annual Meeting of the Controlled Release Society, Long Beach, California, U.S.A., 2007 (Poster presentation).

S. Strübing, H. Metz, K. Mäder
Characterization of floating Kollidon SR matrix tablets, 34th Annual Meeting of the Controlled Release Society, Long Beach, California, U.S.A., 2007 (Poster presentation).

S. Strübing, H. Metz, K. Mäder
Development and characterization of floating Kollidon® SR matrix tablets, Controlled Release Society German Chapter Annual Meeting, Freiburg, Germany, 2007 (Poster presentation).

Literature

[1] K.H. Bauer, K.-H. Frömming, C. Führer, Lehrbuch der Pharmazeutischen Technologie, Wissenschaftliche Verlagsgesellschaft Stuttgart, 8. Auflage (2008) 298-360.

[2] A. Hoffman, Pharmacodynamic aspects of sustained release preparations, Adv. Drug Deliv. Rev. 33(3) (1998) 185-199.

[3] S.A. Eisen, D.K. Miller, R.S. Woodward, E. Spitznagel, T.R. Przybeck, The effect of prescribed daily dose frequency on patient medication compliance, Arch. Intern. Med., 150 (1990) 1881-1884.

[4] L.N. Sansom, Oral extended release products, Aust. Prescr. 22 (1999) 88-90.

[5] M.N.V. Ravi Kumar, N. Kumar, Polymeric controlled drug-delivery systems: Perspective issues and opportunities, Drug Dev. Ind. Pharm. 27(1) (2001) 1-30.

[6] D. Hoichman, L.I. Gromova, J. Sela, Gastroretentive controlled-release drugs, Pharm. Chem. J., 38(11) (2004) 35-38.

[7] S.S. Davis, J.G. Hardy, M.J. Taylor, D.R. Whalley, C.G. Wilson, A comparitive study of the gastrointestinal transit of a pellet and tablet formulation, Int. J. Pharm. 21(2) (1984) 167-177.

[8] G. Van Savage, C.T. Rhodes, The sustained release coating of solid dosage forms: a historical review, Drug Dev. Ind. Pharm., 21 (1995) 93-118.

[9] R.S. Okor, S. Otimenyin, I. Ijeh, Coating of certain matrix cores with aqueous-based systems of acrylate methacrylate, a water-insoluble copolymer and drug release profiles, J. Controlled Release 16(3) (1991) 349-353.

[10] P.A. Elchidana, S.G. Deshpande, Microporous membrane drug delivery system for indomethacin, J. Controlled Release 59 (1999) 279-285.

[11] G.M. Zentner, G.S. Rork, K.J. Himmelsteic, Controlled porosity osmotic pump, U.S. Patent 4968507, 1990.

[12] T. Lindholm, B.A. Lindholm, M. Niskanen, J. Koskiniemi, Polysorbate 20 as a drug release regulator in ethyl cellulose film coatings, J. Pharm. Pharmacol. 38 (1986) 686-688.

[13] H. S. Alkhatib, A. Sakr, Modelling of the effects triethyl citrate and curing conditions on drug release from film coated tablets, Pharm. Ind., 67(2) (2005) 237-242.

[14] B.D. Rohera, N.H. Parikh, Influence of type and level pf water-soluble additives on drug release and surface and mechanical properties of Surelease® films, Pharm. Dev. Techn. 7(4) (2002) 421-432.

[15] F. Siepmann, A. Hoffmann, C. Wahle, S. Zach, B. Leclercq, B. Carlin, J. Siepmann, Aquacoat® ECD-based film coatings for controlled rug delivery: how to adjust desired membrane properties, 33rd Annual meeting of the controlled release society 2006.

[16] P. Rama Rao, P.V. Diwan, Formulation and in vitro evaluation of polymeric films of diltiazem hydrochloride and indomethacin for transdermal application, Drug Dev. Ind. Pharm. 24(4) (1998) 227-236.

[17] P. Sakellariou, R.C. Rowe, The morphology of blends of ethylcellulose with hydroxypropyl methylcellulose as used in film coating, Int. J. Pharm., 125 (1995) 289-296.

[18] F. Siepmann, J. Siepmann, M. Walther, R.J. MacRae, R. Bodmeier, Polymer blends for controlled release coatings, J. Control. Release, 125 (2008) 1-15.

[19] K. Kolter, F. Ruchatz, Kollicoat SR 30D - a new sustained release excipient, 26th Proceedings of the International Symposium on Controlled Release of Bioactive Materials (1999) 867-868.

[20] M.S. Bordaweka, H. Zia A. Quadir, Evaluation of polyvinyl acetate dispersion as a sustained release polymer for tablets. Drug Delivery 13(2) (2006) 121-31.

[21] A. Dashevsky, K. Wagner, K. Kolter, R. Bodmeier, Physicochemical and release properties of pellets coated with Kollicoat SR 30 D, a new aqueous polyvinyl acetate dispersion for extended release, Int. J. Pharm. 290 (1-2) (2005) 15-23.

[22] A. Dashevsky, K. Kolter, R. Bodmeier, pH-independent release of a basic drug from pellets coated with the extended release polymer dispersion Kollicoat SR 30 D and the enteric polymer dispersion Kollicoat MAE 30 DP, Eur. J. Pharm. Biopharm. 58(1) (2004) 45-49.

[23] Technical Information Kollicoat® SR 30 D, BASF, Ludwigshafen, Germany.

[24] A. Dashevsky, K. Kolter, R. Bodmeier, Compression of pellets coated with various aqueous polymer dispersions, Int. J. Pharm. 279 (1-2) (2004) 19-26.

[25] W. Sawicki, R. Lunio, Compressibility of floating pellets with verapamil hydrochloride coated with dispersion Kollicoat SR 30 D, Eur. J. Pharm. Biopharm. 60 (2005) 153-158.

[26] Z.J. Shao, L. Morales, S. Diaz, N.A. Muhammad, Drug release from Kollicoat SR 30D-coated nonpareil beads: Evaluation of coating level, plasticizer type, and curing condition, AAPS PharmSciTech. 3(2) (2002) article 15.

[27] Europäisches Arzneibuch, ISBN 978-3-7692-4063-4, Deutscher Apotheker Verlag 2007

[28] D. Flick, K. Kolter, Polyvinyl acetate dispersion. Development of sustained-release pharmaceutical dosage forms by granulation and tableting. Pharm. Techn. 27(10) (2003) 86-100.

[29] R. Gandhi, C. Issa, R. Malik, Polymer coating composition for taste masking coating, WO 2004052345 (A1) PCT Int. Appl. (2004).

[30] S. Janssens, G. Van Den Mooter, Enhancing solubility and dissolution rate of poorly soluble drugs, 2007115381 (A2) PCT Int. Appl. (2007).

[31] S. Janssens, H. Novoa de Armas, J.P. Remon, G. Van den Mooter, Use Kollicoat IR in the formulation of solid dispersions of itraconazole, Eur. J. Pharm. Sci., 30(3-4) (2007) 288-294.

[32] S.Y. Chan, L.-L. Chen, D.J. Chetty, J.J. Liu, Orally dissolving films for rapid drug release, WO 2005009386(A2) PCT Int. Appl. (2005).

[33] H.-R. Hoffmann, R. Braendli, F. Theobald, Fast-disintegrating wafer-shaped oral delivery systems for opioid combinations, DE 102006027793 (A1) 20071220 Ger. Offen. (2007).

[34] F. Siepmann, A. Hoffmann, B. Leclercq, B. Carlin, J. Siepmann, How to adjust desired drug release patterns from ethylcellulose-coated dosage forms, J. Control. Rel. 119(2) (2007) 182-189.

[35] S. Reza, M.A. Quadir, S.S. Haider, Comparitive evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery, J. Pharm. Pharm. Sci. 6(2) (2003) 282-291.

[36] B.K. Narayan, K. Hall, Polyvinyl acetate applied to controlled-release formulations, Pharm. Techn. (Suppl.) (2003) 34-37.

[37] V. Cailly-Dufestel, C. Herry, J. Bacon, P. Oury, Crush-resistant oxycodone tablets intended for preventing accidental misuse and unlawful diversion, WO2007099154 (A1), PCT Int. Appl. (2007).

[38] E. Draganoiu, M. Andheria, A. Sakr, Evaluation of the new polyvinyl acetate / povidone excipient for matrix sustained release dosage forms, Pharm. Ind. 63(6) (2001) 624-629.

[39] S. Mamajiwalla, S. Frisbee, Modified release formulations of tramadol, WO2007078895(A2), PCT Int. Appl. (2007).

[40] C.-C. Wang, M.R. Tejwani, W.J. Roach, J.L. Kay, J. Yoo, H.L. Surprenant, D.C. Monkhouse, T.J. Pryor, Development of near zero-order release dosage forms using three-dimensional printing (3-DP^{TM}) technology, Drug Dev. Ind. Pharm. 32 (2006) 367-376.

[41] F. Zhang, J.W. McGinity, Properties of hot-melt extruded theophylline tablets containing poly(vinyl acetate). Drug Dev. Ind. Pharm. 26(9) (2000) 931-942.

[42] J. Siepmann, H. Kranz, Calculation of the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles, Int. J. Pharm., 200 (2000) 151-164.

[43] N.A. Kasim, M. Whitehouse, C. Ramachandran, M. Bermejo, H. Lennernäs, A.S. Hussain, H.E. Junginger, S.A. Stavchansky, K.K. Midha, V.P. Shah, G.L. Amidon, Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification, Mol. Pharm. 1 (2004) 85-96.

[44] C.M. Castleden, C.F. George, The effect of ageing on the hepatic clearance of propranolol, Brit. J. Clin. Pharmacol., 7(1) (1979) 49-54.

[45] J.M. Dunn, P.E. Groth, A. DeSimone, Once daily Propranolol, Lancet, 8465 (1985) 1183-1184.

[46] P.B. Bottini, M.E. Caulfield, J.G. Devane, E.J. Geoghegan, D.E. Panoz, Comparative oral bioavailability of conventional propranolol tablets and a new controlled absorption propranolol capsule, Drug Dev. Ind. Pharm., 9 (1983) 1475-1493.

[47] K. Aktories, U. Förstermann, F.B. Hofmann, K. Starke, Allgemeine und spezielle Pharmakologoe und Toxikologie, 9. Auflage, Elsevier GmbH, München, 2005.

[48] N. Ur-Rahman, Y. Kh, W. J. Woei, N.A. Khan, Differential scanning calorimetry and surface morphology studies on coated pellets using aqueous dispersions, Pak. J. Pharm. Sci. 18(2) (2005) 19-23.

[49] P.C. Mora, M. Cirri, P. Mura, Differential scanning calorimetry as a screening technique in compatibility studies of DHEA extended release formulations, J. Pharm. Biomed. Anal., 42 (2006) 3-10.

[50] P.M. Fechner, S. Wartewig, A. Kiesow, A. Heilmann, P. Kleinbudde and R.H.H. Neubert, Interaction of water with different substituted cellulose ethers: A Raman spectroscopy and Environmental Scanning Electron Microscopy study, J. Pharm. Pharmacol. 57 (2005) 689-698.

[51] P.M. Fechner, S. Wartewig, A. Kiesow, A. Heilmann, P. Kleinebudde, R.H.H. Neubert, Influence of water on molecular and mophological structure of various starches and starch derivates, Starch 57 (2005) 605-615.

[52] K. Hauschild, K.M. Picker-Freyer, Evaluation of tableting and tablet properties of Kollidon SR: The influence of moisture and mixtures with theophylline monohydrate, Pharm. Dev. Technol. 11(1) (2006) 125-140.

[53] A.J. Fitzgerald, B.E. Cole, P.F. Taday, Nondestructive analysis of tablet coating thickness using terahertz pulsed imaging, J. Pharm. Sci. 94(1) (2005) 177-183.

[54] L. Ho, R. Müller, M. Römer, K.C. Gordon, J. Heinämäki, P. Kleinebudde, M. Pepper, T. Rades, Y.C. Shen, C.J. Strachan, P.F. Taday, J.A. Zeitler, Analysis of sustained-release tablet film coats using terahertz pulsed imaging, J. Control. Release 119 (2007) 253-261.

[55] W.E. Baille, C. Malveau, X.X. Zhu, R.H. Marchessault, NMR imaging of high-amylose starch tablets. 1. Swelling and water uptake, Biomacromolecules 3 (2002) 214-218.

[56] C. Malveau, W.E. Baille, X.X. Zhu, R.H. Marchessault, NMR imaging of high-amylose starch tablets. 2. Effect of tablet size, Biomacromolecules 3 (2002) 1249-1254.

[57] H. Thérien-Aubin, W.E. Baille, X.X. Zhu, R.H. Marchessault, NMR imaging of high-amylose starch tablets. 3. Initial diffusion and temperature effects, Biomacromolecules 6 (2005) 3367-3372.

[58] C.A. Fyfe, A.I. Blazek-Welsh, Quantitative NMR imaging study of the mechanism of drug release from swelling hydroxypropylmethylcellulose tablets, J. Control. Release 68(3) (2000) 313-333.

[59] I. Katzhendler, K. Mäder, M. Friedman, Correlation between drug release kinetics from protein matrix and matrix structure: EPR and NMR study, J. Pharm. Sci., 89 (2000) 365-381.

[60] I. Katzhendler, K. Mäder, M. Friedman, Structure and hydration properties of hydroxypropyl methyl cellulose matrices containing naproxen and naproxen sodium, Int. J. Pharm. 200(2) (2000) 161-179.

[61] H.E. Williams, V.C. Loades, M. Claybourn, D.M. Murphy, Electron paramagnetic resonance spectroscopy studies of oxidative degradation of an active pharmaceutical ingredient and quantitative analysis of the organic radical intermediates using partial Least-squares regression, Anal. Chem. 78(2) (2006) 604-608.

[62] S. Siepe, W. Herrmann, H.-H. Borchert, B. Lueckel, A. Kramer, A. Ries, R. Gurny, Microenvironmental pH and microviscosity inside pH-controlled matrix tablets: An EPR imaging study, J. Control. Release 112(1) (2006) 72-78.

[63] L.A. Felton, G.S. Timmins, A Nondestructive Technique to Determine the Rate of Oxygen Permeation into Solid Dosage Forms, Pharm. Dev. Technol. 11(1) (2006) 141-147.

[64] S. Mali, M.V.E. Grossmann, M.A. Garcia, M.N. Martino, N.E. Zaritzky, Microstructural characterization of yam starch films, Carbohydrate Polymers 50(4) (2002) 379-386.

[65] M.M. Meier, L.A. Kanis, V. Soldi, Characterization and drug-permeation profiles of microporous and dense cellulose acetate membranes: influence of plasticizer and pore forming agent, Int. J. Pharm. 278(1) (2004) 99-110.

[66] L.A. Felton, Characterization of coating systems. AAPS PharmSciTech. 8(4) (2007): article 112.

[67] K.S. Murthy, D.A. Kubert, M.B. Fawzi, In vitro release characteristics of hard shell capsule products coated with aqueous- and organic-based enteric polymers, J. Biomater. Appl., 3(1) (1988) 52-79.

[68] K.E. Bacon, F. Charles, Encyclopedia of polymer science and technology, Wiley, New York (1971) Vol. 3, p. 209.

[69] K. Johnson, R. Hathaway, P. Leung, R. Franz, Effect of triacetin and polyethylene glycol 400 on some physical properties of hydroxypropyl methyl cellulose free films, Int. J. Pharm. 73(3) (1991) 197-208.

[70] J. Möckel, Mechanismus kontinuierlicher und gepulster Arzneistofffreisetzung aus Hydrokolloideinbettungen, PhD Thesis (1990).

[71] K. Bechtold, Stabilisierung der Enzymaktivität und Verfügbarkeit von Pankreatinpellets bei wässriger Befilmung mit magensaftresistenten Cellulosederivaten, PhD Thesis (1994).

[72] K. Ueberreiter, F. Asmussen, The rate of solution of polymers I. The theoretical treatment of the process and its temperature dependence, Makromo. Chem. 49 (1961) 324-337.

[73] R.T.C. Ju, P.R. Nixon, M.V. Patel, Drug release from hydrophilic matrices. 1. New scaling laws for predicting polymer and drug release based on the polymer disentanglement concentration and the diffusion layer, Europ. J. Sci. 84 (1995) 1455-1463.

[74] K. Mäder, H.M. Swartz, R. Stösser, H.H. Borchert, The application of EPR spectroscopy in the field of pharmacy, Pharmazie 49 (1994) 97-101.

[75] I. Katzhendler, K. Mäder, R. Azoury, M. Friedman, Investigating the structure properties of hydrated hydroxypropyl methyl cellulose and egg albumin matrixes containing carbamazepine: EPR and NMR study, Pharm. Res. 17 (2000) 1299-1308.

[76] J. Raffi, S. Gelly, L. Barral, F. Burger, P. Piccerelle, P. Prinderre, M. Baron, A. Chamayou, Electron paramagnetic resonance of radicals induced in drugs and excipients by radiation or mechanical treatments, Spectrochim. Acta Part A (2002) 1313-1320.

[77] K. Mäder, Y. Crémilleux, A.J. Domb, J.F. Dunn, H.M. Swartz, In vitro/in vivo comparison of drug release and polymer erosion from biodegradable P(FAD-SA) polyanhydrades-a non-invasive approach by the combined use of electron paramagnetic resonance spectroscopy and nuclear magnetic resonance imaging, Pharm. Res. 14 (1997) 820-826.

[78] K. Mäder, G. Bacic, A. Domb, O. Elmalak, R. Langer, H.M. Swartz, Non-invasive in vivo monitoring of drug release and polymer erosion from biodegradable polymers by EPR spectroscopy and NMR Imaging, J. Pharm. Sci. 86 (1997) 126-134.

[79] D.J. Lurie, K. Mäder, Monitoring of drug delivery processes and by EPR and related techniques-principles and applications, Advanced drug delivery reviews 57 (2005) 1171-1190.

[80] K. Takeshita, A. Hamada, H. Utsumi, Mechanisms related to reduction of radical in mouse lung using L-Band EPR spectrometer, Free Radic. Biol. Med. 26 (1999) 951-960.

[81] A. Afdeef, pH-metric logP II: Refinement of partition coefficients and ionization constants of multiprotic substances, J. Pharm. Sci. 82(2) (1993) 183-190.

[82] K. Kolter, S. Gebert, Coated drug delivery systems, ExAct - Excipients and Actives for Pharma Customer Newsletter 11 (2003) 2-3.

[83] USP 30, United States Pharmacopeial Inc., The United States Pharmacopeia, The National Formulary, Rockville, MD, 2007.

[84] K. Ueberreiter, F. Asmussen, The rate of solution of polymers I, The theoretical treatment of the process and its temperature dependence, Makromol. Chem. 49 (1961) 324-337.

[85] R. Bodmeier, O. Paeratakul, Dry and wet strengths of polymeric films prepared form an aqueous colloidal polymer dispersion, Eudragit RS30D, Int. J. Pharm., 96 (1993) 129-138.

[86] R. Gruetzmann, K.G. Wagner, Quantification of the leaching of triethyl citrate/polysorbate 80 mixtures from Eudragit® RS films by differential scanning calorimetry, Eur. J. Pharm. Biopharm. 60(1) (2005) 159-162.

[87] F. Lecomte, J. Siepmann, M. Walther, R. J. MacRae, R. Bodmeier, pH-Sensitive polymer blends used as coating materials to control drug release from spherical

beads: Elucidation of the underlying mass transport mechanisms, Pharm. Res. 22(7) 2005 1129-11.

[88] M. Tarvainen, S. Peltonen, H. Mikkonen, M. Elovaara, M. Tuunainen, P. Paronen, J. Ketolainen, R. Sutinen, Aqueous starch acetate dispersion as a novel coating material for controlled release products, J. Controlled release 96 (2004) 179-191.

[89] R. Bodmeier, O. Paeratakul, Constant potassium chloride release from micro porous membrane-coated tablets prepared with aqueous colloidal polymer dispersions, Pharm. Res. 3 (1991) 355-359.

[90] K. Ofori-Kwakye, J.T. Fell, Leaching of pectin from mixed film containing pectin, chitosan and HPMC intended for biphasic drug delivery, J. Pharm. 250 (2003) 251-257.

[91] B. Romberg, J.J. Kettenes-van den Bosch, T. de Vringer, G. Storm, W.E. Hennink, 1H NMR spectroscopy as a tool for determining the composition of poly(hydroxyethyl-L-asparagine)-coated liposomes, Bioconjugate Chem. 17 (2006) 860-864.

[92] M. Garcia-Fuentes, D. Torres, M. Martín-Pastor, M.J. Alonso, Application of NMR spectroscopy to the characterization of PEG-stabilized lipid nanoparticles, Langmuir 2004 (20) 8839-8845.

[93] E.A.A.M. Vernooij, C.A. Gentry, J.N. Herron, D.J.A. Crommelin, J.J. Kettenes-van den Bosch, ^{1}H NMR Quantification of poly(ethylene glycol)-phosphatidylethanolamine in phospholipid mixtures, Pharm. Res. 1999 (10) 1658-1661.

[94] M.A. Frohoff-Hülsmann, B.C. Lippold, J.W. McGinity, Aqueous ethyl cellulose dispersion containing plasticizers of different water solubility and hydroxypropyl methyl-cellulose as coating material for diffusion pellets II: properties of sprayed films, Eur. J. Pharm. Biopharm., 48 (1999) 67-75.

[95] A.O. Okhamafe, P. York, Characterization of moisture interactions in some aqueous-based tablet film coating formulations, J. Pharm. Pharmacol. 1985 (37) 385-390.

[96] M.E. Aulton, M.H. Abdul-Razzak, J.E. Hogan, The mechanical properties of hydroxypropyl methylcellulose films derived from aqueous systems; Part 1: The influence of plasticisers, Drug Dev. Ind. Pharm. 7 (1981) 649-668.

[97] R. Bodmeier, O. Paeratakul, Mechanical properties of dry and wet cellulosic and acrylic films prepared from aqueous colloidal polymer dispersions used in the coating of solid dosage foms, Pharm. Res. 11 (1994) 882-888.

[98] K. Kolter, S. Gebert, Coated drug delivery systems based on Kollicoat® SR 30 D, The drug delivery companies report Spring/Summer 2004.

[99] K. Kolter, S. Gebert, B. Fussnegger, A. Quadir, Coated pharmaceutical single-unit delayed release forms, based on polyvinyl acetate, WO 2003/075896. Int. Patent.

[100] J.T. Fell, Delivery systems for targeting to specific sites in the gastrointestinal tact, J. Pham. Phamacol. 51 (Suppl.) (1999) 41.

[101] A. Streubel, J. Siepmann, R. Bodmeier, Gastroretentive drug delivery systems, Expert Opin. Drug Deliv. 3(2) (2006) 217-233.

[102] N. Rouge, P. Buri, E. Doelker, Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery, Int. J. Pharm. 136 (1996) 116-122.

[103] J. Drewe, C. Beglinger T. Kissel, The absorption site of cyclosporin in the human GIT, Br. J. Clin. Pharmacol. 33 (1992) 39-43.

[104] S. Harder, U. Fuhr, D. Bergmann, Ciprofloxacin absorption in different regions of the human GIT. Investigations with hf capsule, Br. J. Clin. Pharmacol. 30 (1990) 35-39.

[105] E.A. Klausner, E. Lavy, D. Stepensky, E. Cserepes, M. Barta, M. Friedman, A. Hoffman, Furosemide pharmacokinetics and pharmacodynamics following gastroretentive dosage form administration in healthy volunteers, J. Clin. Pharmacol. 43 (2003) 711-720.

[106] G.L. Chen, W.H. Hao, In vitro performance of floating sustained-release capsule of verapamil, Drug Dev. Ind. Pharm. 24 (1998) 1067-1072.

[107] S.A. Elkheshen, A.E. Yassin, S. Alsuwayeh F.A. Alkhaled, In vitro and in vivo evaluation of floating controlled release dosage forms of verapamil hydrochloride, Pharm. Ind. 66 (2004) 1364-1372.

[108] R. Singh Matharu, N.M. Sanghavi, Novel drug delivery systems for captopril, Drug Dev. Ind. Pharm. 18 (1992) 1567-1574.

[109] R.S. Matharu, N.M. Sanghavi, Novel drug delivery system for captopril, Drug Dev. Ind. Pharm. 18 (1992) 1567-1574.

[110] L. Whitehead, J.H. Collett, J.T. Fell, Amoxycillin release from a floating dosage form based on alginates, Int. J. Pharm. 210 (2000) 45-49.

[111] S. Burton, N. Washington, R.J.C. Steele, Intragastric distribution of ion-exchange resins: A drug delivery system for the topical treatment of the gastric mucosa, J. Pharm. Pharmacol., 47 (1995) 901-906.

[112] M. Oth, M.Franz, J. Timmermans, A. Moës, The bilayer floating capsule: a stomach-directed drug delivery system for misoprostol, Pharm. Res. 9 (1992) 298-302.

[113] V.F. Patel, N.M. Patel, Intragastric floating drug delivery system of cefuroxim axetil: In vitro evaluation, AAPS PharmSciTech, 7(1) (2006) Article 17.

[114] W. Erni, K. Held, The hydrodynamically balanced system: a novel principle of controlled drug release, Eur. Neurol. 27 (1987) 21-27.

[115] N. Washington, C. Washington, C.G. Wilson, S.S. Davis, What is ‘Liquid Gaviscon’? A comparison of four international formulations, Int. J. Pharm. 34 (1986) 105-109.

[116] J.L. Fábregas, J. Claramunt, J. Cucala, R. Pous, A. Siles, In vitro testing of an antacid formulation with prolonged gastric residence time (Almagate Flot-Coat®), Drug Dev. Ind. Pharm. 20 (1984) 1199-1212.

[117] S.-J. Wang, H. Park, K. Park, Gastro retentive drug-delivery systems, Crit. Rev. Ther. Drug Carrier Syst. 15(3) (1998) 243-284.

[118] A.A. Deshpande, C.T. Rhodes, N.H. Shah, A.W. Malick, Controlled-release drug delivery systems for prolonged gastric residence: an overview, Drug Dev. Ind. Pharm. 22(6) (1996) 531-539.

[119] J.H. Meyer, J. Elashoff, V. Porter-Fink, J. Dressman, G.L. Amidon, Human postprandial gastric emptying of 1-3-millimeter spheres, Gastroenterology, 94(6) (1988) 1315–1325.

[120] N. Salessotis, Measurement of the diameter of the pylorus in man. I. Experimental project for clinical application, Am. J. Surg. 124 (1972) 331-333.

[121] A. Streubel, J. Siepmann, R. Bodmeier, Drug delivery to the upper small intestine window using gastroretentive technologies, Curr. Opin. Pharmacol. 6 (2006) 501-508.

[122] K.C. Waterman, A critical review of gastric retentive controlled drug delivery, Pharm. Dev. Technol., 12 (2007) 1-10.

[123] O. Keinke, H.J. Ehrlein, Effect of oleic acid on canine gastroduodenal motility, pyloric diameter and gastric emptying, Quart. J. Exper. Physiol. 68(4) (1983) 675-686.

[124] G. Cuche, C.-H. Malbert, Ileal short-chain fatty acids inhibit transpyloric flow in pigs, Scand. J. Gastroenterol 34(2) (1999) 149-155.

[125] J. Wang, Y. Tabata, D. Bi, K. Morimoto, Evaluation of gastric mucoadhesive properties of aminated gelatin microspheres, J. Control. Release 73 (2001) 223-231.

[126] J.W. Lee, J.H. Park, J.R. Robinson, Bioadhesive-based dosage forms: the next generation, J. Pharm. Sci. 89 (2000) 850-866.

[127] J.A. Fix, R. Cargill, K. Engle, Controlled gastric emptying: Part 3. Gastric residence time of a nondisintegrating geometrical shape in human volunteers, Pharm. Res. 10 (1993) 1087-1089.

[128] E.A. Klausner, E. Lavy, M. Friedman, A. Hoffman, Expandable gastroretentive dosage forms, J. Control. Release 90 (2003) 143-162.

[129] A.A. Deshpande, N.H. Shah, C.T. Rhodes, W. Malick, Development of a novel controlled-release system for gastric retention, Pharm. Res. 14 (1997) 815-819.

[130] S. Desai, S. Bolton, A floating controlled-release drug delivery system: In vitro-in vivo evaluation, Pharm. Res. 10(9) (1993) 1321-1325.

[131] S. Baumgartner, J. Kristl, F. Vrečer, P. Vodopivec, B. Zorko, Optimisation of floating matrix tablets and evaluation of their gastric residence time, Int. J. Pharm. 195 (2000) 125-135.

[132] A. Streubel, J. Siepmann, R. Bodmeier, Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release, Eur. J. Pharm. Sci. 18 (2003) 37-45.

[133] D. Harris, J.T. Fell, H.L. Sharma, D.C. Taylor, Gastrointestinal transit of potential bioadhesive formulations in man: a scintigraphic study, J. Control. Release, 12 (1990) 45-53.

[134] S.J. Jackson, D. Bush, A.C. Perkins, Comparative scintigraphic assessment of the intragstric distribution and residence of cholestyramine, Carbopol 934 P and sucralfate, Int. J. Pharm., 212 (2001) 55-62.

[135] M. Säkkinen, T. Tuononen, H. Jürjensen, P. Veski, M. Marvola, Evaluation of microcristalline chitosans for gastro-retentive drug delivery, Eur, J. Pharm. Sci., 19 (2003) 345-353.

[136] Y. Akiyama, N. Nagahara, E. Nara, M. Kitano, S. Iwasa, I. Yamamoto, J. Azuma, Y. Ogawa, Evaluattium of oral mucoadhesive microspheres in man on the basis of the pharmacokinetics of furosemide and riboflavin, compounds with limited gastrointestinal absorption sites, J Pharm. Pharmacol., 50(2) (1998) 159-166.

[137] E.A. Klausner, E. Lavy, M. Barta, E. Cserepes, M. Friedman, A. Hoffman, Novel gastroretentive dosage forms: evaluation of a gastroretentivity and its effect in levodopa absorption in humans, Pharm. Res., 20 (2003) 1466-1473.

[138] W.J. Curatolo, J. Lo, Gastric retention system for controlled rug release, US Patent 5,443,843, 1995.

[139] T. Sonobe, S. Watanabe, M. Katsuma, N. Takamatsu, Y. Konno, H. Takagi, Gastric retentive device, Eur. Patent 0415671, 1991.

[140] L.J. Caldwell, C.R. Gadner, R.C. Cargill, Drug delivery device which can be retained in the stomach for a controlled period of time, US Patent, 4735804, 1988.

[141] L. Kagan, N. Lapidot, M. Afargan, D. Kirmayer, E. Moor, Y. Mardor, M. Friedman, A. Hoffman, Gastroretentive accordion pill: enhancement of riboflavin bioavailibility in humans, J. Control. Release, 113 (2006) 208-215.

[142] J. Munk, R. Gannaway, M. Hoare, A. Johnson, Gastrointestinal motility in health and disease, H.L. Duthie (Ed.), MTP, Lancaster (1978) 349-359.

[143] S.A. Elkheshen, A.E.B. Yassin, S. Alsuwayeh, F.A. Alkhaled, In vitro and in vivo evaluation of floating controlled release dosage forms of verapamil hydrochloride, Pharm. Ind. 66(11) (2004) 1364-1372.

[144] B.N. Singh, K.H. Kim, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, J. Control. Release, 63(3) (2000) 235-259.

[145] N. Mazer, E. Abisch, J.-C. Gfeller, R. Laplanche, P. Bauerfeind, M. Cucala, M. Lukachich, A. Blum, Intagastric behaviour and absorption kinetics of a normal and ‘’floating’’ modified-release capsule of isradipine under fasted and fed conditions, J. Pharm. Sci., 77 (1988) 647-657.

[146] A.K. Hilton, P.B. Deasy, In vitro and in vivo evaluation of an oral sustained-release dosage form of amoxicillin trihydrate, Int. J. Pharm., 86 (1992) 79-88.

[147] S.S. Davis, A.F. Stockwell, M.J. Taylor, J.G. Hardy, D.R. Walley, C.G. Wilson, H. Bechgaard, F.N. Christensen, The effect of density on gastric emptying of single- and multiple-unit dosage forms, Pharm. Res., 3 (1986) 208-213.

[148] J. Timmermans, A.J. Moës, Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy, J. Pharm. Sci., 83 (1994) 18-24.

[149] J. Timmermans, B. Van Gansbeke, A.J. Moës, Assessing by gamma scintigraphy the in vivo buoyancy of dosage forms having known size and floating force profiles as a function of time, Proc. 5th Int. Conf. Pharm. Technol., Vol. I, APGI, Paris, (1989) 42-51.

[150] K.E. Gabr, T.M. Borg, Formulation and evaluation of buffered floating furosemide delivery systems, S.T.P. Pharm. Sci., 10 (2000) 181-186.

[151] H.M. Ingani, J. Timmermans, A.J. Moës, Conception and in vivo investigation of peoral sustained release floating dosage forms with enhanced gastrointestinal transit, Int. J. Pharm., 35 (1987) 157-164.

[152] W. Phuapradit, S. Bolton, The influence of tablet density on the human oral absorption of sustained release acetaminophen tablets, Drug Dev. Ind. Pharm., 17 (1991) 1097-1107.

[153] G.A. Agyilirah, M. Green, R. duCret, G.S. Banker, Evaluation of the gastric retentive properties of a cross-linked polymer coated tablet versus those of a non-disintegrating tablet, Int. J. Pharm. 75 (1991) 241-247.

[154] W.L. Xu, X.D. Tu, Z.D. Lu, Development of gentamicin sulfate sustained release tablet floating in the stomach, Yaoxue Xuebao, 26(7) (1991) 541-545.

[155] L. Whitehead, J.T. Fell, J.H. Collett, H.L. Sharma, A.-M. Smith, Floating dosage forms: an in vivo study demonstrating prolonged gastric retention, J. Control. Release, 55 (1998) 3-12.

[156] R. Talukder, R. Fassihi, Gastroretentive delivery systems: A mini review, Drug Dev. Ind. Pharm., 30 (2004) 1019-1028.

[157] Y. Kawashima, T. Niwa, H. Takeuchi, T. Hino, Y. Ito, Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics (in vitro) and floating behavior (in vivo), J. Control. Release, 16 (1991) 279-290.

[158] V. Ianuccelli, G. Coppi, R. Sansone, G. Ferolla, Air compartment multiple-unit system for prolonged gastric residence. Part II. In vivo evaluation, Int. J. Pharm., 174 (1998) 55-62.

[159] N.M. Davies, S.J. Farr, I.W. Kellaway, G. Taylor, M. Thomas, A comparison of the gastric retention of alginate containing tablet formulations with and without the inclusion of excipient calcium ions, Int. J. Pharm., 105 (1994) 97-101.

[160] A. Steingoetter, D. Weishaupt, P. Kunz, K. Mäder, H. Lengsfeld, M. Thumshirn, P. Boesiger, M. Fried, W. Schwizer, Magnetic resonance imaging fort the in vivo evaluation of gastric-retentive tablets, Pharm. Res., 20(12) (2003) 2001-2007

[161] B. Berner, M. Cramer, Y.K. Chiang, L. Rowe, W.B. Smith, S.Y.E. Hou, V.E. Cowles, G. Gusler, I.R. Wilding. Pharmacokinetic and clinical case studies of gastric retentive (GR™) tablets, Podium presentation, 33rd CRS Annual Meeting and Exposition, Vienna, Austria (2006).

[162] M. Ichikawa, T. Kato, M. Kawahara, S. Watanabe, M. Kayano, A new multiple-unit oral floating dosage system. II: In vivo evaluation of floating and sustained release characteristics with p-aminobenzoic acid and isosorbide dinitrate as model drugs, J. Pharm. Sci., 80(12) (1991) 1153-1156.

[163] P.R. Sheth, J.L. Tossounian, Sustained release pharmaceutical capsules, US Patent 4126672, 1978.

[164] P.R. Sheth, J.L. Tossounian, Novel sustained release tablet formulations, US Patent 4167558, 1979.

[165] P.R. Sheth, J.L. Tossounian, The hydrodynamically balanced system (HBS^{TM}): A novel drug delivery system for oral use, Drug Dev. Ind. Pharm. 10 (1984) 313-339.

[166] N. Özdemir, S. Ordu, Y. Özkan, Studies of floating dosage forms of furosemide: In vitro and in vivo evaluations of bilayer tablet formulations, Drug Dev. Ind. Pharm., 26(8) (2000) 857-866.

[167] Z. Wei, Z. Yu, D. Bi, Design and evaluation of a two-layer floating tablet for gastric retention using cisapride as a model drug, Drug Dev. Ind. Pharm., 27(5) (2001) 469-474.

[168] Z. Rahman, M. Ali, R.K. Khar, Design and evaluation of bilayer floating tablets of captopril, Acta Pharm. 56 (2006) 49-57.

[169] S. Watanabe, M. Kayano, Y. Ishino, K. Miyao, Solid therapeutic preparation remaining in the stomach, US Patent 3,976,764 1976.

[170] Y. Kawashima, T. Niwa, H. Takiuchi, Hollow microspheres for use as a floating controlled drug delivery system in the stomach, J. Pharm. Sci., 81 (1992) 135-140.

[171] B.C. Thanoo, M.C. Sunny, A. Jayachrischnan, Oral sustained-release drug delivery systems using polycarbonate microspheres capable of floating on the gastric fluid, J. Pharm. Pharmacol. 45 (1993) 21-24.

[172] A. Streubel, J. Siepmann, R. Bodmeier, Floating microparticles based on low density foam powder, Int. J. Pharm., 241 (2002) 279-292.

[173] J.T. Fell, L. Whitehead, J.H. Collett, Prolonged gastric retention using floating dosage forms, Pharm. Techn. 24(3) (2000) 82-90.

[174] M. Ichikawa, S. Watanabe, Y. Miyake, A new multiple-unit oral floating dosage system. I: Preparation and in vitro evaluation of floating and sustained-release characteristics. J. Pharm. Sci. 80(11) (1991) 1062-1066.

[175] F. Atyabi, H.L. Sharma, H.A.H. Mohammad, J.T. Fell, In vivo evaluation of a novel gastric retentive formulation based on ion exchange resins, J. Control. Release, 42 (1996) 105-113.

[176] F. Atyabi, H.L. Sharma, H.A.H. Mohammad, J.T. Fell, Controlled drug release from coated floating ion exchange resin beads, J. Control. Release, 42 (1996) 25-28.

[177] M. Rosa Jiménez-Castellanos, H. Zia, C.T. Rhodes, Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application, Int. J. Pharm. 105 (1994) 65-70.

[178] G. Xu, M.J. Groves, Effect of FITC-dextran molecular weight on its release from floating cetyl alcohol and HPMC tablets, J. Pharm. Pharmacol., 53(1) 2001 49-56.

[179] A.F. Stockwell, S.S. Davies, S.E. Walker, In vitro evaluation of alginate gel systems as sustained release drug delivery systems, J. Control. Release, 3 (1986) 167-175.

[180] M. Ichikawa, S. Watanabe, Y. Miyake, Granule remaining in the stomach, US Patent 4,844,905, 1989.

[181] B.Y. Choi, H.J. Park, S.J. Hwang, J.B. Park, Preparation of alginate beads for floating drug delivery: effects of CO_2 gas forming agents, Int. J. Pharm., 239 (2002) 81-91.

[182] S. Singh, J. Singh, M.S. Muthu, J. Balasubramaniam, B. Mishra, Gastroretentive drug delivery system of metoclopramide hydrochloride: formulation and in vitro evaluation, Curr. Drug Deliv. 4(4) (2007) 269-275.

[183] J. Goole, Ph. Deleuze, F. Vanderbist, K. Amighi, New levodopa sustained-release floating minitablets coated with an insoluble acrylic polymer, Eur. J. Pharm. Biopharm., 68(2) (2008) 310-318.

[184] B.S. Dave, A.F. Amin, M.M. Patel, Gastroretentive drug delivery system of ranitidine hydrochloride: Formulation and in vitro evaluation, AAPS PharmSciTech 5(2) (2004) article 34.

[185] M. Fukuda, N.A. Peppas, J.W. McGinity, Floating hot-melt extruded tablets for gastroretentive controlled drug release system, J. Control. Release 115(2) (2006) 121-129.

[186] M. Fukuda, N.A. Peppas, J.W. McGinity, Floating hot-melt extruded tablets for gastroretentive controlled drug release system, Pharm. Res. 115 (2006) 121-129.

[187] J. Ali, S. Arora, A. Ahuja, A.K. Babbar, R.K. Sharma, R.K. Khar, Formulation and development of floating capsules of celecoxib: In vitro and in vivo evaluation. AAPS PharmSciTech, 8(4) (2007), Article 119.

[188] S.C. Basak, J. Rahman, M. Ramalingam, Design and in vitro testing of floatable gastroretentive tablet of metformin hydrochloride, Pharmazie, 62(2) (2007) 145-148.

[189] V. Iannuccelli, G. Coppi, M.T. Bernabei, R. Cameroni, Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study, Int. J. Pharm. 174 (1998) 47-54.

[190] J. Timmermans, A.J. Moës, How well do floating dosage forms float? Int. J. Pharm. 62 (1990) 207-216.

[191] N. Rouge, E.T. Cole, E. Doelker, P. Buri, Buoyancy and drug release patterns of floating minitablets containing Piretanide and Atenolol as model drugs, Pharm. Dev. Technol., 3(1) (1997) 73-84.

[192] J. Timmermans, A.J Moës, Apparatus and method for resultant-weight measuring system. US Patent 5,076,107 (1991).

[193] J. Goole, F. Vanderbist, K. Amighi, Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms, Int. J. Pharm. 334 (2007) 35-41.

[194] S. Li, S. Lin, Y.W. Chien, B.P. Daggy, H.L. Mirchandani, Statistical optimization of gastric floating system for oral controlled release of calcium, AAPS PharmSciTech, 2(1) (2001) Article 1.

[195] Pharmacopoea Europaea 6.0, Deutscher Apotheker Verlag Stuttgart/Govi-Verlag Eschborn (2008).

[196] S. Baumgartner, J. Smid-Korbar, F. Vrečer, J. Kristl, Physical and technological parameters influencing floating properties of matrix tablets based on cellulose ethers, S.T.P. Pharma Sciences 8(5) (1998) 285-290.

[197] S. Baumgartner, A. Tivadar, F. Vrečer, J. Kristl, Development of floating tablets as a new approach to the treatment of Helicobacter pylori infections, Acta Pharmaceutica 51(1) (2001) 21-33.

[198] A.O. Nur, J.S. Zhang, Captopril floating and/or bioadhesive tablets: Design and release kinetics, Drug Dev. Ind. Pharm. 26 (9) (2000) 965-969.

[199] M.D. Chavanpatil, P. Jain, S. Chaudhari, R. Shear, P.R. Vavia, Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin, Int. J. Pharm., 316 (2006) 86-92.

[200] S. Bolton, S. Desai, Floating sustained release therapeutic compositions, U.S. Patent 4,814,179, 1989.

[201] E. Cedillo-Ramirez, L. Villafuerte-Robles, A. Hernandez-Leon, Effect of added pharmatose DCL11 on the sustained-release of metronidazole from methocel K4M and carbopol 971 NF floating matrices, Drug Dev. Ind. Pharm. 32 (2006) 955-965.

[202] T. Tokumura, Y. Machida, Preparation of amoxicillin intragastric buoyant sustained-release tablets and the dissolution characteristics, J. Control Release, 110 (2006) 581-586.

[203] I.S. Ahmed, J.W. Ayres, Bioavailibility of riboflavin from a gastric retention formulation, Int. J. Pharm., 330 (2007) 146-154.

[204] L.H. Reddy, R.S. Murthy, Floating dosage systems in drug delivery, Crit. Rev. Ther. Drug Carr. Syst., 19(6) (2002) 553-585.

[205] A. Menon, W.A. Ritschel, A. Sakr, Development and evaluation of a monolithic floating dosage form for furosemide, J. Pharm. Sci., 83 (1994) 239-245.

[206] P.L. Bardonnet, V. Faivre, W.J. Pugh, J.C. Piffaretti, F. Falson, Gastroretentive dosage forms: Overview and special case of *Helicobacter pylori*, J. Control. Release, 111 (2006) 1-18.

[207] A.K. Srivastava, S. Wadhwa, D. Ridhurka, B. Mishra, Oral sustained delivery of atenolol from floating matrix tablets - Formulation and in vitro evaluation, Drug Dev. Ind. Pharm. 31 (2005) 367-374.

[208] X. Xiaoqiang, S. Minjie, Z. Feng, H. Yiqiao, Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: In vitro and in vivo evaluation in healthy volunteers, Int. J. Pharm. 310 (2006) 139-145.

[209] G.M. Khan, J.-B. Zhu, Studies on drug release kinetics from Ibuprofen-Carbomer hydrophilic matrix tablets: Influence of co-excipients on release rate of the drug, J. Control. Release, 57 (1999) 197-203.

[210] A. Apicella, B. Capello, M.A. Del Nobile, M.I. La Rotonda, G. Mensitieri, L. Nicolais, Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release, Biomaterials 14 (1993) 83-90.

[211] R.C. DiLuccio, M.A. Hussain, D. Coffin-Beach, G. Torosian, E. Shefter, A.R. Hurwitz, Sustained-release oral delivery of theophylline by use of polyvinyl alcohol and polyvinyl alcohol-methyl acrylate polymers, J. Pharm. Sci.,83 (1994) 104-106.

[212] J.H. Guo, G.W. Skinner, W.W. Harcum, P.E. Barnum, Polymer blend matrix for oral sustained drug delivery, Proc. Int. Symp. Controlled Release Bioact. Mater. 25 (1998) 802-803.

[213] E. Draganoiu, Evaluation of Kollidon SR for pH independent extended release matrix systems, PhD Thesis 2003.

[214] T. Steenpaß, W. Fraunhofer, K. Kolter, The development of sustained release floating systems based on Kollidon® SR, Proc. 3rd World Meeting on Pharm. Biopharm. and Pharm. Technol. 3 (2000) 27-28.

[215] F. Ruchatz, K. Kolter, S. Wittemer, W. Fraunhofer, Kollidon SR. A new excipient for sustained release matrices, Proc. Int. Symp. Contr. Rel. Bioact. Mater. 26 (1999) 869-876.

[216] K. Kolter, W. Fraunhofer, F. Ruchatz, Properties of Kollidon SR as a new excipient for sustained release dosage forms, AAPS PharmSci. 1 (S1), 3237 (1999) www.aapspharmsci.org

[217] H. Kranz, C. Guthmann, T. Wagner, R. Lipp, J. Reinhard, Development of a single unit extended release formulation for ZK 811 752, a weakly basic drug, Eur. J. Pharm. Biopharm. 26 (2005) 47-53.

[218] Z.J. Shao, M.I. Farooqi, S. Diaz, A.K. Krishna, N.A. Muhammad, Effects of formulation variables and post-compression curing on drug release from a new

sustained-release matrix material: polyvinylacetate-povidone, Pharm. Dev. Techn. 6(2) (2001) 247-254.

[219] C.T. Sengel, C. Hascicek, N. Gönül, Development and in-vitro evaluation of modified release tablets including ethylcellulose microspheres loaded with diltiazem hydrochloride, L. Microencapsul., 23(2) (2006) 135-152.

[220] K. Kolter, Compression behaviour of Kollidon SR, Proc. 4th World meeting on Pharm. Biopharm. and Pharm. Technol. 4 (2002) 119-120.

[221] T.C. Rock, T. Steenpaß, F. Ruchatz, K. Kolter, Methods to reduce the initial release rate of sustained release tablets containing Kollidon SR. 27th Proceedings of the International Symposium on Controlled Release of Bioactive Materials (2000) 636-637.

[222] K. Kolter, F. Schoenherr, H. Ascherl, Floating pharmaceutical formulations containing polyvinyl acetate and polyvinylpyrrolidone, EP 1138320(A2) Eur. Pat. Appl. (2001).

[223] S. Engineer Z.J. Shao, N.A. Khagani, Temperature/Humidity Sensitivity of Sustained-Release Formulations Containing Kollidon SR, Drug Dev. Ind. Pharm. 30(10) (2004) 1089-1094.

[224] S.M. Khamanga, R.B. Walker, Evaluation of rate of swelling and erosion of verapamil (VRP) sustained-release matrix tablets, Drug Dev. Ind. Pharm., 32(10) (2006) 1139-1148.

[225] J. Pajander, B. Van Veen, O. Korhonen, R. Lappalainen, J. Ketolainen, Liquid boundary movements in cylindrical and convex hydrophobic matrix tablets: Effects on tablet cracking and drug release, Eur. J. Pharm. Biopharm., 64 (2006) 167-172.

[226] S. Baumgartner, G. Lahajnar, A. Sepe, J. Kristl, Quantitative evaluation of polymer concentration profile during swelling of hydrophilic matrix tablets using ^{1}H NMR and MRI methods, Eur. J. Pharm. Biopharm. 59 (2004) 299-306.

[227] J. Perez, Defect diffusion model for volume and enthalpy recovery in amorphous polymers, Polymer, 29 (1988) 483-489.

[228] M.S. Ali, R.P. Sheldon, Structural changes in glassy polymers, J. Appl. Polym. Sci, 14 (1970) 2619-2628.

[229] D. Hutchings, B. Kuzmak, A. Sakr, Processing considerations for an EC latex coating system: Influence of curing time and temperature, Pharm. Res., 11 (1994) 1474-1478.

[230] Z.J. Shao, D.S. Robins, C. Shih, P.J. Knight, A.S. Huq, Formulation and process variables affecting SCH 209149 release from ethylcellulose-based matrix tablets, Pharm. Sci., 1 (1998) S-324.

[231] E. Draganoiu, A. Sakr, Development and in vitro/in vivo evaluation of extended release propranolol tablets. Part I: Development and vitro evaluation. Pharm. Ind. 68(1) (2006) 111-115.

[232] H. Fessi, J.P. Marty, J.T. Carstensen, F. Puisieux, Biopharmaceutical study of tablets of plastic matrix type: effect of the solubility of active principle and the nature of polymer on the dissolution rate. 1st C.-R. - Congr. Eur. Biopharm. Pharmacokinet. 1 (1981) 475-80.

[233] R.W. Korsmeyer, R. Gurny, E.M. Doelker, P. Buri, N.A. Peppas, Mechanism of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983) 25-35.

[234] N.A. Peppas, Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv. 60 (1985) 110-111.

[235] P. Costa, J.M.S. Lobo, Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 13 (2001) 123-133.

[236] R. Maeki, E. Suihko, O. Korhonen, H. Pitkaenen, R. Niemi, M. Lehtonen, J. Ketolainen, Controlled release of saccharides from matrix tablets, Eur. J. Pharm. Biopharm. 62 (2006) 163-170.

[237] H. Kim, R. Fassihi, Application of binary polymer system in drug release rate modulation. 2. Influence of formulation variables and hydrodynamic conditions on release kinetics, J. Pharm. Sci., 86(3) (1997) 323-328.

[238] J. Siepmann, N.A. Peppas, Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC), Adv. Drug Deliv. Rev. 48 (2001) 139-157.

[239] N. Shah, G. Zhang, V. Apelian, F. Zeng, M.H. Infeld, A.W. Malick, Prediction of drug release from hydroxypropyl methylcellulose (HPMC) matrices: Effect of polymer concentration, Pharm. Res. 10(11) (1993) 1693-1695.

[240] S. Li, S. Lin, B.P. Daggy, H.L. Mirchandani, Y.W. Chien, Effect of formulation variables on the floating properties of gastric floating drug delivery system, Drug Dev. Ind. Pharm. 28(7) (2002) 783-793.

[241] P. Gao, J.W. Skoug, P.R. Nixon, T.R. Ju, N.L. Stemm, K.-C. Sung, Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release, J. Pharm. Sci., 85 (1996) 732-740.

[242] A. Avachat, V. Kotwal, Design and Evaluation of matrix-based controlled release tablets of Diclofenac Sodium and Chondroitin Sulphate, AAPS PharmSciTech. 8(4) (2007) Article 88.

[243] C.M. Lopes, J.M.S. Lobo, P. Costa, J.F. Pinto, Directly compressed mini matrix tablets containing ibuprofen: preparation and evaluation of sustained release. Drug Dev. Ind. Pharm. 32 (2006) 95-106.

[244] E. Papadimitriou, G. Buckton, M. Efentakis, Probing the mechanisms of swelling of hydroxypropyl methylcellulose matrices. Int. J. Pharm. 98 (1993) 57-62.

[245] C.I. Jover, M.E. Garcia, C.M. Minarro, L.P. Perez, R.A. Orriols, N.J.M. Sune, G.J.R. Tico, Modified release oral dosage forms, Ciencia y Tecnologia Pharmaceutica 13 (2003) 129-135.

[246] R. Huettenrauch, Principles of retardation, Pharmazie 30 (1975) 3-16.

[247] N. Follonier, E. Doelker, Biopharmaceutical comparison of oral multiple-unit and single-unit sustained-release dosage forms, S.T.P. Pharma, 2 (1992) 141-158.