Development and investigation of Propranolol HCl pellets coated with poly(vinyl acetate) based polymer films for sustained release applications

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1

Introduction

1.1 Sustained release dosage forms

The oral application of drugs presents the most common way of drug administration. This form of application is mainly driven by a high patience acceptance. The major advantages of oral dosage forms are a non-invasive and therefore pain-free way of administration as well as an easy handling. Drug delivery systems for oral use can be classified into single unit dosage forms such as tablets, dragées and capsules as well as into multi particulate delivery systems like powders, granules and pellets [1].

Immediate drug release has to be differentiated from modified drug release. The former is characterized by a fast increase and decrease of drug plasma levels, i.e. drug plasma fluctuations. This behaviour occurs in particular for drugs with short biological half-life. A disadvantage of this application form is the possible underdose or overdose of the active pharmaceutical ingredient. An underdose leads to a reduction or loss in drug effectiveness whereas an overdose causes the increased appearance of undesirable side effects.

Modified drug release includes systems with sustained, delayed, pH-dependent or pulsed drug liberation [2, 3]. Delayed release dosage forms can be differentiated from sustained release systems as they exhibit a more or less distinctive lag time prior drug release. Sustained release drug delivery systems enable prolonged drug liberation leading to extended therapeutic effects over a certain period of time [4]. Ideally, constant drug plasma levels are attained by the application of sustained release dosage forms. The advantages of oral-controlled drug delivery systems are well known: fewer administrations, greater therapeutic effects and fewer side effects. All aspects result in improved patience compliance especially in case of medical long-term treatment.

Drugs administered in terms of modified release systems are subjected to following parameters:

- the need for constant plasma levels
- short biological half-life

- limited absorption-window
- broad therapeutic window
- meet chronobiological requirements
- release at site of pharmacological action (drug targeting).

Sustained release drug delivery systems include single unit and multiple unit dosage forms as well as coated and matrix devices [5]. Multiple unit dosage forms consist of a multitude of subunits, like granules, minitablets, microparticles or in particular pellets. Usually, the subunits are filled in capsules or sachets or pressed to tablets respectively. Each of these exhibits specific characteristics that generate a desired kind of controlled drug release [3, 6]. Due to biopharmaceutical and technological benefits multiple unit oral controlled-release dosage forms are preferred in comparison with single unit advices.

1.2 Pellets

The term "pellet" is nowadays applied to describe a multitude of commodities used in different industrial sectors. Pellets are established in the fields of food, agriculture, chemistry and energy as well as in the pharmaceutical industry. Different properties and requirements are associated with pellets depending on the field of application. Though, all of them are characterized by a spherical or cylindrical shape.

Pharmaceutical pellets exhibit an almost spherical shape with a typical size of 0.2 to 2 mm. They can be distinguished from conventional pharmaceutical granules due to their well-defined shape and their narrow particle size distribution [7, 8]. Based on their characteristics pellets offer several physiological, biopharmaceutical and technological advantages [9]. The gastric emptying is less dependent on the nutritional state as pellets are small enough to be evacuated through the pylorus during the digestive phase [10, 11, 12, 13]. Consequently, variations in the overall transit time of multi particulates are minimized compared to monolithic devices leading to reduced intra- and inter-subject variabilities of plasma profiles [14, 15]. In contrast to single unit dosage forms pellets and pellet products disperse freely in the gastrointestinal tract [16]. Thus, high local concentrations of active pharmaceutical ingredients (API) in the intestinal mucosa can be avoided cause less side effects. Additionally, the bioavailability of API can be improved.

The effect of few damaged or incomplete coated pellets is negligible due to the high number of those in a multi particulate drug delivery system. Therefore, pellets coated with a modified release film provide a high safety against dose-dumping entailed by damages of the dosage form [7, 17]. As multi particulate dosage forms exhibit a greater surface

area than monolithic devices more film coat material is needed for the coating process of pellets resulting in higher manufacturing costs. Even so, pellets offer a multitude of great facilities for the pharmaceutical development. Various dosage strengths of one drug can be achieved by simple variation of the administered amount of pellets without reformulation. Drug delivery systems with specified release profiles can be realized by combining pellets with different release patterns. Pellets containing different drugs can be blended in multi unit particle systems (MUPS). Thus, even incompatible APIs can be applied in one dosage form. In general, pellets are filled in capsules or sachets or pressed to tablets. Tablets containing coated subunits can be divided. Pellets from capsules or sachets can be spread on food. This can lead to a better swallowing of the dosage form and therefore a better patience compliance. A selection of marked pellet drug delivery systems is given in [Table 1.1].

Table 1.1: Selection of different market products based on pellets

Name	**pharmaceutical company**
Nexium® mups 20/ 40 mg enteric-coated tablets	AstraZeneca
Volmac® 4/ 8 mg retard tablets	GlaxoSmithKline
Arelix® RR 6 retard capsules	Sanofi-Aventis
Ferro Sanol® duodenal capsules	Sanol
Pentasa® Sachet 1000 mg retard granules	Ferring
Dolo-Puren® granule 400/ 600 mg sachet	Actavis
Ciprobay® 5/ 10 % granule and solvent for preparation of a suspension	Bayer Vital

A number of pellet manufacturing processes have been developed for the production of pharmaceutical beads. The most commonly used pelletization techniques in pharmaceutical industry are extrusion/ spheronization and pellet layering processes. Furthermore, direct pelletizing is accomplished for pellet production [17]. Homogeneous pellets are obtained from extrusion/ spheronization and direct pelletization processes. They consist of a homogeneous matrix of excipient and drug. Layering processes produce heterogenous pellets with a starter core (nonpareil) and at least one layer containing drug and a pharmaceutical binder if required.

The extrusion/ spheronization processing option is the eldest known industrial pelletizing technique [18, 19, 20]. This procedure includes two basic manufacturing steps: first drug and excipients are blended, then by adding liquid a wet dough is formed. This mixture is extruded through a perforated screen to form cylindrical extrudates. The cylindrical

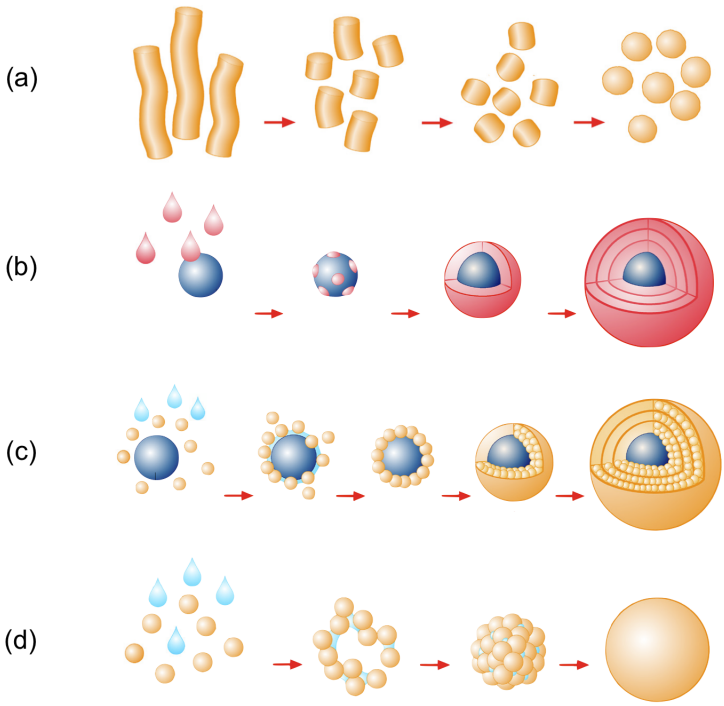


Figure 1.1: Pelletizing techniques: (a) extrusion/ spheronization, (b) fluid bed layering, (c) fluid bed powder layering and (d) direct pelletizing. Pictures provided by Glatt GmbH, Binzen, Germany

extrudates are transferred into a spheronizer with a frictional plate where they break up into smaller pieces and are finally transformed to spherical pellets. The process ends with a subsequent drying step [Figure 1.1(a)]. The minimum particle size of pellets manufactured via extrusion/ speronization is limited to about 500 µm. Even though the process offers a high reproducibility there are some disadvantages. The ratio of liquid, drug and binder must be well adjusted warranting a high yield of homogeneously shaped and sized pellets. Furthermore, the multitude of process steps involves a number of different manufacturing units with a large total product contacting surface.

The most common process in the pharmaceutical industry is the pellet layering process [21]. Pellet starter cores are fluidized by a warm air stream in a fluid bed coater. A drug/ binder solution or suspension is sprayed onto the pellets in the fluid bed. The solvent is evaporated by the warm air while drug and binder are applied on the starter pellets layer by layer. The layering process is continued until the desired drug content is achieved [Figure 1.1(b)]. The binder is necessary to improve the adhesion of drug on the pellets. To achieve uniform drug layers the bottom spray method using a Wurster insert may be the processing method of choice [7, 21].

The powder layering process displays a variation of the classical fluid bed layering pro-

cess. A rotor insert is usually used for this processing option. Generally, micronized drug is fed from an external charge hopper into the fluid bed system. Simultaneously, binder solution is sprayed onto the pellet starter cores in order to bind the powder on the nuclei. As water evaporates solid bridges are build from liquid bridges. The process continues until the desired drug content is obtained [Figure 1.1(c)]. At the end of the drug layering process the pellets are dried in the fluid bed processing unit. Today starter cores from 100 to 1000 µm are available for fluid bed processing. The major advantage of the fluid bed drug layering process is the use of only one equipment for all processing steps. Furthermore, a smaller size distribution and a higher sphericity of the product can be achieved easily.

Direct pelletizing is usually performed in a rotor fluid bed system [Figure 1.1(d)]. A wetted powder mixture is applied for creating starter nuclei using the snow-ball method. Very small starter cores of only 50 - 500 µm can be required by direct pelletizing implementing special techniques like CPS® -(Complex Perfect Spheres) fluid bed technology [22, 23].

1.3 Film Coating

Film coating is widely used to control drug liberation from solid pharmaceutical dosage forms. Usually, small spherical particles like pellets are coated in fluid bed systems. The film coatings can be applied either from organic solutions or from aqueous dispersions [24, 25]. The use of aqueous dispersions instead of organic solutions offers various advantages, including reduced toxicity caused by the handling of organic solvents, the avoidance of explosion proof manufacturing equipment and environment including controlled discharge of solvents considering the emission limits [24, 26]. As water exhibits a high heat of vaporization lengthy process times using aqueous coating liquids seemed to have a great economic disadvantage despite its environmental advantages [26]. Though, the development of aqueous polymeric latexes and pseudolatexes in the 1970s overcome these disadvantages by their high polymeric concentrations as well as their low viscosities compared to the respective organic solutions [25, 26].

However, the film formation process is fundamentally different for both coating techniques. The individual polymer chains are highly flexible in organic solutions. Immediately after solvent evaporation a homogenous film with a high degree of chain entanglement is formed on the pellet surface [27, 28]. Upon spraying aqueous polymer dispersions, the polymer particles are spread on the pellet surface [Figure 1.2].

The film formation from aqueous colloidal polymer dispersions is more complex. Due to the water evaporation and facilitated by interfacial tension between water and polymer

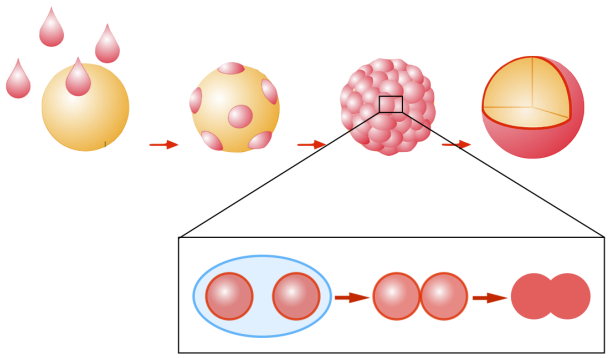
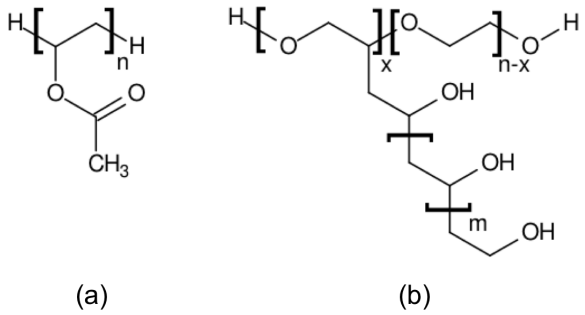


Figure 1.2: Principle of aqueous film coating. Polymer particles (red) are applied on the pellet surface. Water (blue) evaporation leads to increasing interfacial tension between water and polymer molecules. Colloidal particles come into direct contact. At a further step capillary forces lead to coalescence of the polymer molecules above the minimum film temperature. Picture adapted from Glatt GmbH, Binzen, Germany

the colloidal particles come into close contact with each other and form an ordered structure. Driven by capillary forces and interfacial tension the particles lose their individual character ("coalesce") [25]. Significant coalescence takes place only at temperatures exceeding the minimum film formation temperature (MFT). There, a clear and continuous film is formed during the drying process. The film formation can be supported by the addition of a plasticizer which lowers the minimum film formation temperature, mobilizes the polymer particles and relieves their coalescence.

Polymers which are used for the manufacturing of membrane controlled drug delivery systems include cellulose derivates, polymethacrylates, poly(vinyl acetate) and poly(vinyl pyrrolidone) [24, 29, 30]. Usually, polymer coats are applied to obtain a particular release profile being adapted to the pharmacokinetic characteristics of the drug. For this purpose different formulation and processing parameters can be varied, for example the type of polymer, coating thickness or type of plasticizer. However, variations of these parameters are generally restricted [30]. Too low coating thicknesses can lead to accidental film rupturing and consequently the variability of the drug release behaviour increases and thus becomes less controllable than at higher coating thicknesses. On the other hand, too high coating levels result in high costs and long processing times. High amounts of added plasticizer may be accompanied by intense sticking, but too low amounts result in brittle films.

Thus, the use of polymer blends represents a very interesting approach to overcome these limitations. Generally, the applied polymers exhibit different physico-chemical characteristics such as water and drug permeability, mechanical stability and solubility along the gastro-intestinal tract (GIT) [30, 31, 32]. Blends of a GIT-insoluble polymer and a polymer that is soluble throughout the GIT are frequently used in pharmaceutical industry



(a) (b)

Figure 1.3: Chemical structure of (a) Kollicoat® SR 30D (n ∼ 5226) and (b) Kollicoat® IR (m ∼ 175, n ∼ 136, x = 2 - 3)

and science. Coating compositions of ethylcellulose and hydroxypropyl methyl cellulose (HPMC) are commonly used so far [33, 34, 35]. A great disadvantage of these mixtures is the appearance of flocculation or sedimentation of aqueous ethylcellulose dispersions upon addition of HPMC [36]. To eliminate these problems Kollicoat® IR, a poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer) soluble macromolecule was implemented in ethylcellulose based film coatings successfully by Siepmann et al [37, 38]. Drug release profiles of coated pellets could be adjusted easily by varying the polymer ratio. Additionally, the coated pellets showed a very good storage stability [39]. Furthermore, PVA-PEG was added to aqueous dispersions of poly(vinyl acetate) (Kollicoat® SR 30 D) for tablet as well as for pellet coating [32, 40, 41, 42, 43, 44].

Both Kollicoat® SR 30 D and Kollicoat® IR are relatively new polymers for film coating purposes [Figure 1.3].

A Kollicoat® SR 30D monograph was published in the European Pharmacopoeia in July 2007 [3]. Kollicoat® SR 30D is marketed as a ready-to-use coating dispersion of poly(vinyl acetate). The aqueous dispersion comprises 27 % poly(vinyl acetate) stabilized with 0.3 % sodium lauryl sulphate and 2.7 % povidone. The latter acts as a pore former in film coatings [45]. Kollicoat® SR 30D is characterized by water insolubility and a low minimum film forming temperature of 18 °C . Due to its insolubility in any physiological release medium Kollicoat® SR 30D provides remarkable sustained release characteristics. Furthermore, Kollicoat® SR 30D displays a high tensile strength. Elongation at break is up to about 350 % with an amount of 10 % triethyl citrate as a plastizicer [46, 47]. This quality is of exceptional importance concerning the compression of coated pellets. Kollicoat® SR 30D is utilized in combination with various other polymers for sustained release purposes. Besides its use in combination with Kollicoat® IR, Kollicoat® SR 30D served as extended release polymer for drug delivery systems for weakly basic drugs in addition to Kollicoat® MAE 30D [48, 49]. Recently, Wei et al. investigated the charac-

teristics of chitosan/ Kollicoat® SR 30D films for colonic drug delivery [50, 51].

The soluble polymer Kollicoat® IR represents a spray dried white powder of poly(ethylene glycol)-poly(vinyl alcohol) (PEG-PVA) graft copolymer. It is produced by grafting of vinyl acetate onto polyethylene glycol. This step is followed by saponification of the poly(ethylene glycol)-poly(vinyl acetate) graft copolymers. The final product includes PEG units and PVA units in a ratio of 25:75, forming a comb-like structure. Kollicoat® IR is distinguished by an excellent water solubility as well as by a high water dissolution rate. The low viscosity of Kollicoat® IR coating solutions results in significantly reduced processing times compared to commonly used HPMC instant release coating solutions [47, 52]. Aqueous PVA-PEG graft copolymer solutions form clear, colourless and highly flexibly films since PEG is covalently bonded to the polymer and acts as a plasticizer. Kollicoat® IR is mainly utilized as fast dissolving film forming polymer for taste masking or protection against light and humidity. As mentioned above Siepmann et al. used PVA-PEG graft copolymer as a pore former for ethylcellulose film coatings. One of the advantages of the products was demonstrated by the considerable storage stability of the coated pellets [37, 39]. Furthermore, the exceptional water solubility of Kollicoat® IR was used in the development of solid dispersions to improve the bioavailability of poorly soluble drugs via melt extrusion [53] and spray drying [54]. A draft Ph. Eur. monograph for Kollicoat® IR was published in 2008.

Polymer films of Kollicoat® SR 30D and Kollicoat® IR exhibit a high mechanical resistance against mechanical stress as well as a low minimum film formation temperature [44, 55, 56]. These properties offer a lot of advantages for the coating of pharmaceutical dosage forms. Due to the high mechanical resistance coated pellets can be pressed into tablets without film rupturing [57]. Low process temperatures as well as low plasticizer concentrations are necessary based on the low MFT of the polymer blends. Despite these benefits only few publications concerning the application of Kollicoat® SR 30D and Kollicoat® IR blends have been released.

1.4 Drug release mechanisms

Understanding the drug release mechanisms of membrane controlled drug delivery systems offers considerable possibilities for the system optimization to improve the release profiles. The underlying release mechanism of a coated dosage form mainly depends on the type of coating material and the method by which it is applied [25, 58]. Various physicochemical phenomena might be involved in the control of drug liberation from the coated drug delivery system such as:

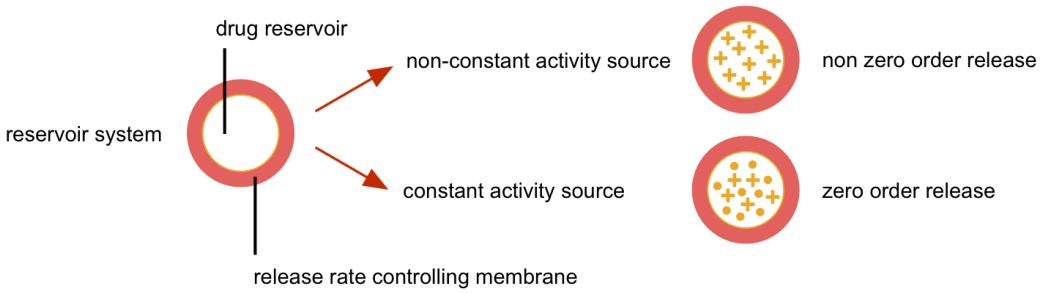


Figure 1.4: Classification system for primarily diffusion controlled drug delivery systems comprising a drug reservoir. Stars represent individual drug molecules, circles illustrate drug crystals/ amorphous aggregates. Picture adapted from [59].

- water penetration into the drug delivery device (through pores and/ or continuous polymer networks)
- drug and excipient dissolution
- creation of water-filled pores
- pore closing due to polymer swelling
- creation of significant hydrostatic pressure within the delivery system
- diffusion of drug and/ or excipients out of the dosage form [59].

Reservoir devices comprising a drug depot which is surrounded by a release rate controlling membrane are illustrated in [Figure 1.4] [59].

Reservoir systems with non-constant activity source can be distinguished from systems with constant activity source. The former are characterized by a fast solubilization of the total amount of drug upon water penetration into the dosage form. The released drug molecules are not replaced and the drug concentration within the controlled release system decreases with time. The drug release rate decreases as the drug concentration gradient which is the driving force for drug release decreases. If the polymer membrane does not swell or dissolve, if perfect sink conditions are provided throughout the drug release period and if the drug permeability through the membrane remains constant, first order release kinetics result [59].

If the initial drug concentration within the reservoir system exceeds the drug solubility, released molecules will be replaced by the dissolution of drug crystals/ amorphous aggregates. Thus, constant drug concentrations within the dosage form are provided leading to zero order release kinetics if the properties of the release rate controlling membrane remain constant and if perfect sink conditions are existent throughout the release period [59]. As

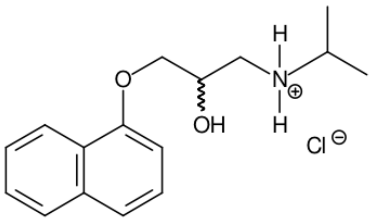


Figure 1.5: Chemical structure of R,S - Propranolol HCl.

soon as the drug excess is exhausted the system represents a non-constant activity source and non zero order kinetics (e.g. first order kinetics) will be obtained.

In practice film coatings show crack formation or significant swelling caused by hydrostatic pressure built up within the drug delivery system. If the coating comprises an insoluble and a soluble polymer pores can be formed as soluble parts are dissolved from the release rate controlling polymer membrane leading to deviations from these "ideal" systems [60, 61].

1.5 Research objectives

The lipophilic, non-selective antagonist on β_1 - and β_2 -adrenoreceptors, Propranolol Hydrochloride (HCl) [62], was selected as a model drug [Figure 1.5]. It is used as an antiarrhythmic and antihypertensive drug as well as for migraine prophylaxis [62]. Propranolol HCl is classified as a BCS I drug [63] as it exhibits a good solubility in water and a sufficient permeability in vivo. 90 % of Propranolol are resorbed within the gastro intestinal tract. Though, Propranolol HCl is subjected to a strong first pass metabolism. In consequence, the bioavailability of the drug is decreased to 30 - 36 % after oral application [64, 65]. Propranolol HCl shows an elimination half-life of around 2 - 4 hours [62, 64].

Due to these properties Propranolol HCl represents a suitable model drug for a controlled release delivery system which should be capable to achieve constant plasma levels. By means of extending the drug release from the delivery device the frequency of application can be reduced leading to a better patience compliance [1, 66].

An ideal membrane polymer coating should fulfill various requirements e.g. robust production processes, suitability for many drugs and/ or excipients, no storage effects, low glass transition temperature, strong and mechanical robust films as well as reproducibility of release rates in vivo and in vitro. In addition, changes in film coat composition and film coating process should result in predictable changes of release rate and release profile. PVAc/PVA-PEG (Kollicoat® SR 30D/ Kollicoat® IR) polymer blends were implemented to control Propranolol HCl delivery from a multiple unit oral dosage form within the

present thesis. Both polymers entered the market only some years ago. Their high mechanical resistance is reported frequently [44, 46, 47]. The predicability of changes in release rate and release profiles upon changes in the coating formulation was published by Strübing and Ensslin [32, 40, 43].

Film formation from aqueous-based polymer dispersions is a complex process depending on several film coating formulation and process parameters. Release instability of controlled-release coatings from aqueous polymer dispersions such as Kollicoat® SR 30D is frequently reported [67, 68]. An additional curing step at higher temperature may improve the polymer particles coalescence to a physically stable state [67, 69, 70].

In the development of new pharmaceutical formulations for oral drug delivery it is essential to study the properties of the film, in order to elucidate the drug release mechanism, to optimize the coating design as well as to optimize the desired drug release pattern [71]. The basic mechanism of drug release from membrane controlled drug delivery systems is correlated with the diffusion of solubilized drug through the polymer film. Thus, the characterization of water penetration behaviour into the coated dosage form initializing solubilization of drug leads to a deeper understanding of the drug release mechanism.

Nuclear magnetic resonance (NMR) relaxometry can be used to investigate the water penetration behaviour [72, 73]. In addition, electron paramagnetic resonance spectroscopy (EPR) has been utilized in the field of pharmacy to determine water penetration behaviour into drug delivery systems. EPR spectroscopy has been applied to HPMC matrix systems to describe drug release processes [74, 75]. Furthermore, EPR offers the possibility to detect the oxidative degradation of active pharmaceutical ingredients in the solid state [76]. Oxygen permeation kinetics through HPMC coated tablets was investigated by EPR spectroscopy [77]. EPR imaging (EPRI) can be applied to monitor pH values inside tablets affected by incorporated pH modifiers, their solubility and leaching behaviour [78, 79].

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

- investigate the impact of formulation modifications and coating conditions on the drug release from PVAc/PVA-PEG coated pellets in vitro
- establishment of a stable fluid bed coating process for the coating of Propranolol HCl pellets with PVAc/PVA-PEG
- examine the influence of osmotic activity within the pellet formulation on drug release from PVAc/PVA-PEG coated Propranolol HCl pellets
- development of a mathematical model to determine drug release parameters
- study the influence of curing conditions on PVAc/PVA-PEG polymer films and analyze the impact of curing conditions on release stability

- examine morphological changes in polymer film coat induced by curing or storage conditions implementing Environmental Scanning Electron Microscopy (ESEM)
- monitoring the water influx into PVAc/PVA-PEG coated pellets by NMR relaxometry
- non-invasive monitoring of the solubilized drug concentration inside the pellets by EPR spectroscopy
- elucidate the underlying drug release mechanism of PVAc/PVA-PEG coated Propranolol HCl pellets.

2

Materials and Methods

2.1 Materials

2.1.1 Pellet Starter Cores

Cellets® 700 (700 - 1000 µm) were obtained from IPC Process Center GmbH & Co. KG (Dresden, Germany). Propranolol HCl matrix cores (700 - 1000 µm) were provided by Glatt GmbH (Binzen, Germany) and Glatt Air Techniques (Ramsey, USA).

2.1.2 Excipients for Pellet coating

Kollicoat® SR 30D (Poly(vinyl acetate), PVAc) and Kollicoat® IR (Poly(vinyl alcohol)-poly(ethylene glycol), PVA-PEG) were provided by BASF AG (Ludwigshafen, Germany). Triacetin was purchased from Fluka. Triethyl citrate was received from Sigma Aldrich (Taufkirchen, Germany). Hydroxypropyl methyl cellulose (Methocel® E5 Premium LV) was delivered by Colorcon (Great Britain). Poly(ethylen glycol) 1500 (Rotipuran® 1500) was obtained from Carl Roth GmbH (Karlsruhe, Germany). Poly(ethylen glycol) 6000 (Lipoxol® 6000 MED) was provided by Sasol GmbH (Germany). Sodium chloride was received from Grüssing GmbH (Germany). Talc and titanium dioxide were purchased from Caesar & Loretz GmbH (Germany). Syloid® 244 FP was obtained from GRACE Davison (Germany).

2.1.3 Excipients

Methanol, Propranolol HCl and 4-Hydroxy-2,2,6,6,-tetramethylpiperidin-1-oxyl (TEMPOL; TL) were purchased from Sigma Aldrich (Taufkirchen, Germany). Hydrochloride acid was obtained from Grüssing GmbH (Germany). Disodiumphosphate dihydrate, citric acid and deuterated dimethyl sulfoxide (DMSO-d6) were received from Carl Roth GmbH (Karlsruhe, Germany).

2.2 Methods

2.2.1 Preparation of coating dispersions

2.2.1.1 Hydroxypropyl methyl cellulose (HPMC) sub coating

PEG 6000 was dissolved in 300 ml distilled water. Methocel® E5 was added while stirring continuously with a magnetic stirrer. The mixture was heated for 15 min. Afterwards the solution was stirred constantly overnight to guarantee complete solubilization of HPMC. Talc was dispersed in the remaining distilled water using an Ultra turrax (T 25 basic, IKA, Germany). The talc dispersion was added to the HPMC solution and the mixture [Table 2.1] was blended for at least 30 min at 100 rpm prior the coating process.

Table 2.1: Composition of HPMC sub coating suspension

Components [g]		**solids content [%]**
Methocel® E5	35.8	
Talc	10.8	
PEG 6000	4.2	
Distilled water	503.3	
	554.1	10.1

2.2.1.2 Osmotically active sub coating (Type A: ionic)

Sodium chloride and PEG 6000 were dissolved in 800 ml or 500 ml distilled water respectively. Then the sodium chloride/HPMC coating suspension was manufactured as described in section 2.2.1.1. The coating suspensions [Table 2.2] were used for the preparation of pellets containing an ionic osmotically active sub coating.

Table 2.2: Composition of sodium chloride/HPMC coating suspensions

Components [g]	**15 % NaCl**	**7.5 % NaCl**	**solids content [%]**
Methocel® E5	37.5	37.5	
Sodium chloride	75.0	37.5	
Talc	10.8	10.8	
PEG 6000	4.2	4.2	
Distilled water	1147.5	810.0	
	1275.0	900.0	10.0

2.2.1.3 Osmotically active sub coating (Type B: non-ionic)

Both PEG 1500 and PEG 6000 or PEG 6000 were dissolved in 800 ml distilled water respectively. Then the PEG/HPMC coating suspension was prepared as described in section 2.2.1.1. The coating suspensions [Table 2.3] were used for the manufacturing of pellets containing a non-ionic osmotically active sub coating.

Table 2.3: Composition of PEG/HPMC coating suspensions

Components [g]	**PEG 1500**	**PEG 6000**	**solids content [%]**
Methocel® E5	37.5	37.5	
Talc	10.8	10.8	
PEG 1500	75.0	-	
PEG 6000	4.2	79.2	
Distilled water	1147.5	1147.5	
	1275.0	1275.0	10.0

2.2.1.4 Kollicoat® SR 30D (PVAc) based sustained release coatings

The final coating compositions for PVAc/PVA-PEG coatings are given in Chapter 3. Triethyl citrate and PVA-PEG were dissolved in distilled water using a blade stirrer (MR 25, MLW, Germany) at 100 rpm. Syloid® 244 FP and titanium dioxide were added to the solution and blended. The dispersion was homogenized for 3 min using an Ultra turrax (T 25 basic, IKA, Germany). Kollicoat® SR 30D was sieved through a 200 µm sieve. The pigment dispersion was added to the polymer dispersion through a 500 µm sieve subsequently. The final coating dispersion was blended for at least 30 min at 100 rpm.

2.2.2 Fluid Bed Coating

A GPCG 1.1 fluid bed coater with a 6″ wurster insert (Glatt GmbH Binzen, Germany) was used for pellet coating. The GPCG 1.1 fluid bed coater was equipped with a type C air distribution (orifice) plate to guarantee an optimal fluidization of the product within the down-bed zone. The discharge of powder particles that might be generated during the coating process was assured by the implementation of a trap basket. The fluid bed coater was connected to a dehumidifier (Paradair, Lorch - Waldhausen, Germany). A cold water tempering unit (teco cw 60, Gesellschaft Wärme Kältetechnik mbH, Kierpse, Germany) was used for cooling the dehumidifier subunit at an effective dehumidifying temperature of

3 °C to 4 °C. The absolute residual moisture content of the inlet air was 7.62 g water/m^3 dry air (dew point 5 °C).

2.2.2.1 HPMC based sub coatings

The fluid bed coater was preheated for 10 min at 50 °C inlet air temperature before start of coating with HPMC based sub coatings. 500 g Propranolol HCl starter cores were filled into the product chamber and preheated for 5 min at 50 °C; by this means a product temperature of 40 °C was reached. Then the pellets were coated with polymer dispersion according to [Table 2.4]. The coating dispersion was stirred with a magnetic stirrer during the whole coating process to prevent settling of talc. The coating run was finished when the required coating quantity was sprayed onto the pellets. The pellets were dried for 15 min at 50 °C inlet air temperature to a product temperature of 45 °C in the fluid bed coater subsequently.

Table 2.4: Coating parameters for pellet coating with HPMC based sub coatings

Parameter	
Inlet air temperature	50 °C
Inlet air moisture	7.62 g water/m^3 dry air
Product temperature	35 - 40 °C
Air flow	110 - 120 m^3/h
Nozzle diameter	1.2 mm
Atomizing air pressure	2.0 bar
Air distribution plate	type C
Partition height	25 mm

2.2.2.2 PVAc based sustained release coatings

The fluid bed coater was preheated for 10 min at 35 °C inlet air temperature before coating with PVAc/PVA-PEG. 500 g Propranolol HCl starter cores were filled in the product chamber of the GPCG 1.1 and the beads were heated for 5 min to attain a product temperature of 30 °C. After this the pellets were coated with PVAc/PVA-PEG dispersions according to [Table 2.5]. The pellets were dried for 15 min at 50 °C inlet air temperature in the fluid bed coater until 45 °C product temperature was achieved. For final film formation the pellets were cured for 24 h at 40 °C in a drying oven. A detailed description

of the development of the coating process with PVAc/PVA-PEG polymer blends is given in Chapter 3.

Table 2.5: Coating parameters for pellet coating with PVAc/PVA-PEG polymer blends using a GPCG 1.1 fluid bed coater (6″ wurster)

Parameter	
Inlet air temperature	35 - 40 °C
Inlet air moisture	7.62 g water/m^3 dry air
Product temperature	29 - 30 °C
Air flow	110 - 120 m^3/h
Nozzle diameter	1.2 mm
Atomizing air pressure	2.0 bar
Air distribution plate	type C
Partition height	25 mm

2.2.3 Agglomerate Analysis

Laser diffraction was implemented to detect agglomerates in three different Kollicoat® SR 30D batches which were used for pellet coating. The measurements were accomplished using a Mastersizer 2000 (Malvern Instruments Ltd., UK).

2.2.4 Specific Surface Area Analysis

The specific surface area (SSA) of Propranolol HCl starter cores as well as Propranolol HCl pellets coated with HPMC based sub coats was determined. The specific surface area of the pellets was calculated by the following equation:

$$SSA[\frac{cm^2}{g}] = \frac{3}{0.5 \cdot d_{[3;2]} \cdot \rho} \tag{2.1}$$

where d is the surface weighted mean diameter and ρ is the density of the pellets. The density of the pellets was determined with a helium pycnometer (Accupyk 1330, Micromeritics GmbH, Mönchengladbach, Germany). The pellet size was measured with a laser diffractometer (Mastersizer 2000, Malvern Instruments Ltd., UK). The determination of the specific surface area was necessary to calculate the total surface area (TSA) of the pellets:

$$TSA[cm^2] = SSA \cdot m, \tag{2.2}$$

Based on the total surface area of the pellets the amount of coating polymer per cm^2 for the final coating level could be determined. Support on specific surface area measurements was offered by the analytical department of Glatt GmbH, Binzen, Germany.

2.2.5 Particle Size Analysis

A sieve analysis was carried out to separate and detect agglomerates after pellet coating. Furthermore, the mean pellet size of coated Propranolol HCl pellets should be investigated. A AS 200 equipment (Retsch GmbH, Haan, Germany) was used. For sieve analysis 50 g of the pellets were weighted in exactly and sieved through six sieves (1400, 1000, 800, 710, 630, 500 µm) for 5 min at 1.5 mm amplitude. Differential weighting was accomplished to determine the mass of the sieve fractions. The percentage of each sieve fraction refers to the summation of all fractions.

2.2.6 Preparation of free polymer films

Kollicoat® SR 30D (PVAc) was used as received and only blended before casting the film. Polymer dispersions with different PVAc/PVA-PEG ratios [Table 2.6] were prepared by adding triethyl citrate and Kollicoat® IR (PVA-PEG) to distilled water and subsequent blending with a magnetic stirrer. Afterwards Syloid® 244 FP and titanium dioxide were added. Homogenization of the pigment suspension was always carried out for 3 min using an Ultra turrax (T 18 basic, IKA, Germany) at 18 000 rpm. Then the pigment suspension was incorporated into the polymer dispersion and blended again using the magnetic stirrer.

Amounts of 10 ml film dispersions were cast onto teflon plates. The films were dried in an oven at 40 °C for 24 hours subsequently. Polymer films were removed from the teflon plates and stored at 20 °C/ 60 % relative humidity for 7 days. Film thickness was determined using a manual micrometer at 15 random positions of the films [Table 2.7].

2.2.7 Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) analysis was performed to investigate glass transition temperatures (T_g) of free PVAc/PVA-PEG films. The measurements were performed on a DSC 200 (Netzsch GmbH, Selb, Germany). Samples of 12 to 15 mg were placed into aluminum pans with a perforated lid. The specimen were heated in two cycles with a heating rate of 10 K/min within a temperature range of −20 °C to 100 °C. Nitrogen was used as a flushing gas with a flow rate of 10 ml/min. The data of the second heating curves were analyzed for the determination of the T_g.

Table 2.6: Composition of PVAc/PVA-PEG (SR/IR) polymer films

Components [g]	**SR/IR 8/2**	**SR/IR 9/1 5 % TEC**	**SR/IR 9/1 10 % TEC**	**SR/IR 10/0**
Kollicoat® SR 30D	10.9	12.8	12.8	13.6
Kollicoat® IR	0.8	0.4	0.4	-
Triethyl citrate	0.4	0.2	0.4	0.4
Syloid® 244 FP	0.4	0.4	0.4	0.4
Titanium dioxide	0.1	0.1	0.1	0.1
Distilled water	7.4	6.1	5.9	5.5

Table 2.7: Film thickness of free PVAc/PVA-PEG (SR/IR) films

Film	**Kollicoat® SR 30D**	**SR/IR 8/2**	**SR/IR 9/1 5 % TEC**	**SR/IR 9/1 10 % TEC**	**SR/IR 10/0**
thickness [µm]	101 ± 10	105 ± 9	96 ± 11	88 ± 9	102 ± 12

2.2.8 Drug Content Analysis

Drug content of two different batches of Propranolol HCl pellets (PM070297, Glatt Air Techniques, Ramsey, USA and P07057L, Glatt GmbH Binzen, Germany) was analyzed. The pellet cores were dissolved in methanol/ distilled water (50/50 % w/w) using an ultrasonic bath. Afterwards, the samples were shaken in a horizontal shaker for 30 min. The insoluble parts of the pellets were removed by filtration (0.2 µm polytetrafluoroethylene (PTFE) filter) subsequently. The drug concentration was detected UV spectrophotometrically at 319 nm using UV/VIS diode-array spectrophotometer SA 500 (Pharma Test AG, Hainburg, Germany). Calibration equations were used for calculating the dissolved drug amount. Each batch was analyzed fivefold.

2.2.9 In vitro Dissolution Test

The dissolution tests were performed according to basket method 1 USP 31 [80] using an automatic dissolution tester (PTWS 310, Pharma Test, Hainburg, Germany). All tests were run at 37 °C and 100 rpm basket rotation speed. Dissolution tests were carried out in 900 ml simulated gastric fluid (SGF) without enzyme (pH 1.2) with a media change to 900 ml phosphate citrate buffer (pH 6.8) after two hours. The amount of dissolved drug

was determined by measuring UV absorption at 319 nm (UV/VIS diode-array spectrophotometer SA 500, Pharma Test AG, Hainburg, Germany) and calculated using calibration equations. Drug release rates in media with different osmolality were investigated as described above. However 0.5 mol/l or 1 mol/l sodium chloride were added to SGF pH 1.2 and phosphate citrate buffer pH 6.8 prior drug release experiments. Additionally, the resulting osmolality was analyzed with a semi micro osmometer (Knauer GmbH, Germany) (Chapter 2.2.12). All dissolution tests were performed in triplicate.

2.2.10 Determination of drug release parameters

Drug release parameters like lag time, maximum release rate and mean dissolution time were calculated from raw data of the dissolution tests. A logistic fit [Figure 2.1] was exercised to determine these variables:

$$c(t) = \frac{c_0 - c_1}{1 + \left(t/t_{1/2}\right)^p} + c_1. \tag{2.3}$$

Three parameters are included in this model. c_0 describes the drug concentration at the beginning of the dissolution test, c_1 characterizes the final drug concentration and $t_{1/2}$ stands for the mean dissolution time. The equation was differentiated with respect to t.

$$c'(t = t_{1/2}) = \frac{c_1 - c_0}{4t_{1/2}} \cdot p \tag{2.4}$$

Finally this term was inserted into following equation:

$$c(t)^{lin} = c'(t = t_{1/2}) \cdot (t - t_{1/2}) + (\frac{c_0 + c_1}{2}). \tag{2.5}$$

By means of this equation a linear correlation was obtained [Figure 2.1 (linear function)]. Using this data a linear fit was executed. Thus, the maximum drug release rate could be specified as the slope of the linear fit. The lag phase equals the quotient of y-intercept and slope of the linear regression.

2.2.11 Determination of drug solubility

The solubility of Propranolol HCl was determined in simulated gastric fluid pH 1.2 and phosphate citrate buffer pH 6.8. Excess of drug amounts were placed in contact with medium at 37 °C in an orbital shaker at 200 rpm (Orbital mixing SC20, Torrey Pines Scientifique Inc., USA) for at least 48 hours. Every 12 hours samples were withdrawn, centrifuged and analyzed for their drug content as described in section 2.2.7 until equi-

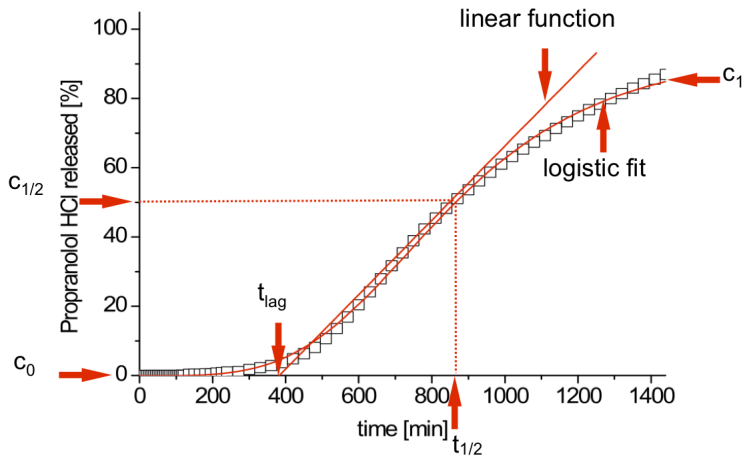


Figure 2.1: Determination of release parameters. A logistic fit was conducted with drug release data.

librium was reached. Spekol 1200 (Analytik Jena AG, Germany) was used for the spectrophotometrical measurements.

2.2.12 Osmotic pressure measurements

The osmotic pressure of simulated gastric fluid pH 1.2, phosphate citrate buffer pH 6.8 and both media with 0.5 mol/l or 1 mol/l sodium chloride added was measured using semi micro osmometer (Knauer GmbH, Germany). In addition, the osmotic pressure of saturated Propranolol HCl solution in distilled water, simulated gastric fluid and phosphate citrate buffer was determined.

2.2.13 Swelling of coated Pellets

Swelling of the pellets was determined in 15 ml medium in 8.5 cm petri dishes using an image analysis system (analySIS® FIVE, Olympus Soft Imaging Solutions GmbH, Germany). The experiment was performed at room temperature. The average diameter of 15 pellets of the 1.0 - 1.4 mm sieve fraction was measured at predetermined times utilizing an impinging light microscope (Olympus SZX 9 stereo zoom microscope, Olympus GmbH, Hamburg, Germany). The zoom of the camera was adjusted to maximum magnification and resolution. Swelling was calculated in percent from increase of average feret diameter related to the first measured diameter [81].

2.2.14 Environmental Scanning Electron Microscopy

The surface as well as the cross section of pellets was analyzed using environmental scanning electron microscopy (ESEM, Philips ESEM XL 30 FEG, Philips Electron Optics). Cross section cuts were prepared with a scalpel. SEM micrographs were obtained by using WET-mode (1.7 mbar, acceleration voltage of 12 keV). Secondary electron images as well as backscattering electron images were comprised. An energy dispersive X-ray detector (EDX) was used to investigate the distribution of specific atoms.

2.2.15 Nuclear Magnetic Resonance (NMR) Spectroscopy

2.2.15.1 ^1H NMR Spectroscopy

^1H NMR Nuclear magnetic resonance (^1H NMR) measurements were performed to analyze the content of acetic acid within PVAc dispersions (Kollicoat® SR 30D). ^1H NMR spectra were acquired from a 400 MHz ^1H NMR spectrometer (Varian Gemini 2000, Varian GmbH, Darmstadt, Germany). Thus, 15 or 35 mg acetic acid were added to 5 g PVAc dispersion and blended using a magnetic stirrer. Then both mixtures as well as pure PVAc dispersion were casted onto teflon plates. The films were dried at 50 °C for 24 h in a drying oven. 50 mg of each film was weighted exactly and filled into an Eppendorf tube. Remaining water was removed from the samples by means of lyophilization. Subsequently, 1 ml DMSO-d6 were added to the polymer film samples and the films were dissolved within the solvent for the ^1H NMR measurements.

2.2.15.2 Benchtop NMR (BT-NMR)

NMR relaxometry measurements were carried out using a MARAN DR X2 Benchtop-NMR spectrometer (Oxford Instruments, United Kingdom) with at a high frequency of about 20 MHz. The measurements were performed at 25 °C. Samples of 0.9 to 1.1 g pellets were placed into a 10 mm NMR tube and were wetted with 2 ml dissolution medium (simulated gastric fluid pH 1.2 or phosphate-citrate buffer pH 6.8). Within the present thesis the transversal relaxation time T_2 (spin-spin relaxation) was determined using the Carr-Purcell-Meiboom-Gill (CPMG) sequence [82]. BT-NMR measurements were accomplished in accordance with [Table 2.8].

The CPMG decay curves were evaluated using WinDXP package (Resonance Instruments, Ltd., Oxfordshire, U.K.). The T_2 relaxation curves were analyzed using the inverse Laplace transformation.

Table 2.8: Parameters for BT-NMR relaxometry

Parameter	
B_0 field	0.5 T
number of scans	16
number of echos	24000
relaxation delay	30 s
90° pulse	3.65 µs
180° pulse	7.3 µs
recycle delay	135 µs

2.2.16 Electron Paramagnetic Resonance

PVAc/PVA-PEG coated Propranolol HCl pellets were analyzed using Electron Paramagnetic Resonance (EPR). As a spin probe 4 mmol/kg TEMPOL (TL) were implemented into the HPMC based sub coat of coated pellets. EPR measurements were performed with a L-band EPR spectrometer (Magnettech GmbH, Berlin, Germany) working at a microwave frequency of about 1.3 GHz. EPR experiments were carried out according to [Table 2.9].

Table 2.9: Parameters for EPR measurements

Parameter	
B_0 field	49.0 mT
Scan range	8 mT
Scan time	30 s
Modulation amplitude	0.12 mT

For EPR experiments 2 g PVAc/PVA-PEG coated Propranolol HCl pellets were filled into a flow through cell and fixed with glass wool. The cell was placed into the EPR spectrometer. It was flooded with dissolution media (simulated gastric fluid pH 1.2 or phosphate citrate buffer pH 6.8) at 1 ml/min media flow subsequently.

3

Formulation and process development for PVAc/PVA-PEG coated pellets

3.1 Motivation and objectives

Propranolol HCl core pellets comprising of 60 % drug were used for the development of a multiple unit dosage form. The benefits of this drug delivery system were already mentioned in Chapter 1.2. Due to the good solubility of Propranolol HCl the drug was selected to demonstrate the drug release from coated pellets which is only slightly influenced by solubility issues.

An aqueous dispersion of PVAc (Kollicoat® SR 30D) was used as a coating polymer for membrane controlled drug delivery. Water soluble PVA-PEG copolymer (Kollicoat® IR) was added as a pore forming agent to accelerate drug release from the pellets. The use of PVAc/PVA-PEG graft copolymer blends as coating material for solid dosage forms was reported by the polymer supplier BASF [83]. Strübing et al. adapted BASF film coating formulations for tablet coating studies [32, 40, 41]. Similar polymer blends were implemented for the coating of pellets by Ensslin et al. [42, 43, 44].

The coating of Propranolol HCl pellets with PVAc/PVA-PEG polymer blends was accomplished in a GPCG 1.1 fluid bed coater (Glatt GmbH, Binzen, Germany) with a 6″ wurster insert. The Wurster-based fluid bed coating process is a high-velocity circulation fluid bed system [84, 85]. It involves several regions with quite different fluidization properties [23]. In contrast to fluid bed systems in the traditional sense the Wurster-based fluid bed coating exhibits well-defined product movement into and out of the spray zone [85, 86]. Thus, the Wurster-based coating process is a complex process. Many interrelated concurrent processes have to be considered. Therefore, much effort should be directed towards the optimization of process parameters. The main components of the fluid bed coating process are

- Substrate (e.g. pellets)

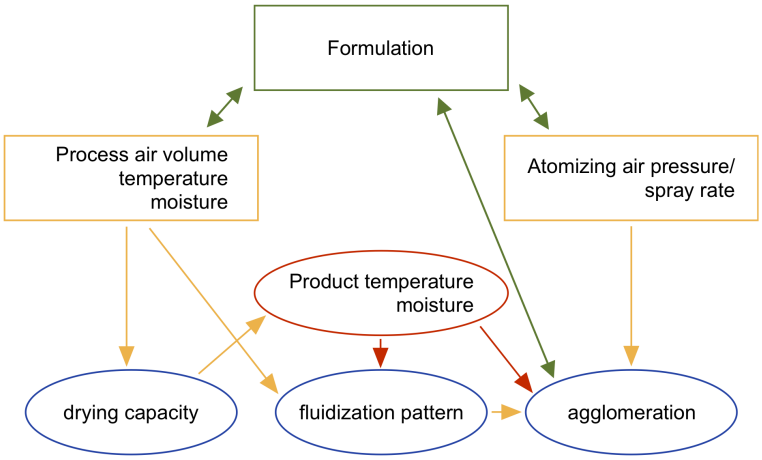


Figure 3.1: Components of the fluid bed coating process. Process parameters (orange), product properties (red) and formulation strongly affect the result of a fluid bed process. Adapted by Grave et al. [23].

- Fluidization medium
- Coating solution [85].

The fluidization medium is of particular importance for the coating process. Very often atmospheric air is used for the fluid bed process. The atmospheric air is mostly heated in order to increase the energy input to the process. The humidity of the inlet air should be controlled as well. The inlet air and its air volume mainly affects the particle fluidization pattern, but also the drying capacity, substrate properties and thus agglomeration during the fluid bed process [Figure 3.1 orange].

Another key element of the coating process is the atomization of the coating solution/ dispersion into droplets of suitable size in order to distribute the coating material on the surface of the substrate. The droplets ideally spread over the surface of the substrate with enough solvent left to ensure coalescence into a preliminary film. At the same time the drying must not be too slow as this might facilitate particle agglomeration [Figure 3.1 orange]. The most important parameter concerning the substrate within the fluid bed coating process is the product temperature: it results from the interplay of inlet air temperature and coating liquid spraying rate. The product temperature and thereby the product moisture strongly influence the particle fluidization pattern and agglomeration tendencies during the process cycle [Figure 3.1 red]. A too dry coating process may on the other hand provide spray drying of coating liquids which will have a considerable impact on the in vitro dissolution behaviour of pellets after controlled-release coating.

The following section describes the formulation and process development for PVAc/PVA-PEG coatings on Propranolol HCl pellets.

3.2 Formulation and process development for pellet coating

The first coating experiments with PVAc/PVA-PEG polymer blends were carried out using Cellet® 700 starter cores. These starter cores consist of 100 % microcrystalline cellulose. As they are not soluble in water they are easy to handle during a coating process with aqueous coating suspension. The composition of the first polymer blend based on data from Strübing et al. [32] [Table 3.1]. The total surface area of the starter cores was determined according to Chapter 2.2.4. The pellets should be coated with 12 mg polymer/cm^2.

Coating experiments were performed with a GPCG 1.1 Wurster-based fluid bed equipment (Glatt GmbH, Binzen, Germany). Coating parameters for this fluid bed system were published by BASF [47] and were utilized for the initial experiments with PVAc/PVA-PEG coatings [Table 3.2]. The first coating experiments could not be finished successfully. Sticking of the pellets led to agglomeration of the substrate after some time. Various challenges concerning the formulation as well as the coating process could be observed.

Table 3.1: PVAc/PVA-PEG (SR/IR) polymer blends for film coating based on coating composition from Strübing et al. [32]

Components [g]	**SR/IR 8/2**	**SR/IR 9/1**	**solids content [%]**
Kollicoat® SR 30D	982.6	1105.6	
Kollicoat® IR	73.7	36.8	
Triacetin	16.4	16.4	
Talc	80.6	80.6	
Titanium dioxide	11.6	11.6	
Distilled water	1070.7	984.6	
	2235.6	2235.6	21.3

First of all, settlement of pigment within the coating suspension was distinguished despite continuous stirring during the process. The suspension contained 21.7 % talc based on the dry polymer mass. For the following process the talc contingent was decreased to 10 % based on the dry polymer mass. Triacetin was used as a plasticizer for PVAc/PVA-PEG film coating first (4.4 % based on the dry polymer mass). For further coating experiments triacetin was substituted by 10 % triethyl citrate based on dry polymer mass. Several publications from the polymer supplier BASF demonstrate the efficiency of triethyl citrate within PVAc based coatings to lower the minimum film temperature [46, 47, 87]. A concentration of 10 % plasticizer within the films is recommended by the authors if a

Table 3.2: Coating parameters from BASF [47]

Parameter	
Inlet air temperature	50 - 55 °C
Product temperature	35 - 40 °C
Air flow	90 m^3/h
Nozzle diameter	1.2 mm
Atomizing air pressure	1.2 bar
Air distribution plate	type B
Partition height	25 mm

high plasticity of the resulting films is required e.g. when the coated pellets should be compressed to tablets. The literature reveals a similar increase in elongation for break for PVAc films plasticized with both plasticizers [46, 47]. Bodmeier et al. investigated the plasticizer uptake by aqueous colloidal polymer dispersions [88]. An equal distribution of triethyl citrate between the polymer and the aqueous phase of Aquacoat® compared to triacetin was found. This phenomenon was explained by the higher solubility of triacetin in water. The association coefficient of triethyl citrate for several aqueous polymer dispersions was found to be higher than for triacetin. The association coefficient reflects the affinity of a plasticizer for the polymer. Thus, triethyl citrate was chosen as a plasticizer for future coating experiments with PVAc/PVA-PEG polymer blends.

As mentioned before, intense sticking of the pellets followed by agglomeration of the complete substrate yielded a process break down. The product temperature recommended by BASF was found to be too high for the present coating formulation. The inlet air temperature was reduced from 50 - 55 °C to 45 °C. The product temperature was decreased to 30 - 35 °C by adjusting the spraying rate. Additionally, the atomizing air pressure (AAP) was increased from 1.2 bar to 2.0 bar in order to achieve a finer coating liquid droplet size which is more feasible to avoid agglomeration than larger droplets.

The following coating process with PVAc/PVA-PEG 8/2 was still not running stable. Several issues regarding both, coating formulation and process had to be optimized. Within the coating suspension talc settlement could still not be abandoned as no micronized material was available. The presence of a lubricant is of great importance for the coating composition as it should prevent agglomeration of the substrate during the coating process. To resolve this difficulty talc was replaced by amorphous silica Syloid® 244 FP. Its main benefits are the great specific surface area, high bulk density and a very small particle size. Consequently, particle settlement blocking the spray nozzle and leading to

agglomeration of coated particles could be abandoned. The final coating composition is demonstrated in table [Table 3.3].

Table 3.3: Composition of PVAc/PVA-PEG (SR/IR) coating dispersions for Propranolol HCl pellet coating

Components [g]	**SR/IR 8/2**	**SR/IR 9/1**	**SR/IR 10/0**	**solids content [%]**
Kollicoat® SR 30D	870.8	980.0	1088.9	
Kollicoat® IR	65.4	32.7	-	
Triethyl citrate	32.7	32.7	32.7	
Syloid® 244 FP	32.7	32.7	32.7	
Titanium dioxide	8.2	8.2	8.2	
Distilled water	590.3	514.0	438.3	
	1600.1	1600.3	1600.8	25.0

In a next step the coating process was optimized. During the previous coating experiments the fluidization of the substrate was found to be not optimal. Substrate remained at the bottom plate assuming that the air flow was too low. A higher air flow causes an increased velocity of the substrate within the fluid bed coater. Thus, an increased velocity might decrease agglomeration tendencies of the beads as they pass the coating area more quickly and are moved more vigorously in the down-bed area. Within the further coating experiments the air flow was increased from 90 m^3/h to 120 m^3/h. This led to a better fluidization pattern and less agglomeration of the material. Schlütermann et al. [89] suggest a product temperature of around 30 °C and an inlet air temperature of 35 °C for coating with PVAc. Thus, the initial process air temperature was set to 35 °C. After 15 min the inlet air temperature was increased to 40 °C.

The spraying rate was adjusted to keep the product temperature at around 30 °C for the coating process. The result of the coating process performed with these parameters was satisfying. The coated pellets were free flowing. Still some agglomerates (> 1400 µm) were found within the product. The process air was taken from the atmosphere. Therefore, it was assumed that the humidity of the inlet air might be too high and not consistent as well. An inlet air dehumidifier was implemented leading to reproducible conditions for the coating processes. For all following coating experiments the dew point of the process air was set to 5 °C. Implementing all the optimized process parameters, the first successful pellet coating experiment was performed [Table 3.4]. The product exhibited only few agglomerates (> 1400 µm, < 1.0 %), was free flowing and of nice appearance.

Now the coating process was transferred to Propranolol HCl starter cores consisting of

Table 3.4: Coating parameter for pellet coating with PVAc/PVA-PEG blends using a GPCG 1.1 fluid bed coater

Parameter	
Inlet air temperature	35 - 40 °C
Inlet air moisture	7.62 g water/m^3 dry air
Product temperature	29 - 30 °C
Air flow	110 - 120 m^3/h
Nozzle diameter	1.2 mm
Atomizing air pressure	2.0 bar
Air distribution plate	type C
Partition height	25 mm

60 % Propranolol HCl and 40 % microcrystalline cellulose (MCC) [Figure 3.2 (a)]. The batch size for Propranolol HCl pellet coating was 500 g. The total surface area of the Propranolol HCl starter cores was determined according to Chapter 2.2.4. Based on the result the amount of polymer for a coating level of 12 mg polymer/cm^2 was calculated. The substrate was coated with three different PVAc/PVA-PEG polymer blends as specified in [Table 3.3]. The empty fluid bed coater was preheated at 35 °C inlet air temperature for 10 min before starting the coating process. Then, the substrate was heated to a product temperature of 30 °C to prevent overwetting during the initial application of the coating suspension. The coating process was run as described above. After finishing the coating process the pellets were dried within the fluid bed equipment for 10 min at 45 °C. The drying step was followed by a cooling of the product to 25 °C. At this temperature the sticking of the pellets could be minimized. Consequently, possible film rupture during the removal of the pellets from the fluid bed equipment was prevented. All processes run stable using the optimized parameters from [Table 3.4]. Only few agglomerates ($>$ 1400 µm, $<$ 0.65 %) were detected during the sieve analysis of the products.

ESEM pictures were taken from PVAc/PVA-PEG 9/1 coated Propranolol HCl pellets. The surface of the Propranolol HCl starter cores appears rough [Figure 3.2 (a)] whereas the PVAc/PVA-PEG coated pellets exhibit a smooth surface [Figure 3.2 (b)]. The film coat is uniform and without visible defects. Cross sections of coated pellets were made using a razor blade. They allowed for a clear differentiation between starter core and polymer coating [Figure 3.2 (c, d)]. The cross sectional view provides a homogenous thick coating.

The glass transition temperature (T_g) of free PVAc/PVA-PEG films was determined by

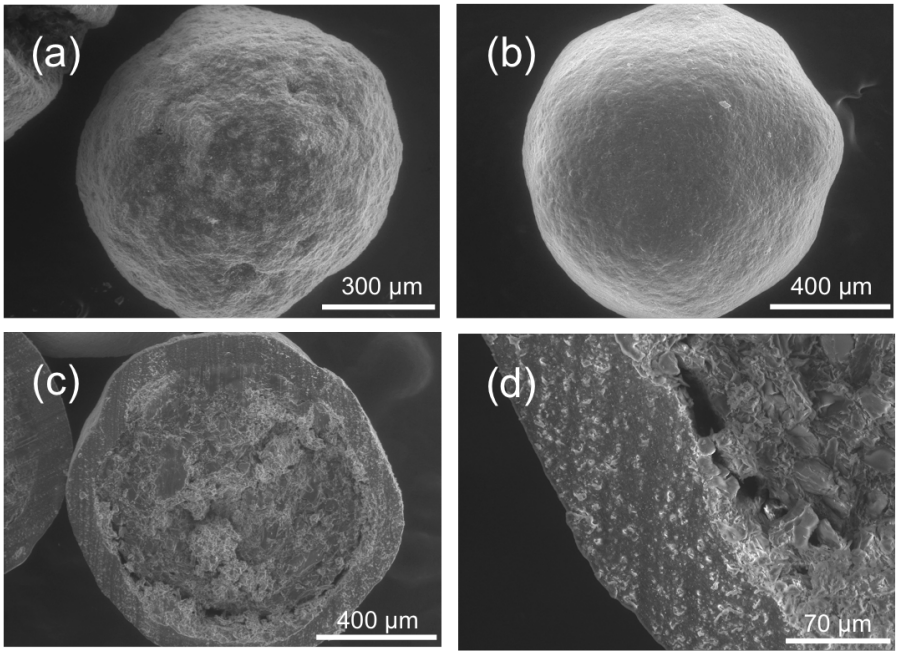


Figure 3.2: ESEM picture of a Propranolol HCl starter core (a). Surface of a PVAc/PVA-PEG 9/1 coated starter core (b). Cross section of the coated starter core (c), (d).

means of Differential scanning calorimetry (DSC). The glass transition temperature of a polymer is defined as the transformation of a substance from the amorphous and glassy to a rubbery state [90]. It is associated with increased polymer chain segment motion. T_g depends on the molecular weight, internal constitution and chemical properties of the polymer chains as well as on crystallinity of the substance [90]. As an amorphous solid is not in a thermodynamically balanced state, the transition to the rubbery state represents a kinetically controlled relaxation process. Thus, the glass transition process is not fixed to a certain temperature but a temperature range. DSC studies were performed by detecting the heat flux being proportional to the temperature difference between sample and reference. The glass transition temperature appears as an endothermic step in DSC curves. The inflexion point of the curve represents the glass transition temperature T_g [Figure 3.3].

Unplasticized films of Kollicoat® SR 30D exhibited a glass transition temperature of 34.1 °C [Table 3.5]. This value was significant lower compared to results reported by Strübing (40.6 °C) [91], Ensslin (42.5 °C) [56] and Müller (41.4 °C) [92]. The difference of the T_g might be due to different water residuals in the examined polymer films as water is acting as a plasticizer for many polymers [33, 93, 94, 95]. PVAc film plasticized with 10 % triethy citrate exhibited a glass transition temperature of 18.3 °C. This value was significantly lower compared to the unplasticized PVAc film. Thus, triethyl citrate is

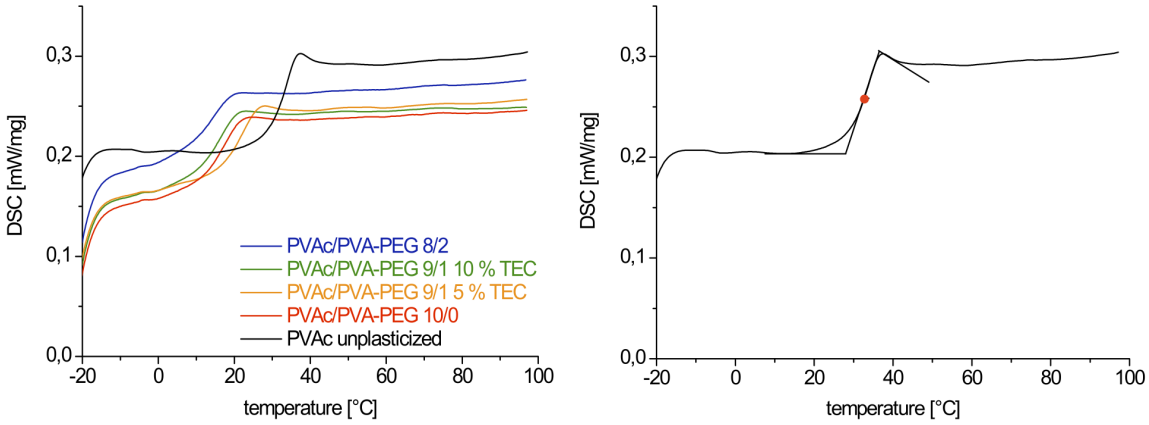


Figure 3.3: DSC curves of free PVAc/PVA-PEG polymer films. The T_g is determined by the inflexion point of the DSC curve (red dot, right picture).

Table 3.5: Glass transition temperatures (T_g) of PVAc/PVA-PEG blends

Film coating polymer	**plasticizer [%]**	**T_g**
PVAc	-	34.1
PVAc	10	18.3
PVAc/PVA-PEG 9/1 ratio	10	16.8
PVAc/PVA-PEG 9/1 ratio	5	22.2
PVAc/PVA-PEG 8/2 ratio	10	13.9

suitable as a plasticizer for PVAc polymer films. The addition of 10 % PVA-PEG graft copolymer to plasticized PVAc reduced T_g to 16.8 °C. T_g was further decreased by adding 20 % of PVA-PEG (13.9 °C). This phenomenon was reported earlier [56, 91, 92]. It can be concluded that the soluble polymer PVA-PEG acts as a plasticizer within these polymer blends. The plasticizing properties of PVA-PEG are due to the PEG chains which are covalently bond within the macromolecules. Polymer films with a PVAc/PVA-PEG ratio 9/1 were plasticized with different amounts of triethyl citrate (5 % vs. 10 %). The result emphasizes the influence of the plasticizer triethyl citrate in comparison with PVA-PEG. A T_g of 18.3 °C was measured for 10 % TEC plasticized PVAc film vs. 22.2 °C for 5 % TEC plasticized PVAc/PVA-PEG 9/1 film. The plasticizing capacity of PVA-PEG is low compared to plasticizer TEC. Therefore, the addition of a plasticizer like triethyl citrate is considered to be essential if the sustained release film coat should be flexible and not brittle in order to be able to resist strong mechanical forces e.g. during a tableting process.

3.3 Conclusion

Coating formulations with PVAc/PVA-PEG polymer blends were developed. The formulations were improved regarding particle settlement by the use of Syloid® 244 FP instead of talc. Thus, an easy-to-process and effective antitacking agent available within the coating suspension inhibiting substrate agglomeration during the coating process efficiently. Triethyl citrate was introduced as a plasticizer for PVAc/PVA-PEG film coatings. Due to the results of DSC measurements, the plasticizer effectively decreased the glass transition temperature of PVAc/PVA-PEG polymer blends.

Furthermore, a stable film coating process for the coating of Propranolol HCl pellets with PVAc/PVA-PEG was established. The process air temperature was decreased to 40 °C from previously applied 55 °C. The inlet air humidity was set to a dew point of 5 °C by introducing a dehumidifier to the coating process leading to reproducible coating conditions. The air flow was increased resulting in improved fluidization of the substrate during the coating process as well as reduced agglomeration. An increase of the atomizing air pressure caused further decrease of substrate agglomeration by providing smaller droplets of the coating liquid.

In a next step, drug release from PVAc/PVA-PEG coated Propranolol HCl pellets was investigated. The influence of formulation changes as well as of process variable product temperature on drug release were analyzed.

4

Analysis of drug release from coated pellets

4.1 Determination of dissolution characteristics

4.1.1 Motivation and objectives

The current section elucidates the release of Propranolol HCl from PVAc/PVA-PEG coated pellets. First of all, the influence of water soluble PVA-PEG content within PVAc polymer coatings on drug release was analyzed. The use of polymer blends is an interesting tool to control drug liberation from coated dosage form and is frequently reported in the literature [32, 37, 38, 42, 96]. Additionally, the film coat thickness of the functional film coat was varied to modify drug release from coated dosage forms.

Pellets with a supplementary barrier layer of HPMC between drug containing pellet core and functional polymer coating were manufactured. The application of a water soluble sub coating is a reasonable approach to eliminate drug migration into the polymer film [29, 69, 70, 97]. The sub coat should consist of a polymer in which the drug is insoluble, eliminating the diffusion of drug into the functional film coat [69].

Furthermore, the influence of plasticizer amount on drug liberation was investigated. Ensslin [56] examined the influence of different propylene glycol concentrations on Chlorpheniramine maleate release from PVAc/PVA-PEG coated pellets and found no significant impact. Propranolol HCl release from pellets coated with PVAc did not change implementing different triethyl citrate concentrations [29]. Otherwise, a strong influence of the plasticizer concentration on drug release from PVAc/PVP coated pellets was noticed by Guthmann [48]. Due to these results the impact of triethyl citrate concentration on drug release from PVAc/PVA-PEG coated Propranolol HCl pellets was studied within this thesis.

The influence of the process variable product temperature on drug liberation from PVAc/PVA-PEG coated pellets was examined.

Finally, the influence of the pH of the dissolution medium on Propranolol HCl release was investigated. PVAc and PVA-PEG represent uncharged polymers [29, 47]. Therefore, pH

independency of drug release from PVAc/PVA-PEG coated pellets was expected. Ensslin [56] described different release behaviour in phosphate citrate buffer pH 6.8 compared to simulated gastric fluid pH 1.2 or 0.1 mol/l HCl pH 1.0 respectively. Due to these results, the impact of medium pH on Propranolol HCl release from PVAc/PVA-PEG coated pellets was examined within this work.

4.1.2 Influence of polymer ratio and HPMC sub coat

The influence of the PVAc/PVA-PEG ratio on Propranolol HCl release from coated pellets was analyzed. Propranolol HCl starter cores were coated with 12 mg polymer/cm^2 film coat according to [Table 4.1 1-3]. The pellets were cured in a drying oven for 24 h at 40 °C after finishing the fluid bed process.

Table 4.1: Formulation of Propranolol HCl pellets coated with different polymer ratios

No. Formulation	**HPMC sub coat [% m/m]***	**PVA-PEG [% m/m]****
1	-	20
2	-	10
3	-	0
4	10	20
5	10	10
6	10	0

* related on starter core mass

**related on dry PVAc polymer mass

The drug release profiles demonstrated a combination of delayed and sustained release with a sigmoid shape. They are characterized by an initial lag phase without drug liberation followed by a proliferated continuous drug release [Figure 4.2 (b)]. Pellets coated with PVAc/PVA-PEG 8/2 exhibited a short lag phase of only 25 min whereas the lag phase raised up to 4 h (PVAc/PVA-PEG 9/1) or even 18 h (PVAc/PVA-PEG 10/0). More than 95 % Propranolol HCl were liberated within 10 h from pellets coated with PVAc/PVA-PEG 8/2. In contrast, only 84 % Propranolol HCl were released within 24 h from PVAc/PVA-PEG 9/1 coated pellets and only 23 % from pellets with a PVAc/PVA-PEG 10/0 film coat. Thus, the release of Propranolol HCl is strongly influenced by the polymer ratio of PVAc/PVA-PEG.

Next, the influence of a HPMC sub coat on drug release was investigated. A HPMC

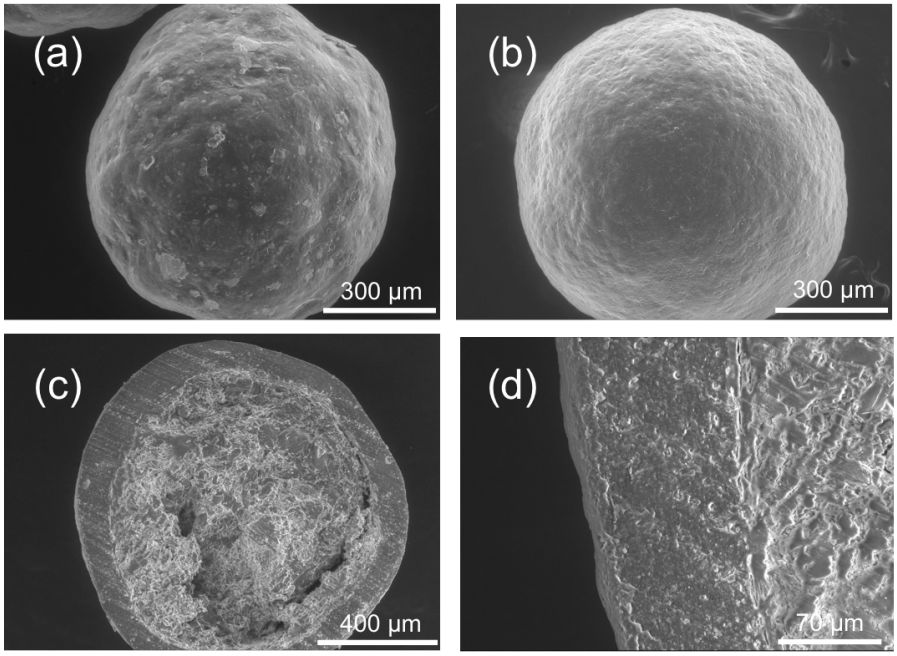


Figure 4.1: ESEM picture of a HPMC coated Propranolol HCl starter core (a). PVAc/PVA-PEG 9/1 coated pellet (b). Cross section of a Propranolol HCl pellet coated with 10 % HPMC and 12 mg polymer/cm^2 PVAc/PVA-PEG 9/1 (c), (d).

layer (10 % related on starter core mass) was coated on Propranolol HCl pellets [Figure 4.1 (a)]. The drug release from pellets coated with 10 % HPMC is demonstrated in [Figure 4.2 (a)]. The Propranolol HCl release is not affected significantly by the HPMC coat compared to uncoated starter cores. The drug release from both samples was completed after 20 min. The HPMC layered Propranolol HCl pellets were coated with 12 mg polymer/cm^2 PVAc/PVA-PEG [Table 4.1 4-6] [Figure 4.1 (b) - (d)]. The pellets were cured at 40 °C for 24 h in a drying oven immediately after the coating step.

The application of the HPMC sub coating [Figure 4.1 (c), (d)] resulted in reduced drug release in the early stages of the dissolution analysis [Figure 4.2 (b)]. The lag phase before drug release started increased for all PVAc/PVA-PEG ratios comprising of a HPMC sub layer [Table 4.1 4-6]. Pellets coated with PVAc/PVA-PEG 8/2/ HPMC show a lag phase of 52 min compared to 25 min without HPMC. The lag phase of PVAc/PVA-PEG 9/1/ HPMC coated pellets extends up to 6 h. A lag phase more than 24 h was calculated for PVAc/PVA-PEG 10/0/ HPMC coated pellets. Nevertheless, similar amounts of Propranolol HCl were liberated within the same time for pellets coated with or without HPMC sub layer and PVAc/PVA-PEG 8/2 or 9/1 respectively. As the lag phase of pellets coated with PVAc/PVA-PEG 10/0/ HPMC was more than 24 h only a small amount of drug (6 %) was released within 24 h.

The release parameters are summarized in [Table 4.2] and [Figure 4.3]. The decreased

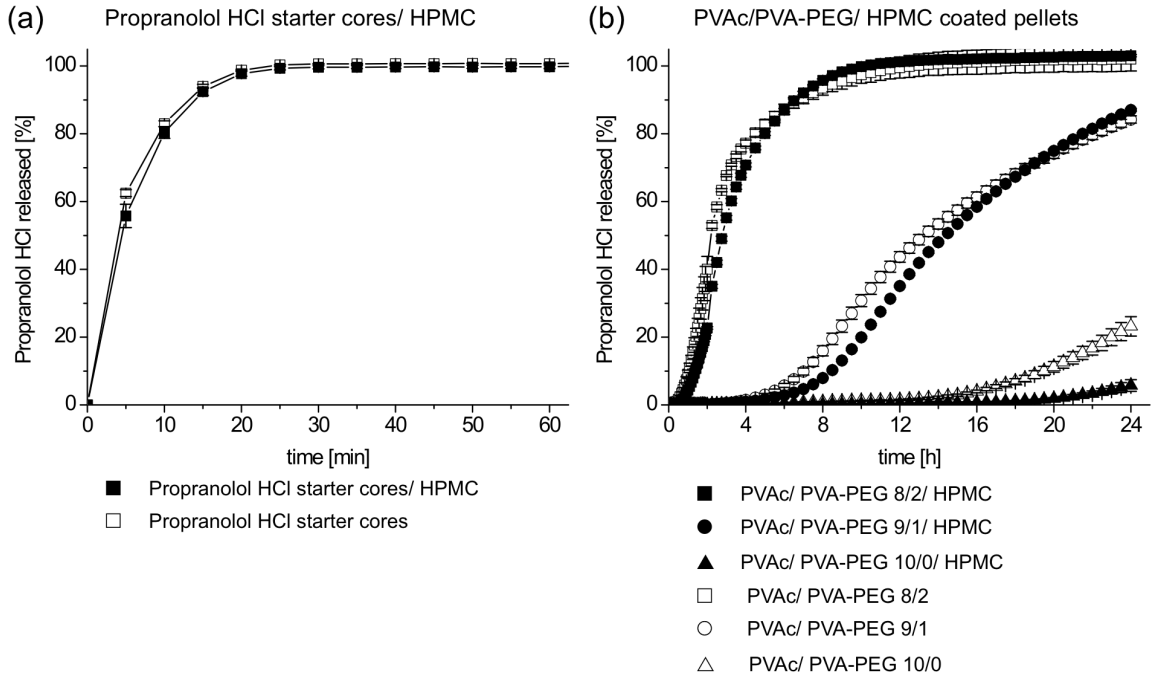


Figure 4.2: Propranolol HCl release from uncoated starter cores compared with the drug release from pellets coated with 10 % HPMC (related on pellet starter mass) (a). The drug release remains nearly unchanged with the HPMC coating. Influence of the PVAc/PVA-PEG ratio on Propranolol HCl release: Propranolol HCl pellets coated with 12 mg polymer/cm^2 functional film coat (Formulation No. 1-3) (b, open symbols). The influence of a 10 % HPMC sub coat (related on pellet starter mass) on drug release from PVAc/PVA-PEG coated pellets is demonstrated (c, closed symbols). The influence of the HPMC sub layer increases with decreasing PVA-PEG ratio.

Table 4.2: Release parameters of Propranolol HCl pellets coated with different polymer ratios. Influence of the HPMC sub coat.

Formulation	**lag phase [min]**	**drug release rate [%/min]**
PVAc/ PVA-PEG 8/2	25 ± 2	0.43 ± 0.04
PVAc/ PVA-PEG 9/1	248 ± 1	0.09 ± 0.00
PVAc/ PVA-PEG 10/0	1081 ± 37	0.07 ± 0.00
PVAc/ PVA-PEG 8/2/ HPMC	52 ± 1	0.39 ± 0.01
PVAc/ PVA-PEG 9/1/ HPMC	376 ± 5	0.11 ± 0.00
PVAc/ PVA-PEG 10/0/ HPMC	1487 ± 61	0.08 ± 0.02

drug release rates of PVAc/PVA-PEG/ HPMC coated pellets are caused by the application of the HPMC sub coat as water has to penetrate and dissolve an additional diffusion barrier within the pellets. Thus, also the lag phases of pellets comprising the HPMC sub coat are prolonged.

4.1.3 Influence of PVAc/PVA-PEG coating level

The influence of the coating level on drug release from PVAc/PVA-PEG coated pellets was investigated. PVAc/PVA-PEG films in three different ratios were applied to Propranolol HCl starter cores comprising a HPMC sub coat. Pellet samples were removed from the coating process at coating levels of 3, 6, 9 and 12 mg polymer/cm^2. All pellets were cured in a drying oven for 24 h at 40 °C after finishing the fluid bed process.

Drug release from pellets coated with different PVAc/PVA-PEG blends according to [Table 4.1 4-6] at various coating levels is demonstrated in [Figure 4.4]. As expected, higher coating levels resulted in extended lag phases and in decreased drug release rates by reason of increased diffusion pathways. The calculated lag phases and drug release rates for PVAc/PVA-PEG coated pellets with different coating levels are summarized in [Table 4.3]. An increase in lag phase due to increasing coating levels for pellets coated with PVAc/PVA-PEG 8/2/ HPMC is found except for the highest coating level; the reason therefor is unclear. A distinctive impact of coating level on lag phase of PVAc/PVA-PEG 8/2/ HPMC or PVAc/PVA-PEG 9/1/ HPMC coated pellets can be observed. Still, the effect is less pronounced at higher film levels (9 or 12 mg polymer/cm^2). At the same time the drug release rates for these pellets decrease with increasing coating level. The drug release rate is almost bisected when 3 mg polymer/cm^2 are added. At higher coating levels the differences in drug release are less pronounced compared to lower coating levels.

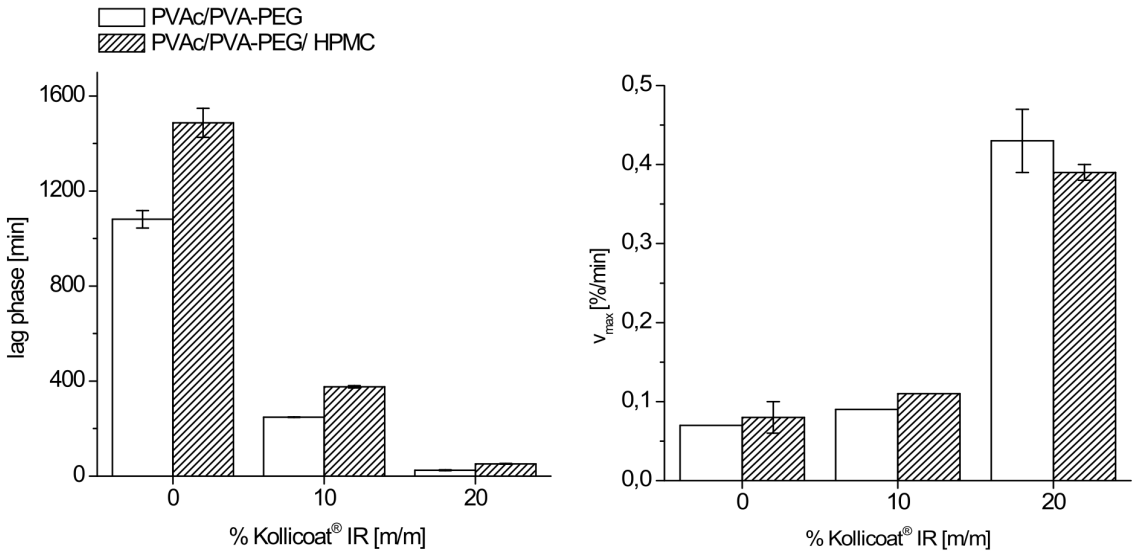


Figure 4.3: The drug release parameters lag phase and drug release rate as a function of amount of polymer PVA-PEG. The lag phase is specified as the interception of the linear fit with the abscissa according to Chapter 2.2.10.

PVAc/PVA-PEG 10/0/ HPMC coated pellets exhibit considerably different lag phases for all investigated coating levels. Regarding these results one can conclude that the PVAc/PVA-PEG ratio has a predominant impact on Propranolol HCl release compared to the coating thickness.

4.1.4 Influence of plasticizer concentration

In the previous coating experiments 10 % triethyl citrate (based on the dry PVAc/PVA-PEG polymer mass) were applied to plasticize PVAc/PVA-PEG coatings. Additionally, a concentration of 5 % triethyl citrate was used as plasticizer to examine the influence of the plasticizer concentration on drug release from PVAc/PVA-PEG coated Propranolol HCl pellets [Table 4.4]. The pellets were coated with 12 mg polymer/cm^2 PVAc/PVA-PEG film coat after HPMC layering. The pellets were cured using dry heat for 24 h at 40 °C after finishing the fluid bed process.

The release profiles of formulations 7 and 8 are shown in [Figure 4.5]. The release profile of PVAc/PVA-PEG 9/1/ HPMC 5 % TEC 2010 coated pellets remained unchanged compared to the release profile of pellets coated with PVAc/PVA-PEG 9/1/ HPMC 10 % TEC 2010. A slight difference between the lag phases (463 min vs. 423 min) is observed. Still, there is no clear distinction between the both products verifying previous publications from Ensslin et al. [43, 56]. Interestingly, PVAc/PVA-PEG 9/1/ HPMC 10 % TEC 2009 coated pellets showed a shorter lag time (376 min) and a slightly increased drug release

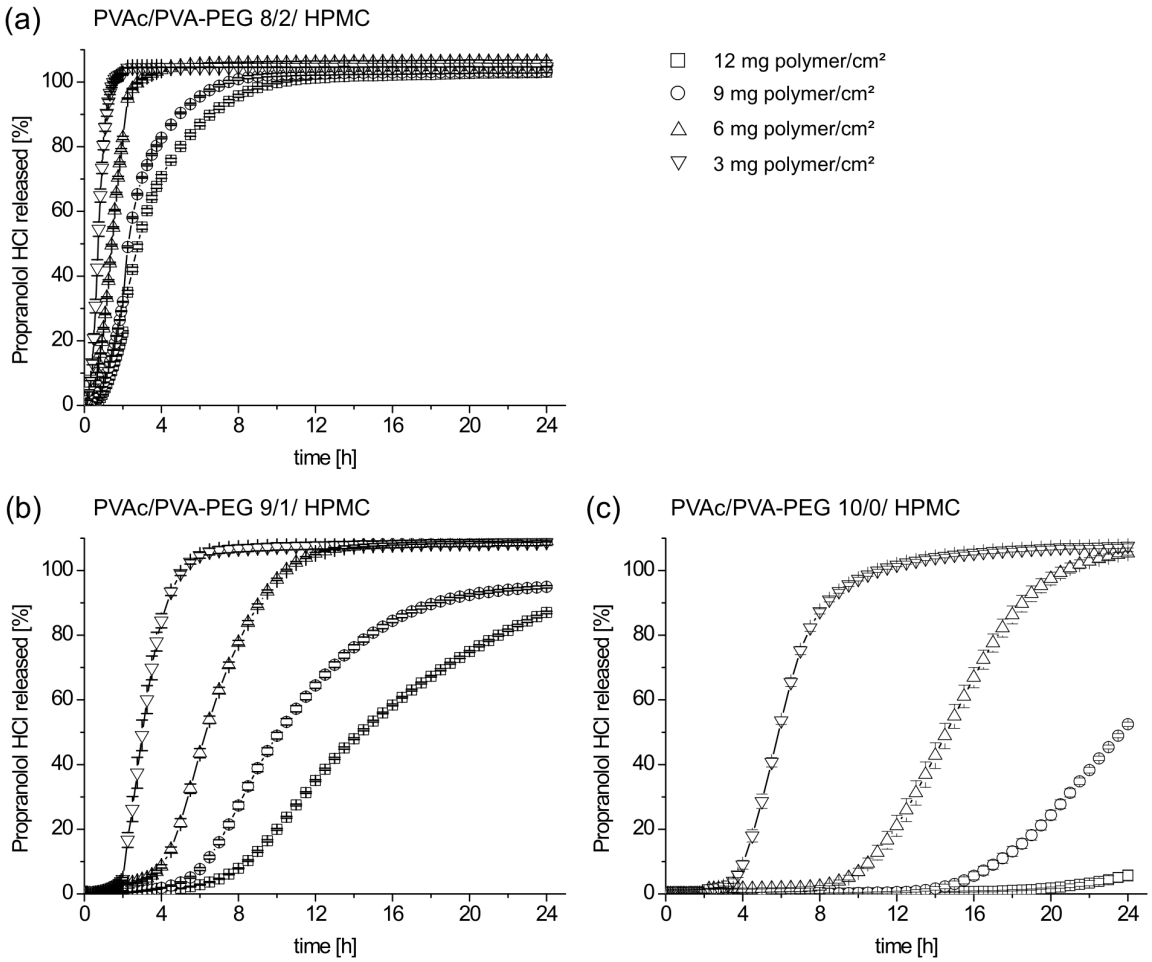


Figure 4.4: Influence of coating level on Propranolol HCl release from PVAc/PVA-PEG/ HPMC coated pellets. The pellets were coated with PVAc/PVA-PEG in a ratio of 8/2 (a), 9/1 (b) and 10/0 (c).

Table 4.3: Release parameters of Propranolol HCl pellets coated with different coating levels.

Formulation	**coating level mg polymer/cm^2**	**lag phase [min]**	**drug release rate [%/min]**
PVAc/ PVA-PEG 8/2	3	23 ± 0	2.29 ± 0.03
	6	43 ± 0	1.12 ± 0.01
	9	58 ± 0	0.55 ± 0.00
	12	51 ± 1	0.39 ± 0.01
PVAc/ PVA-PEG 9/1	3	124 ± 4	0.79 ± 0.03
	6	246 ± 5	0.34 ± 0.00
	9	332 ± 2	0.18 ± 0.00
	12	376 ± 5	0.11 ± 0.00
PVAc/ PVA-PEG 10/0	3	232 ± 6	0.39 ± 0.01
	6	669 ± 27	0.21 ± 0.02
	9	963 ± 5	0.13 ± 0.00
	12	1487 ± 61	0.08 ± 0.02

rate (0.11 %/min) in comparison with PVAc/PVA-PEG 9/1/ HPMC 10 % TEC 2010 coated product (0.09 %/min). Differences in drug release from these pellets can be related to the use of different Kollicoat® SR 30D lots and will be discussed more in detail in chapter 4.1.6.

However, an amount of 10 % triethyl citrate (based on dry polymer mass) was chosen as standard plasticizer concentration for PVAc/PVA-PEG coated Propranolol HCl pellets. A concentration of up to 10 % plasticizer is also recommended for PVAc coated pellets which are intended to be compressed to tablets [98].

4.1.5 Influence of product temperature

The product temperature is a highly important parameter for the coating process. It is related to the inlet air temperature and humidity as well as to the coating liquid spraying rate. Thus, the product temperature results from the drying capacity of the fluid bed process. The product temperature and humidity affect the fluidization pattern of the fluid bed process and in conclusion potential agglomeration of the substrate. Moreover, different product-related tackiness of the film can occur providing potential differences in the in vitro dissolution behaviour of the active substance incorporated in the pellets. In order to guarantee a good film formation the product temperature of the coating process

Table 4.4: Formulation of PVAc/PVA-PEG coated Propranolol HCl pellets comprising different amounts of plasticizer triethylcitrate

No. Formulation	HPMC sub coat [% m/m]*	PVA-PEG [% m/m]**	triethyl citrate [% m/m]**
7	10	10	10
8	10	10	5

* related on starter core mass

** related on dry polymer mass

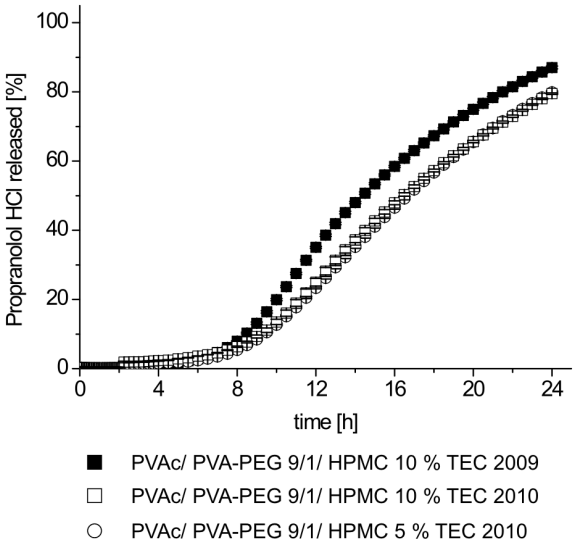


Figure 4.5: Influence of plasticizer concentration on Propranolol HCl release from PVAc/PVA-PEG 9/1 12 mg polymer/cm^2 coated pellets. The plasticizer concentration exhibited no influence on drug release from coated pellets. The polymer batch influenced the drug release rate.

should be approximately 20 °C above the minimum film formation temperature [29].

A product temperature of 30 °C was found to be suitable for the coating process with PVAc/PVA-PEG. To further investigate the influence of the product temperature during the coating process on Propranolol HCl release from PVAc/PVA-PEG coated pellets, the coating process was additionally accomplished at product temperatures of 33 °C or 36 °C respectively [Table 4.5]. Starter cores with a HPMC sub layer were coated with 12 mg polymer/cm^2 film coat. All pellets were cured in a drying oven for 24 h at 40 °C after finishing the fluid bed process.

The drug release from PVAc/PVA-PEG 9/1/ HPMC coated Propranolol HCl pellets was independent of the product temperature within the investigated range [Figure 4.6]. Higher product temperatures do not affect the drug release significantly. The lag phase of

Table 4.5: Formulation of PVAc/PVA-PEG 9/1/ HPMC coated Propranolol HCl pellets - different product temperatures

No. Formulation	HPMC sub coat [% m/m]*	PVA-PEG [% m/m]**	temperature [°C]
9	10	10	30
10	10	10	33
11	10	10	36

* related on starter core mass

** related on dry polymer mass

all three drug release profiles are very similar: 376 min (30 °C), 394 min (33 °C) and 338 min (36 °C). The release rates remain unchanged for all three batches (0.11 ± 0.01 %/min). Still, it was not so easy to operate the coating process at higher product temperatures than 33 °C as the pellets tend to agglomerate and stick together above this temperature. Even when different product temperature levels do not have a significant impact on the drug release, lower product temperatures should be selected in order to provide stable and more convenient technical processing conditions.

4.1.6 Influence of different PVAc lots

Table 4.6: Formulation of PVAc/PVA-PEG coated Propranolol HCl pellets comprising different PVAc lots

No. Formulation	HPMC sub coat [% m/m]*	PVA-PEG [% m/m]**	PVAc lot
12	10	10	A 2007
13	10	10	B 2008

* related on starter core mass

** related on dry polymer mass

Drug release profiles from pellets coated with different Kollicoat® SR 30D batches deviated from each other as illustrated in chapter 4.1.4. Thus, the influence of different material in drug release was investigated. Two more coated samples of PVAc/PVA-PEG 9/1/ HPMC coated pellets were prepared in addition to formulations 5 and 7 [Table 4.6].

The shelf life of batch A 2007 was expired for some months whereas batch A 2008 was used only 2 weeks after the shelf life ended. Both aqueous polymer dispersions were pro-

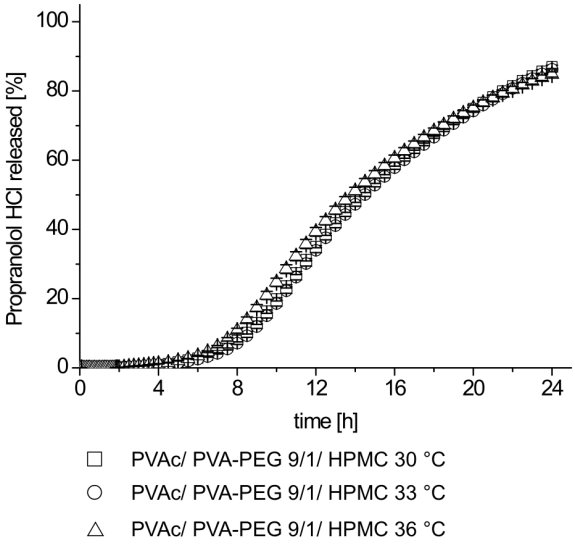


Figure 4.6: Influence of product temperature on Propranolol HCl release from PVAc/PVA-PEG 9/1 12 mg polymer/cm^2 coated pellets.

vided in 25 kg containers and not freshly opened before use. The PVAc batches A 2009 and A 2010 were originally sealed before usage for coating experiments. They were delivered shortly before usage in 1 kg sample boxes.

The dissolution profiles of formulations 5, 7, 12 and 13 are illustrated in [Figure 4.7]. As mentioned in chapter 4.1.4 a slight difference between the lag phases of pellets coated with PVAc/PVA-PEG 9/1 A 2009 or A 2010 can be noticed. Furthermore, the drug release rate of PVAc/PVA-PEG 9/1 A 2009 (0.11 %/min) is a little increased in comparison to those of PVAc/PVA-PEG 9/1 A 2010 (0.09 %/min). Still, the release pattern of both samples are not basically different. Pellets coated with PVAc/PVA-PEG 9/1 B 2008 exhibited a clearly shortened lag phase (around 5 h). The drug release from these pellets is completed after 20 h. Drug release from PVAc/PVA-PEG 9/1 A 2007 coated pellets was even faster. The lag phase prior drug release was further reduced (lag phase is around 4 h). More than 95 % Propranolol HCl were released within 9 h.

In order to explain the increased drug release a hydrolysis of poly(vinyl acetate) within the aqueous dispersion upon prolonged storage was considered. The pH of the different lots was determined. This information should provide an indication of the formation of acetic acid from hydrolyzed poly(vinyl acetate). Furthermore, ^1H NMR measurements were carried out to examine the amount of free acetate within the polymer dispersion samples. The particle size of Kollicoat® SR 30D dispersions was detected by laser diffraction. The results of the analysis are summarized in [Table 4.7]. Regrettably, no retention sample of PVAc lot A 2007 was available for further investigations.

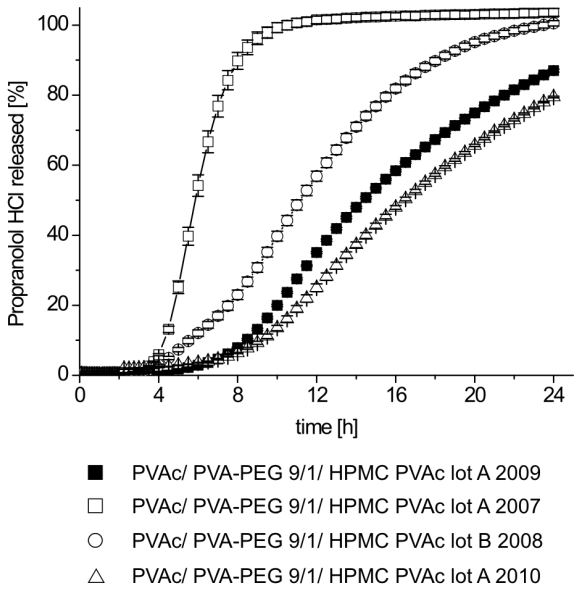


Figure 4.7: Influence of the Kollicoat® SR 30D batch on Propranolol HCl release: Propranolol HCl pellets coated with 12 mg polymer/cm^2 functional film coat and 10 % HPMC seal coat.

Table 4.7: Analysis of different PVAc lots: pH, particle size and acetate groups

PVAc lot	pH	particle size [nm]	acetate groups [%]
B 2008	4.13	121	29.1
A 2009	4.07	125	28.8
A 2010	4.03	117	29.2

The pH as well as the amount of acetate groups and the polymer droplet size of the investigated PVAc dispersions is similar. Therefore, the reason for the great deviations of the drug release from pellets coated with different PVAc dispersions is still unclear. The amount of acetic acid within the Kollicoat® SR 30D dispersion should be analyzed by means of high performance liquid chromatography (HPLC) according to the test specification of the polymer supplier BASF in the future.

Nevertheless, the study demonstrates that only new polymer dispersion lots should be used for coating purposes in order to assure reproducible drug release from controlled release systems.

4.1.7 Influence of the pH of the dissolution media

Poly(vinyl acetate) as well as poly(vinyl alcohol) poly(ethylene glycol) graft copolymer exhibit nonionic polymer structures [45, 47]. Nevertheless, different release behaviour at

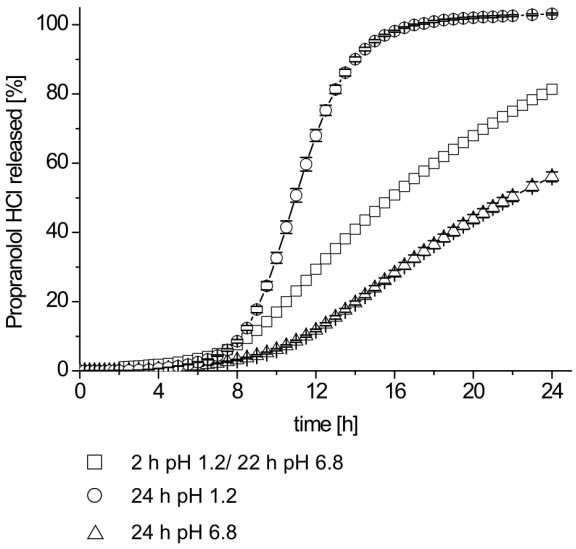


Figure 4.8: Influence of media pH on Propranolol HCl release from PVAc/PVA-PEG 9/1/ HPMC coated pellets. The drug release rate was faster in pH 1.2 (0.24 %/min) compared to drug liberation in pH 6.8 (0.05 %/min) or with media change (0.11 %/min) respectively.

different pH values was reported for PVAc coated Ambroxol HCl pellets by Dashevsky et al. [29]. A slight pH dependency of Chlorpheniramine maleate release from PVAc/PVA-PEG graft copolymer coated pellets was published in [56]. The results could not be explained by solubility differences of the drugs within the investigated media.

In a next step, the influence of the pH of the dissolution media on Propranolol HCl liberation from PVAc/PVA-PEG 9/1/ HPMC (12 mg polymer/cm^2) coated pellets was investigated. Usually, drug release studies were accomplished with a media change setup. In addition, drug release was investigated in simulated gastric fluid without enzyme (pH 1.2) as well as in phosphate citrate buffer (pH 6.8) for 24 h in each case. Propranolol HCl release from pellets coated with PVAc/PVA-PEG 9/1/ HPMC in different release media is illustrated in [Figure 4.8].

The media pH has a considerable influence on the liberation of Propranolol HCl from PVAc/PVA-PEG 9/1/ HPMC coated pellets. Regarding the three drug release profiles no clear differences between the lag phases can be distinguished. The calculated lag phase for release with media change setup is around 6 h. In pH 1.2 as well as in pH 6.8 the calculated lag phase is around 8 h. In contrast, the drug release rates for pellets coated with PVAc/PVA-PEG 9/1/ HPMC are clearly different within the investigated media [Table 4.8]. Propranolol HCl release is completed within 24 h in pH 1.2 whereas only 56 % (pH 6.8) and 87 % (media change) of the drug are liberated after 24 h.

A lag phase of around 16 h was calculated for pellets coated with PVAc/PVA-PEG

Table 4.8: Release parameters of Propranolol HCl pellets coated with PVAc/PVA-PEG in various ratios. Influence of media pH on release parameters.

Formulation	**pH**	**lag phase [min]**	**drug release rate [%/min]**
PVAc/ PVA-PEG 8/2/ HPMC	1.2	34 ± 0	3.39 ± 0.04
PVAc/ PVA-PEG 9/1/ HPMC	1.2	515 ± 6	0.24 ± 0.00
PVAc/ PVA-PEG 10/0/ HPMC	1.2	962 ± 36	0.13 ± 0.01
PVAc/ PVA-PEG 8/2/ HPMC	6.8	25 ± 2	1.20 ± 0.07
PVAc/ PVA-PEG 9/1/ HPMC	6.8	499 ± 36	0.05 ± 0.01
PVAc/ PVA-PEG 10/0/ HPMC	6.8	1575 ± 155	0.03 ± 0.01

10/0/ HPMC in pH 1.2 [Figure 4.9]. Thus, the lag phase in pH 1.2 is lower than in pH 6.8 (1575 min ± 155 min) [Figure 4.9] or with media change (1487 min ± 61 min). Propranolol HCl release is considerably faster in pH 1.2 (0.13 %/min ± 0.01 %/min) compared to pH 6.8 (0.03 %/min ± 0.01 %/min) or with media change (0.08 %/min ± 0.02 %/min). Again, these findings result in lower drug release at higher pH (60 % in pH 1.2 and 5 % in pH 6.8). The lag phase for PVAc/PVA-PEG 8/2/ HPMC coated pellets was similar within the investigated media [Table 4.8] or with media change. More than 100 % drug are released within 24 h in both investigated media even drug release is more slowly in pH 6.8 than in pH 1.2. These results could not be explained by the different solubility of Propranolol HCl in both media. The solubility was determined experimentally as described in chapter 2.2.11. According to this, the solubility of Propranolol HCl is 117 mg/ml in simulated gastric fluid pH 1.2 and 202 mg/ml in phosphate citrate buffer pH 6.8. Other results concerning the solubility of Propranolol HCl are reported by different groups [91, 99, 100, 101]. However, Propranolol HCl represents the characteristics of a weakly base with a pK_a value of 9.03 - 9.09 [102]. In theory, weakly basic drugs show pH-dependent solubility. Thus, Propranolol HCl release from PVAc/PVA-PEG coated pellets decreases with increasing pH value. At higher pH, Propranolol HCl exists in ionized state and the PVAc/PVA-PEG coating might be less permeable for the ionized drug molecules resulting in a lower release rate.

The drug release rate was minor in phosphate citrate buffer pH 6.8. The osmotic pressure of simulated gastric fluid pH 1.2 (220 mosmol/kg) and phosphate citrate buffer (370 mosmol/kg) pH 6.8 was determined. The osmotic pressure of saturated aqueous Propranolol HCl solution was found to be 307 mosmol/kg. Thus, the osmotic pressure difference was higher between pellet core and simulated gastric fluid pH 1.2 leading to increased drug delivery rates within this medium. Due to these results an osmotically

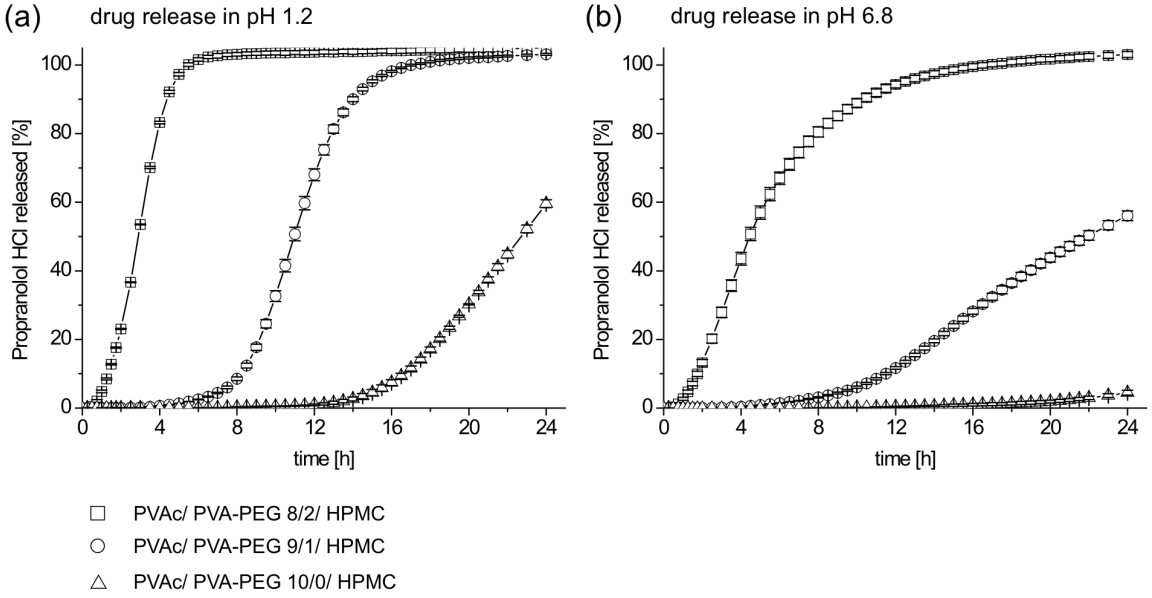


Figure 4.9: Influence of media pH on Propranolol HCl release from PVAc/PVA-PEG/ HPMC coated pellets. Drug release in pH 1.2 from pellets coated with different PVAc/PVA-PEG ratios (a). Drug liberation in pH 6.8 from from coated pellets (b). Drug release in pH 1.2 is faster compared to drug release in pH 6.8 or with media change respectively.

driven drug release was considered.

4.2 Determination of Propranolol HCl release from osmotically driven drug delivery pellets

4.2.1 Motivation and objectives

The release profiles of PVAc/PVA-PEG/ HPMC coated Propranolol HCl pellets were sigmoid shaped. The pronounced lag phase was followed by continuous drug release (delayed release). Similar sigmoid shaped release patterns were described by Narisawa et al. for pellets coated with cationic polymer Eudragit RS [103, 104, 105]. An osmotic pumping effect controlled by organic salts was reported as predominant release mechanism. Osmotic drug release was also discussed by Schultz et al. [81, 106] for pellets with sodium chloride containing cores coated with ethylcellulose. Ensslin et al. implied a combination of osmotic and diffusion controlled drug release for Chlorpheniramine maleate pellets coated with PVAc/PVA-PEG [42, 56]. The osmotic pressure within these pellets was only generated by a high concentration of the drug in solution. Similar release pattern were observed for PVAc/PVA-PEG/ HPMC coated pellets in the current thesis containing

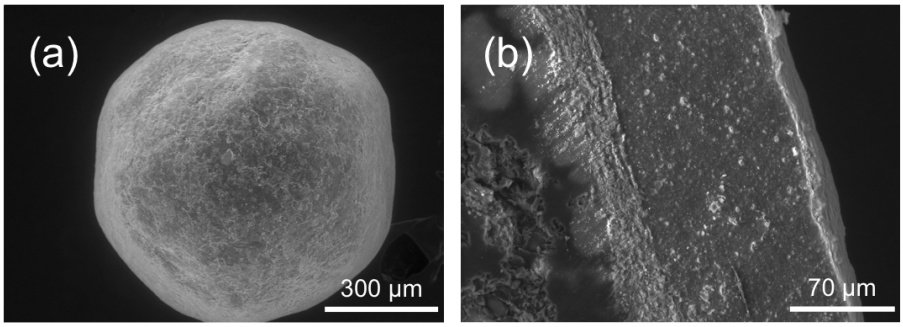


Figure 4.10: ESEM picture of the surface (a) of Propranolol HCl starter cores coated with a 15 % sodium chloride layer (related on starter cores mass). Sodium chloride is distributed evenly within the film. Figure 4.7 (b) shows the cross section of a pellet comprising a 15 % sodium chloride layer and a PVAc/PVA-PEG 9/1 film coating (12 mg polymer/cm^2).

soluble Propranolol HCl (117 mg/ml in pH 1.2 and 202 mg/ml in pH 6.8).

The addition of osmotically active ingredients to a drug delivery system coated with a semipermeable membrane results in proliferated drug release [107, 108, 109, 110]. The imbibing of aqueous fluid into the coated pellet cores is increased by the osmotically active additive. A saturated solution is generated inside the beads leading to high hydrostatic pressure within the drug delivery devices. Finally, this will entail the release of drug solution through the film coat. Ionic sodium chloride as well as non-ionic polyethylene glycol were added to the HPMC layer of Propranolol HCl starter cores to investigate the influence of an osmotic active ingredient on Propranolol HCl release from PVAc/PVA-PEG coated pellets.

4.2.2 Influence of sodium chloride

Two different concentrations of sodium chloride (7.5 % and 15 % based on the starter core mass) were incorporated in the HPMC sub coat of Propranolol HCl starter cores to increase drug release [Figure 4.10]. The pellets were coated with 12 mg polymer/cm^2 PVAc/PVA-PEG 9/1 [Table 4.9]. After finishing the fluid bed coating process the pellets were cured in a drying oven for 24 h at 40 °C.

Propranolol HCl release from pellets comprising sodium chloride was investigated and compared to drug release from pellets without sodium chloride [Figure 4.11]. As expected the lag phase prior drug release decreased due to the addition of sodium chloride. Propranolol HCl pellets containing 7.5 % sodium chloride exhibited a lag phase of 260 min whereas the lag time of pellets with 15 % sodium chloride was 126 min. Pellets without osmotically active agent showed a longer lag phase of 376 min Table 4.10].

During the lag phase water influx into the drug delivery system is induced by the

Table 4.9: Formulation of PVAc/PVA-PEG coated Propranolol HCl pellets comprising sodium chloride

No. Formulation	**sodium chloride [% m/m]***	**PVA-PEG [% m/m]****
14	7.5	10
15	15	10

* related on starter core mass

** related on dry polymer mass

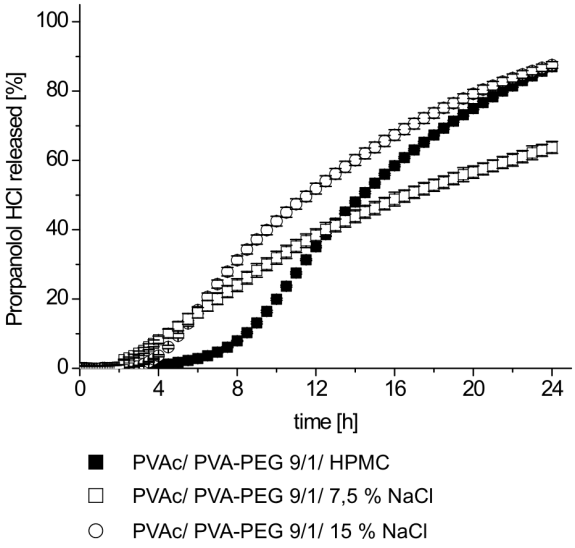


Figure 4.11: Influence of sodium chloride concentration in the sub coat on Propranolol HCl release from PVAc/PVA-PEG 9/1 coated pellets (12 mg polymer/cm^2). The addition of sodium chloride to the sub coat leads to reduced lag times and decreased drug release rates.

difference in osmotic pressure [61, 96]. Solubilization of drug starts inside the pellets creating a hydrostatic pressure inside the pellets. Simultaneously, soluble parts of the film coat are dissolved. Reduced tensile strength caused by an increased permeability of the PVAc/PVA-PEG coat finally initiates Propranolol HCl release from the pellets. The osmotic pressure is a colligative property. Colligative properties only depend on the number of solute particles in a given volume but not on their nature. The osmotic pressure of a dilute solution can be approximated according to following equation:

$$\pi = i \cdot m \cdot R \cdot T \tag{4.1}$$

where i is the dimensionless van′ t Hoff factor (number of osmotic active molecules), m

stands for molality, R represents the gas constant and T is the absolute temperature. Higher concentrations of soluble ingredients within the pellets cause proliferated water influx into the system resulting in fast solubilization of Propranolol HCl and sodium chloride. Thus, drug release is initiated earlier for pellets containing 15 % sodium chloride in contrast to pellets with 7.5 % sodium chloride or without osmotically active ingredient.

Higher drug release rates were anticipated for pellets including sodium chloride. PVAc/PVA-PEG 9/1/ HPMC coated Propranolol HCl pellets without osmotically active ingredient exhibit a drug release rate of 0.11 %/min. Surprisingly, drug release rates of 0.04 %/min (7.5 % sodium chloride) and 0.09 %/min (15 % sodium chloride) are obtained. The release profile of pellets comprising of 7.5 % sodium chloride is not sigmoid shaped but exhibits a zero-order like release pattern. Both, the osmotic pressure inside the pellets as well as the osmotic pressure gradient are important for drug dissolution [49]. The osmotic pressure within pellets with lower sodium chloride levels is minor thus leading to lower pressure gradients and therefore slower drug release rates. Curiously, Propranolol HCl release from pellets without osmotically active ingredient was still accelerated compared to pellets containing sodium chloride.

Table 4.10: Release parameters of Propranolol HCl pellets coated with PVAc/PVA-PEG 9/1. Influence of sodium chloride on Propranolol HCl release.

Formulation	**lag phase [min]**	**drug release rate [%/min]**
PVAc/ PVA-PEG 9/1/ HPMC	376 ± 5	0.11 ± 0.00
PVAc/ PVA-PEG 9/1/ 7.5 % NaCl	260 ± 12	0.04 ± 0.00
PVAc/ PVA-PEG 9/1/ 15 % NaCl	126 ± 3	0.09 ± 0.00

A reason for this finding might be an interaction of water with the sodium chloride containing sub coat layer. Imbibing water dissolves sodium chloride within the sub coat layer before it penetrates into the drug containing pellet core. Additionally, a high sensitivity of hydrochloride salts to the common ion effect of chloride ions was reported by Miyazaki et al. [111, 112]. Thomas et al. found relatively large salting-out tendencies for Propranolol HCl in sodium chloride solutions with a range of 0 to 0.512 mol/l [113]. These effects might also cause a decreased drug release from PVAc/PVA-PEG.

4.2.3 Influence of polyethylene glycol

Two different types of Polyethylene glycol (PEG 1500 and PEG 6000) were integrated in the HPMC sub coat of Propranolol HCl starter cores as non-ionic osmotically active

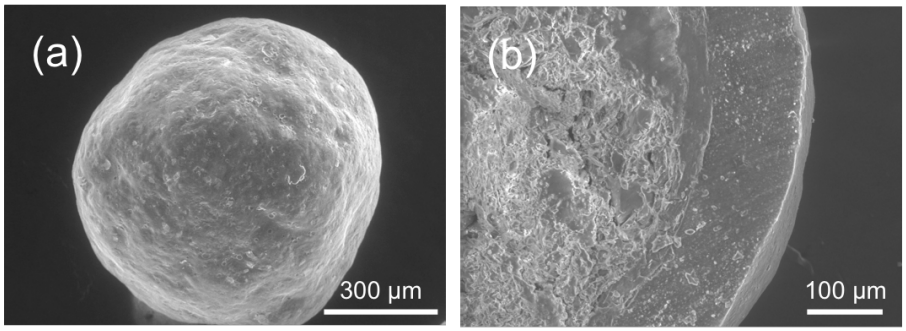


Figure 4.12: ESEM picture of the surface (a) of Propranolol HCl starter cores coated with a sub coat layer containing 15 % PEG 6000 (related on starter cores mass). PEG 6000 is distributed evenly within the film but some talc particles can be seen. Figure 4.8 (b) shows the cross section of a pellet comprising a 15 % PEG 6000 layer and a PVAc/PVA-PEG 9/1 film coating (12 mg polymer/cm^2).

ingredients [Figure 4.12]. The pellets were coated with 12 mg polymer/cm^2 PVAc/PVA-PEG 9/1 subsequently [Table 4.11]. After finishing the fluid bed coating process the pellets were cured in a drying oven for 24 h at 40 °C.

Table 4.11: Formulation of PVAc/PVA-PEG coated Propranolol HCl pellets containing polyethylene glycol

No. Formulation	**PEG 1500** [% m/m]*	**PEG 6000** [% m/m]*	**PVA-PEG** [% m/m]**
16	15	-	10
17	-	15	10

* related on starter core mass

** related on dry polymer mass

Propranolol HCl release from pellets including PEG types was examined and compared to drug liberation from pellets without osmotically active ingredient [Figure 4.13]. The lag phase before drug release starts is decreased by the addition of polyethylene glycol. A lag phase of 165 min is found for pellets including PEG 1500 and a lag phase of 233 min is calculated for pellets containing PEG 6000. Thus, the addition of PEG 1500 results in a more pronounced decrease of the lag phase than the addition of PEG 6000.

As mentioned before, the osmotic pressure only depends on the number of solute molecules independently of their nature. In both cases 15 % PEG was used. Due to its lower molecular weight PEG 1500 exhibits a higher molar concentration within the solution compared to PEG 6000. This leads to a higher osmotic pressure inside the pellets [114] resulting in a decreased lag phase. Furthermore, the drug release profiles of pellets

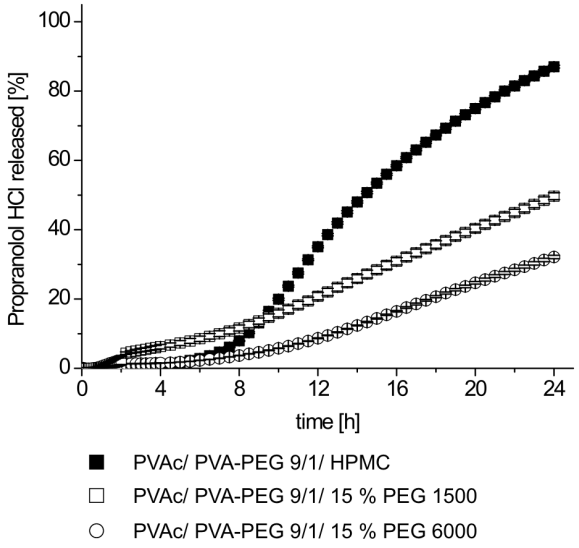


Figure 4.13: Influence of PEG 1500 and PEG 6000 in the sub coat on Propranolol HCl release from PVAc/PVA-PEG 9/1 coated pellets (12 mg polymer/cm^2). The addition of PEG to the sub coat resulted in modified drug release profiles. The lag times prior drug release increased and the drug release rates decreased.

containing polyethylene glycol considerably changed compared to the release pattern of pellets without osmotically active ingredient. Double-staged release profiles comprising a lag time followed by a zero-order like drug liberation are obtained. The drug release rate of pellets comprising PEG 1500 or PEG 6000 respectively decreases compared to pellets without osmotically active agent [Table 4.12]. Possibly the imbibing water is absorbed by the hygroscopic polyethylene glycol chains. Thus, it is not available for the solubilization of drug. As a consequence, the dissolution of Propranolol HCl is prolonged resulting in decreased drug release rates. Furthermore, the presence of PEG 1500 or PEG 6000 leads to an increased viscosity [115, 116] within the HPMC diffusion layer resulting in decreased Propranolol HCl release rates.

Table 4.12: Release parameters of Propranolol HCl pellets coated with PVAc/PVA-PEG 9/1. Influence of PEG on drug release.

Formulation	**lag phase [min]**	**drug release rate [%/min]**
PVAc/ PVA-PEG 9/1/ HPMC	376 ± 5	0.11 ± 0.00
PVAc/ PVA-PEG 9/1/ PEG 1500	165 ± 98	0.03 ± 0.00
PVAc/ PVA-PEG 9/1/ PEG 6000	233 ± 30	0.03 ± 0.00

4.2.4 Influence of the pH of the dissolution media

The influence of the pH of the dissolution media on Propranolol HCl release from PVAc/PVA-PEG coated pellets is described earlier. The present section discusses the influence of the pH of the dissolution media on drug release from PVAc/PVA-PEG 9/1 coated pellets comprising osmotically active ingredients. Propranolol HCl release was studied in simulated gastric fluid pH 1.2 and phosphate citrate buffer pH 6.8 for 24 h in each case. A summary of the calculated release parameters is given in [Table 4.13].

Table 4.13: Release parameters of Propranolol HCl pellets coated with PVAc/PVA-PEG 9/1 comprising osmotically active additives. Influence of media pH on release parameters.

Formulation	**pH**	**lag phase [min]**	**drug release rate [%/min]**
PVAc/ PVA-PEG 91/ 7.5 % NaCl	1.2	190 ± 5	0.17 ± 0.00
PVAc/ PVA-PEG 9/1/ 15 % NaCl	1.2	470 ± 7	0.28 ± 0.00
PVAc/ PVA-PEG 9/1/ 15 % PEG 1500	1.2	369 ± 12	0.14 ± 0.00
PVAc/ PVA-PEG 9/1/ 15 % PEG 6000	1.2	636 ± 24	0.14 ± 0.00
PVAc/ PVA-PEG 91/ 7.5 % NaCl	6.8	435 ± 12	0.03 ± 0.00
PVAc/ PVA-PEG 9/1/ 15 % NaCl	6.8	334 ± 10	0.03 ± 0.00
PVAc/ PVA-PEG 9/1/ 15 % PEG 1500	6.8	682 ± 30	0.02 ± 0.00
PVAc/ PVA-PEG 9/1/ 15 % PEG 6000	6.8	426 ± 60	0.01 ± 0.00

The lag phase before drug release starts is decreased by the addition of sodium chloride compared to pellets without osmotically active ingredient in all investigated dissolution media. In contrast, the introduction of polyethylene glycol results in slightly decreased lag phases or similar lag phases compared to those of pellets without osmotically active agent. Interestingly, pellets comprising osmotically active agent exhibit a different release pattern in simulated gastric fluid pH 1.2 or phosphate citrate buffer pH 6.8 respectively [Figure 4.14].

Sigmoid release profiles are derived in simulated gastric fluid pH 1.2 for all pellets coated with PVAc/PVA-PEG 9/1. The release profiles for sodium chloride containing PVAc/PVA-PEG coated pellets in pH 6.8 display a lag phase followed by a slow and constant drug release. For Propranolol HCl pellets with polyethylene glycol sub layer the release pattern basically changed within pH 6.8. A zero-order like drug release is acquired. Thus, the release of Propranolol HCl from PVAc/PVA-PEG 9/1 coated pellets including osmotically active agent was not only decreased within pH 6.8 compared to pH 1.2 but resulted in different drug release pattern independently from the type of osmotically active

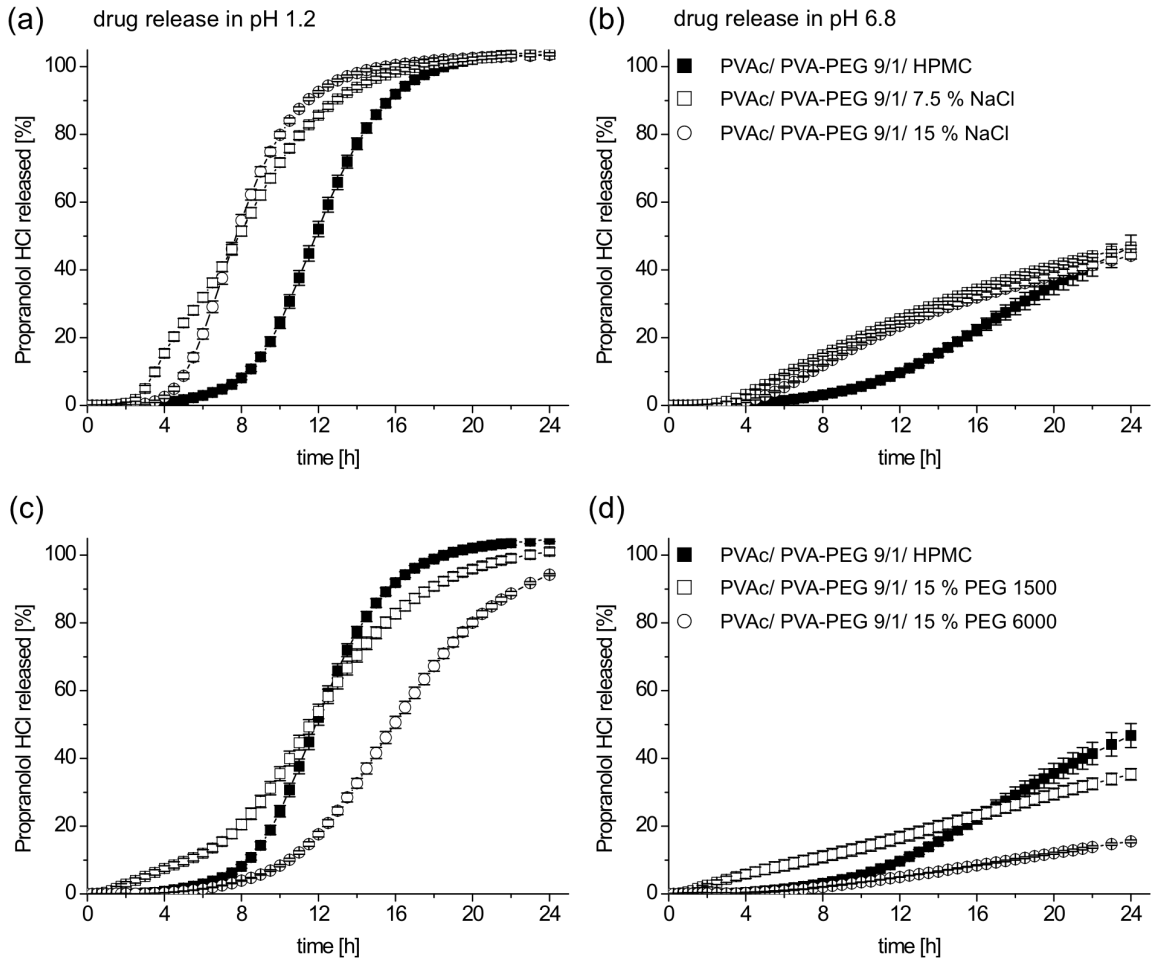


Figure 4.14: Influence of the pH of the dissolution media on Propranolol HCl release from PVAc/PVA-PEG coated pellets containing osmotically active ingredients. The dissolution profiles in simulated gastric fluid pH 1.2 exhibit a sigmoid release pattern (a,c). In contrast, the release pattern change to a zero-order like release profile in phosphate citrate buffer pH 6.8 (b,d).

compound. These results indicate that Propranolol HCl release from PVAc/PVA-PEG coated pellets is dominated by the release characteristics in phosphate citrate buffer as drug release starts after a lag phase of more than 2 hours. The decreased drug release rate within pH 6.8 compared to simulated gastric fluid pH 1.2 can be explained by a minor permeability of the PVAc/PVA-PEG film coat for the ionized state of Propranolol HCl.

4.2.5 Influence of the osmolality of the dissolution media

To verify the hypothesis of an osmotically driven drug release, dissolution studies from different PVAc/PVA-PEG coated pellets were carried out in media with different osmotic pressure. In case of osmotically driven drug release decreased drug liberation is expected

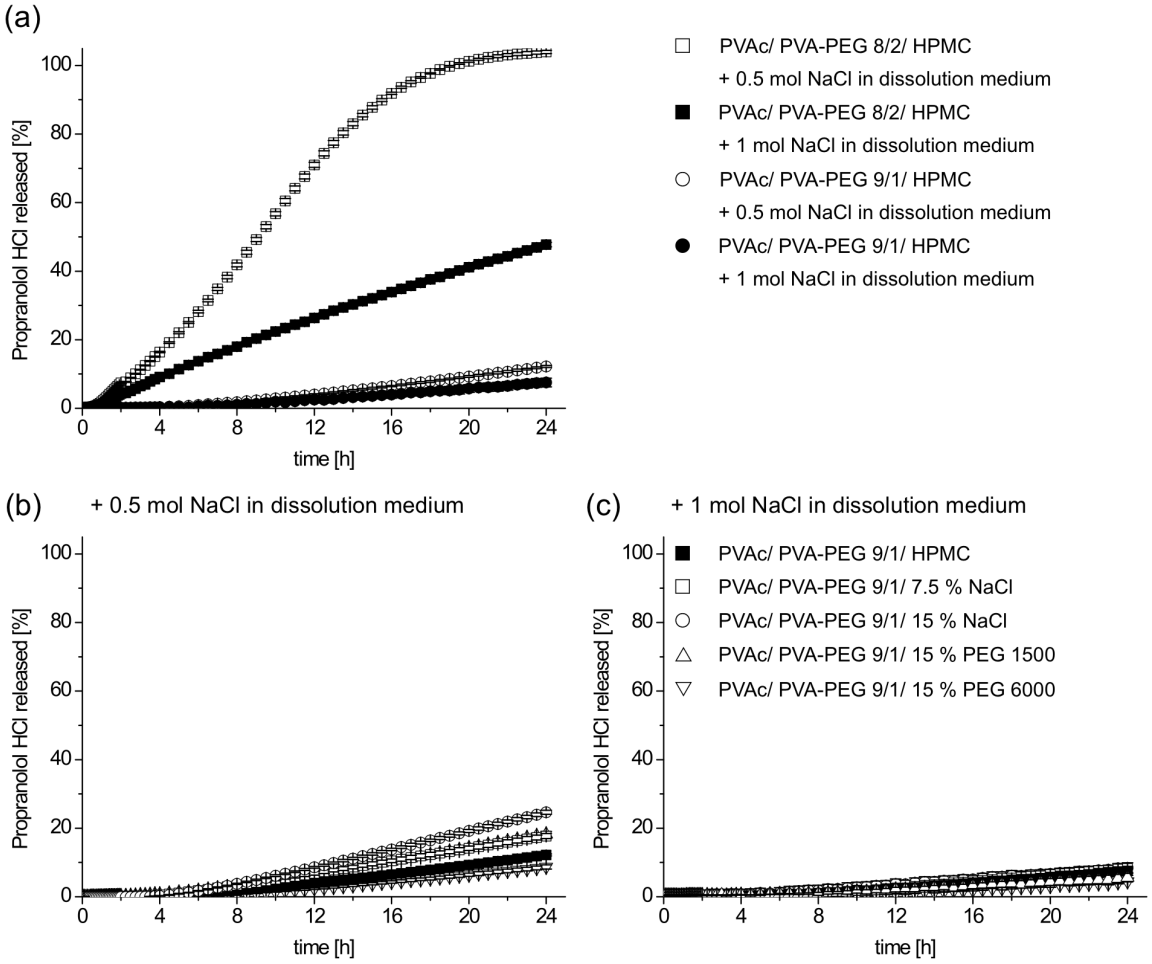


Figure 4.15: Influence of osmolality of the dissolution media on drug release. The drug release pattern changes from a sigmoid release profile to a linear release pattern upon increasing the osmolality of dissolution media. The effect was more distinctive for pellets coated with PVAc/PVA-PEG 8/2/ HPMC than for PVAc/PVA-PEG 9/1/ HPMC coated ones (a).

due to the reduced osmotic pressure difference between pellets and medium [71, 117, 118]. The lowering of the osmotic pressure difference can be achieved by adding osmotically active agents to the dissolution medium. Thus, 0.5 mol or 1 mol sodium chloride were added to simulated gastric fluid pH 1.2 and phosphate citrate buffer pH 6.8 for the following dissolution experiments.

First of all, Propranolol HCl release from Propranolol HCl pellets coated with PVAc/PVA-PEG/ HPMC 8/2 and PVAc/PVA-PEG/ HPMC 9/1 was studied [Figure 4.15 (a)]. Drug release from coated pellets decreased significantly with increasing osmolality of the dissolution medium. PVAc/PVA-PEG/ HPMC 8/2 coated pellets exhibit a short lag time followed by a constant drug liberation in medium with 0.5 mol sodium chloride. A further increase in sodium chloride content results in linear drug release from

the pellets. Only 48 % Propranolol HCl are liberated within 24 h. The drug release from PVAc/PVA-PEG/ HPMC 9/1 coated pellets is manifested in a zero-order like release pattern with 0.5 or 1 mol sodium chloride respectively. The drug release after 24 h was only 12 % (0.5 mol sodium chloride) or 6 % (1 mol sodium chloride). Thus, the increase of osmolality of the dissolution medium effects a tremendous decrease of drug release from PVAc/PVA-PEG coated Propranolol HCl pellets. Furthermore, the resulting drug release profiles display a zero-order release instead of a sigmoid release pattern.

In a next step, drug liberation from pellets comprising sodium chloride or polyethylene glycol was investigated [Figure 4.15 (b), (c)]. All release profiles show a zero-order like release. Within medium with 0.5 mol sodium chloride the drug release of pellets containing 15 % sodium chloride was faster than of those containing 7.5 % sodium chloride or polyethylene glycol respectively. When 1 mol sodium chloride was added to the dissolution medium all release profiles overlapped.

The results of these dissolution studies agree with the hypothesis of osmotically driven drug release. With increasing osmotic pressure of the dissolution medium the in vitro drug release rates decreased significantly. These findings emphasize that drug release from PVAc/PVA-PEG coated pellets was strongly driven by osmotic effects nevertheless if they comprise of osmotically active ingredient or not.

4.3 Stability of PVAc/PVA-PEG coated pellets

4.3.1 Motivation and objectives

Using aqueous colloidal polymer dispersion the film formation mechanism is a complex process [119, 120, 121]. Polymer particles deform due to capillary pressure effect upon water evaporation. Particle deformation is followed by coalescence of the polymer particles to form a continuous film. In practice, it is often difficult to assure complete film formation during the coating process. Therefore, a thermal time triggered post-treatment (curing step) at temperatures above the glass transition temperature directly after the coating step is recommended in order to complete polymer particle coalescence [24, 122]. The curing step may have an impact on drug release when compared to uncured dosage forms.

Various studies have been reported in the literature focusing on the importance of the curing step for the resulting drug release rate and storage stability [69, 94, 95]. The influence of curing conditions on Kollicoat® SR 30D (PVAc) coated pellets was investigated earlier [29, 123, 124]. Dashevsky et al. observed no significant influence of curing time and temperature on Propranolol HCl release from Kollicoat® SR 30D coated pellets. Though, the thermal post-treatment of Kollicoat® SR 30D coated Ibuprofen pellets led to increased

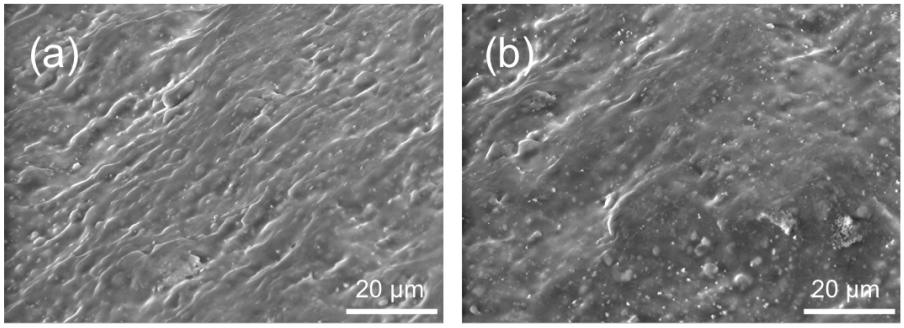


Figure 4.16: ESEM pictures of the surface of PVAc/PVA-PEG 9/1 coated pellets. Uncured pellet surface (a). Coating surface after 24 h curing at 40 °C (b).

drug release that was probably caused by the high affinity of the drug to the polymer film. Shao et al. studied the release of Diphenhydramine HCl from Kollicoat® SR 30D coated pellets. The influence of curing temperature on drug release was examined. The authors noticed that an increase in curing temperature resulted in decreased dissolution.

In addition, instability during long term storage is still one of the major challenges concerning controlled release dosage forms coated with aqueous polymer dispersions. Sometimes, the film formation is not completed even after the curing process. Further particle coalescence might occur during long term storage resulting in denser polymer film structures. Thus, the permeability of the film coatings is decreased leading to reduced permeabilities for water and drug solution. As a consequence, drug release rates decrease in particular under accelerated storage conditions [125, 126, 127].

The effect of curing conditions on PVAc/PVA-PEG polymer blends was not investigated before. Thus, the influence of curing time and temperature on PVAc/PVA-PEG coated Propranolol HCl pellets was analyzed within this thesis. Furthermore, a main interest of the study was to monitor drug release profiles from these pellets after 12 months storage compared to drug release before storage.

4.3.2 Influence of curing time and curing temperature on drug release

To examine the influence of curing time and curing temperature on drug liberation formulations 4, 5 and 6 were analyzed. All pellets were dried for 10 min at 45 °C in the fluid bed equipment after the coating process. Subsequently, the coated beads were dried at room temperature (uncured) or oven-cured directly after the coating step using dry heat (40 °C or 60 °C). The curing with dry heat was performed for time periods of 12 or 24 hours respectively. The surfaces of uncured (a) or cured (24 h at 40 °C (b)) coated pellets are shown in [Figure 4.16]. Both samples demonstrate a dense coating layer. The surface

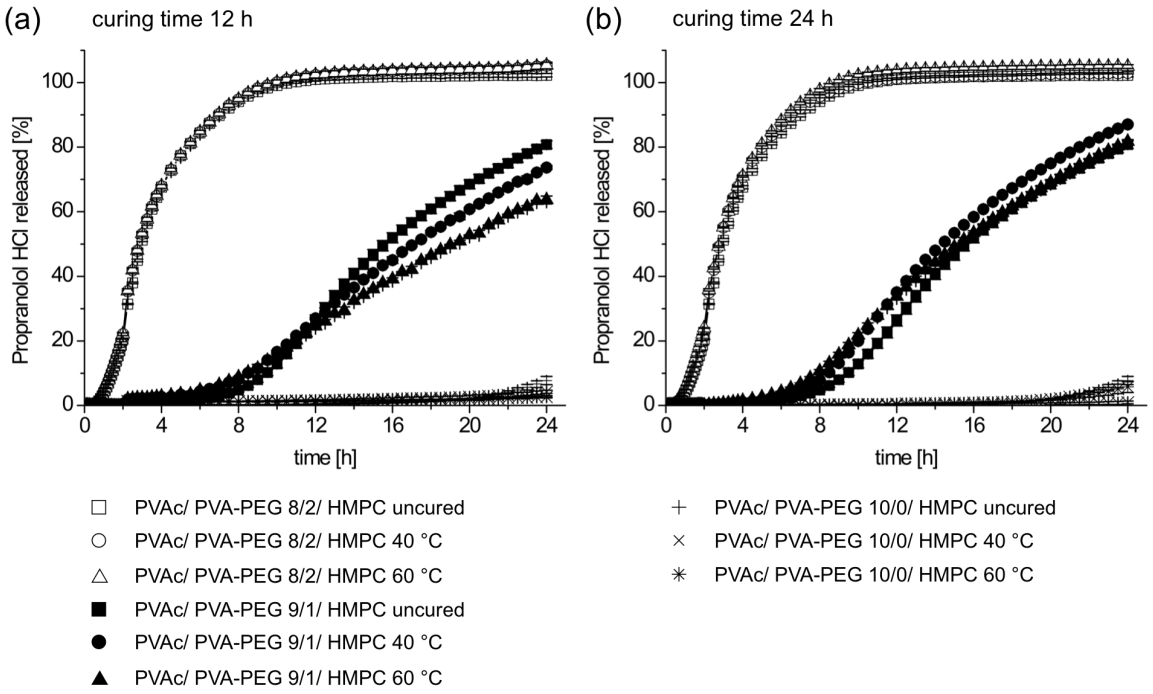


Figure 4.17: Influence of curing time and curing temperature on Propranolol HCl release from PVAc/PVA-PEG coated pellets comprising a 10 % HPMC sub coat. The investigated pellets were coated with 12 mg polymer/cm^2.

of the uncured pellet appears slightly rougher than those of the cured one. Though, only few sections of the pellets surface can be displayed and the difference is marginal.

[Figure 4.17] displays the effect of curing time and curing temperature on drug release from PVAc/PVA-PEG/ HPMC coated pellets. Thus, drug release from these pellets is independent of curing within the investigated conditions. Minor deviations between different release profiles of PVAc/PVA-PEG 9/1/ HPMC coated pellets can be observed.

Significant influences of curing conditions on drug release are often noticed for polymer films with higher glass transition temperature (T_g) [95, 128]. Very low glass transition temperatures were determined for PVAc/PVA-PEG polymer blends (Chapter 3) via differential scanning calorimetry. Due to the low glass transition temperature of the polymer film sufficient mobility of the polymer chains for polymer particle coalescence during the coating process can be expected. This would explain why a curing step is not necessarily required for such formulations.

4.3.3 Influence of anti-tacking agent addition

Particle agglomeration was noted during thermal post-treatment of PVAc/PVA-PEG coated Propranolol HCl pellets. The stickiness of PVAc/PVA-PEG coated pellets in-

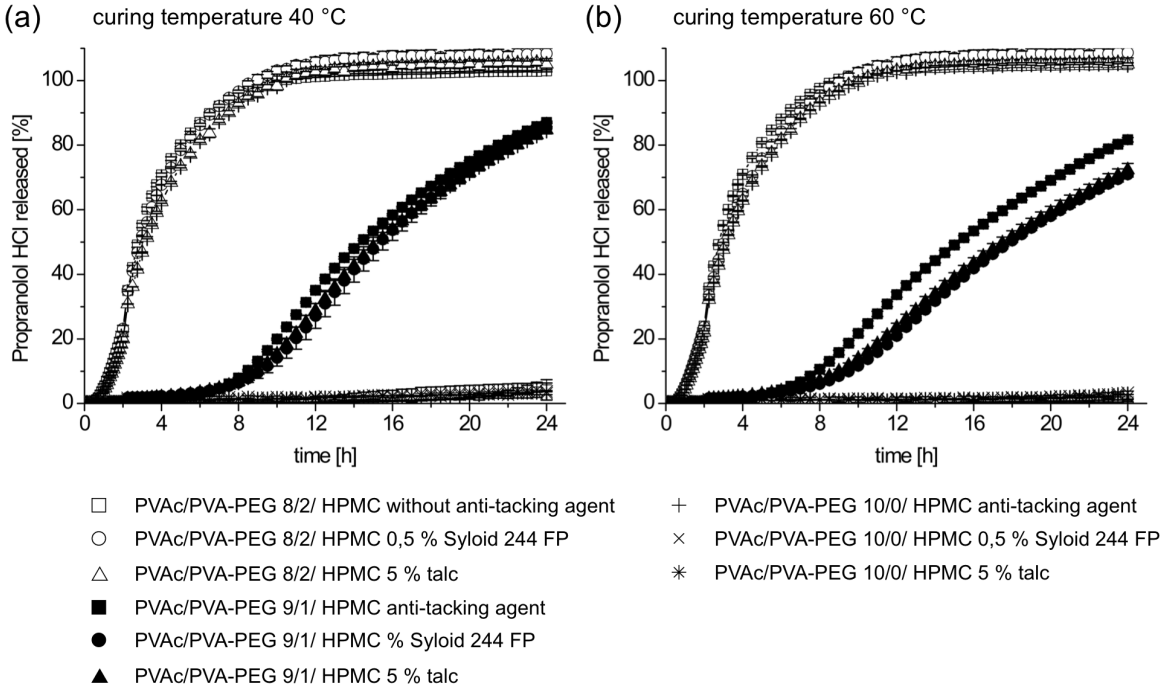


Figure 4.18: Influence of the addition of anti-tacking agents on PVAc/PVA-PEG/ HPMC coated pellets during thermal post-treatment. The pellets were coated with 12 mg polymer/cm^2. The curing was accomplished for 24 h in an oven using dry heat.

creased with decreasing PVA-PEG content. Contrary, the glass transition temperatures increased with decreasing PVA-PEG content. Even though, the appearance of pellet agglomeration was related to the low glass transition temperatures of the polymer blends. Intense agitation was necessary to separate sticking pellets especially at higher curing temperature (60 °C). Thus, the intactness of the polymer film cannot be assured for these products when pellets sticking to each other intermediately are separated from each other by such intense agitation.

The high flexibility of PVAc film coatings especially when plasticized with a suitable plasticizer is well known [29, 129]. Ensslin et al. [44] studied the robustness of PVAc/ PVA-PEG film coatings to mechanical forces by treating coated pellets with a needle or razor blade. The release profiles from pellets after needle treatment were similar to undamaged pellets whereas the razor blade cuts resulted in different release profiles. A swelling based self-repair mechanism was discussed which prevented burst release even after mechanical damage. A similar self-repair mechanism was also reported by Meyer et al. [55] for PVAc/PVA-PEG coated tablets.

Even though, no burst release was observed after mechanical damage, the release profile of PVAc/PVA-PEG changed considerably [44, 56]. Therefore, 0.5 % Syloid® 244 FP or

5 % talc (based on pellets mass) were added to the coated pellets prior to curing within this study. The influence of anti-tacking agent addition on drug release is demonstrated in [Figure 4.18].

Obviously, the addition of anti-tacking agent has no influence on Propranolol HCl liberation from PVAc/PVA-PEG coated pellets. Still, the admixing of anti-tacking agent to the coated pellets has a beneficial effect as it prevents particle agglomeration during curing process as well as during storage.

4.3.4 Storage stability of coated pellets

Four samples of PVAc/PVA-PEG coated pellets [Table 4.14] were stored at 25 °C/60 % relative humidity (rH), 30 °C/65 % rH and 40 °C/75 % rH according to ICH guidelines. Amounts of 1.5 g coated pellets were stored in sealed glass vials for 12 months in climate chambers. The coated pellets were removed from the climate chambers for dissolution analysis after 1.5 months, 3 months, 6 months, 9 months and after complete storage of 12 months.

Table 4.14: PVAc/PVA-PEG coated pellets for storage stability analysis (0 - 12 months)

Sample	Formulation	Curing	anti-tacking agent
A	PVAc/ PVA-PEG 9/1/ HPMC	24 h 40 °C	-
B	PVAc/ PVA-PEG 9/1/ HPMC	24 h 40 °C	0.5 % Syloid® 244 FP
C	PVAc/ PVA-PEG 9/1	24 h 40 °C	0.5 % Syloid® 244 FP
D	PVAc/ PVA-PEG 9/1/ HPMC	-	-

After storage the pellets were investigated visually implementing light microscopy. At 25 °C the coated pellets appeared unaltered. The pellet colour changed from white to slightly yellow after 12 months at 30 °C and after 6 months at 40 °C. The colour change started after 3 months at 40 °C and was intensified with storage time. Additionally, sticking of the pellets which were stored without anti-tacking agent was observed after storage at 40 °C/75 % rH. Gentle agitation was sufficient to separate pellets from each other after 1.5 and 3 months storage. At later times, a more intense treatment was necessary to separate the pellets. Interestingly, pellets which were not cured before storage (sample D) tend to stick even more than cured pellets. Increased stickiness of these pellets was noticed even at 25 °C and 30 °C after 3 months and after 1.5 months at 40 °C. Sticking of the pellets might be due to storage conditions above the glass transition temperature T_g. PVAc/PVA-PEG 9/1 comprising 10 % plasticizer triethyl citrate exhibit a T_g of 16.8 °C. Although all pellets were stored at temperatures above the glass transition temperature sticking of

pellets occurred in particular at elevated temperature and relative humidity. This is a well-known phenomenon and storage of PVAc based coated dosage forms at temperatures above 30 °C and at a higher relative humidity than 70 % is not recommended by the polymer supplier BASF [130].

Pellets coated with PVAc/PVA-PEG 9/1/ HPMC showed a lag phase of 6 to 7 hours. The lag time of pellets without a seal coat was around 4 hours. Approximately 85 % Propranolol HCl were released from these pellets after 24 h.

After 12 months storage at long term conditions (25 °C/60 % rH) the release profiles for sample A were very similar with those before storage [Figure 4.19 (a)]. The sigmoid release pattern remained unchanged and the lag phases stayed nearly constant. The drug release rate from sample A was decreased with storage time resulting in reduced Propranolol HCl release within 24 h. Before storage around 87 % Propranolol HCl were released from sample A within 24 h. After 3 months storage at long term conditions only 76 % drug were released from those pellets. Only 69 % Propranolol HCl were liberated from the pellets after complete storage of 12 months.

Drug release profiles of sample A after storage at intermediate conditions (30 °C/65 % rH) were similar to release patterns after storage at long term conditions (25 °C/60 % rH) [Figure 4.19 (a)]. The lag phase prior drug release remained constant. The drug release decreased to 71 % within 24 h instead of 87 % after 3 months. After 12 months only 64 % Propranolol HCl were released within 24 h. Thus, even less drug was released than at long term storage conditions after one year.

Storage at accelerated conditions (40 °C/75 % rH) resulted in altered release profiles for sample A [Figure 4.19 (a)]. The lag phase before drug release started slightly decreased with increasing storage time. The drug release rates of sample A decreased involving a more linear release pattern. After 3 months only 67 % Propranolol HCl were released. With proceeding storage time drug liberation increased up to 75 % within 24 h.

Similar results were obtained for sample B. The release pattern did not change after 12 months storage at long term conditions (25 °C/60 % rH) and the lag phases stayed nearly constant [Figure 4.19 (b)]. The drug release rate from sample B was decreased with storage time leading to reduced Propranolol HCl liberation within 24 h. After 6 months storage only 75 % drug were released from sample B compared to 87 % before storage. At the end of the stability study 69 % drug were liberated.

Drug release profiles of sample B at intermediate conditions (30 °C/65 % rH) were similar to release patterns after storage at long term conditions (25 °C/60 % rH) [Figure 4.19 (b)]. The lag phase of sample B at intermediate conditions remained constant for 9 months. After 12 months storage the lag phase prior drug release clearly decreased. Propranolol HCl release from sample B is considerably decreased (73 % within 24 h) after

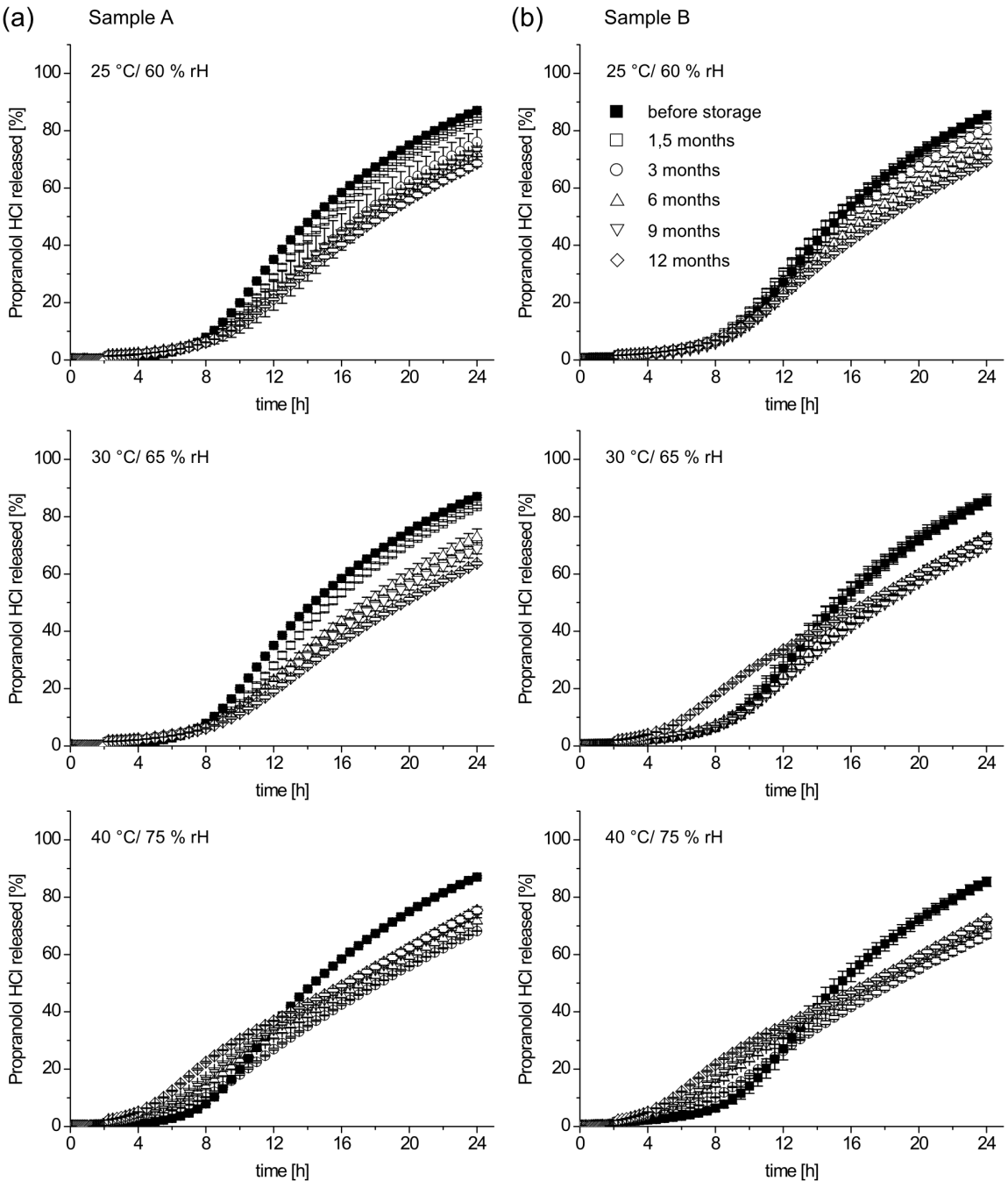


Figure 4.19: Drug release profiles of PVAc/PVA-PEG 9/1/ HPMC coated pellets cured for 24 h at 40 °C without antitacking agent (a) and with 0.5 % Syloid® 244 FP (b) before and after storage.

only 3 months storage at 30 °C but then remained unchanged until the stability study was finished.

Altered release profiles were obtained for sample B after storage at accelerated conditions (40 °C/75 % rH) [Figure 4.19 (b)]. The lag phase prior drug release slightly decreased with increasing storage time. At the same time the drug release rate of sample B decreased, attended by a more linear release pattern. After 3 months only 68 % Propranolol HCl were released. With proceeding storage time drug release increased up to 72 % within 24 h.

The drug release profiles of uncured sample D after 12 months storage at long term conditions (25 °C/60 % rH) were very similar with those before storage [Figure 4.20 (d)]. The sigmoid release pattern stayed unchanged but the lag phase of sample D slightly decreased after 1.5 months storage. Interestingly, the released drug amount increased from 81 % to 91 % within 24 h after 1.5 months. At later times the amount of liberated drug decreased and was around 77 % after 12 months. Thus, similar amounts of Propranolol HCl were released from uncured sample D after the complete study compared to the beginning.

The drug release profiles as well as drug release from sample D after storage at intermediate conditions were similar to drug liberation at long term conditions within the investigated time [Figure 4.20 (d)]. Drug release increased after 1.5 months and decreased at later times. Though, the lag phase prior drug release decreased further after 12 months storage at 30 °C/65 % rH.

The drug release from uncured sample D changed dramatically at accelerated conditions (40 °C/75 % rH) [Figure 4.20 (d)]. The lag time prior drug release is initiated decreased from around 7 hours before storage to around 4 hours after 3 months storage at 40 °C/75 % rH. The lag phase was further reduced to around 3 hours after 6 months. After the lag phase drug liberation followed a zero-order like release pattern. The drug release rate was slightly reduced after only 1.5 months storage and remained constant until the stability study was finished. Interestingly, the drug release from uncured sample D increased with storage time. Only 81 % Propranolol HCl were released from those pellets before storage. After 1.5 months storage at accelerated storage conditions 99 % Propranolol HCl were released within 24 h. Later (3 to 12 months), around 95 % drug were liberated from the coated material within 24 h.

The release pattern of sample C (coated without HPMC sub layer) remained sigmoid after 12 months storage at long term conditions (25 °C/60 % rH) [Figure 4.20 (c)]. Still, the lag phase prior drug release considerably decreased even after 1.5 months. The drug release rate of sample C increased after 1.5 months and decreased again after 3 months. Before storage, around 84 % Propranolol HCl were liberated within 24 h. After 1.5 months storage the drug release increased to 105 % within 24 h. Later, Propranolol HCl release

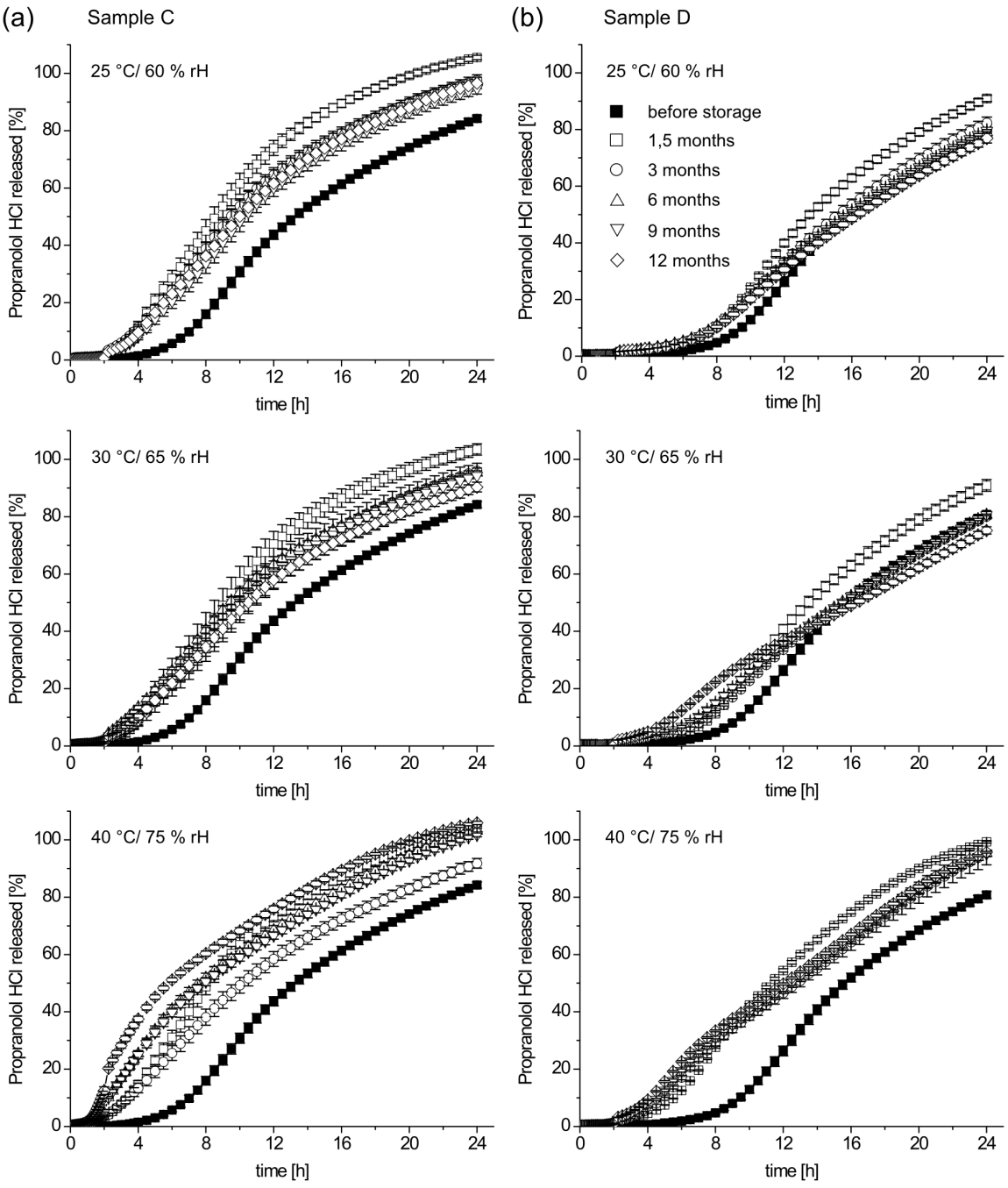


Figure 4.20: Drug release profiles of PVAc/PVA-PEG 9/1 coated pellets cured for 24 h at 40 °C with 0.5 % Syloid® 244 FP (c) and uncured PVAc/PVA-PEG/ HPMC 9/1 coated pellets before and after storage.

decreased again and remained constant at around 97 % within 24 h (3 to 12 months).

Drug release from sample C after storage at intermediate conditions (30 °C/65 % rH) was similar to drug liberation after storage at long term conditions [Figure 4.20 (c)]. The lag phase before Propranolol HCl release started to decrease after 1.5 months and remained nearly constant during the stability study. The drug release increased after 1.5 months (103 % within 24 h) and decreased again after 3 months (96 % within 24 h). After complete storage of 12 months, the drug release was further reduced to 90 % within 24 h.

An extended Propranolol HCl release from PVAc/PVA-PEG 9/1 coated pellets (sample C) after storage was observed at long term (25 °C/60 % rH) and intermediate conditions (30 °C/65 % rH). Comparable results were found for sample C after storage at accelerated conditions (40 °C/75 % rH) [Figure 4.20 (c)]. The lag phase prior drug liberation started decreased from around 4 h before storage to around 2 h after 1.5 months and was further reduced to around 1 h with storage time. Drug release accumulated from 84 % to 104 % within 24 h after 1.5 months. After 3 months only 92 % Propranolol HCl were liberated within 24 h. At later times (6 to 12 month) drug release rose again to 104 % within 24 h.

Propranolol HCl pellets coated with PVAc/PVA-PEG 9/1 comprising a HPMC sub coat (samples A, B and D) demonstrated a decreased drug release after 12 months storage at long term and intermediate storage conditions. A curing step prior storage (sample A and B) led to slightly better results for drug release after storage. The drug liberation from those pellets was reduced after storage but did not cause decreasing lag phases, whereas shorter lag phases were calculated for sample D. Storage at accelerated conditions caused shorter lag phases with storage time for all three sample. This effect was most distinctive for sample D. Interestingly, more drug is released from sample D after several months storage at 40 °C/75 % rH. The results of the stability study are summarized in [Figure 4.21].

The reduced drug release from PVAc/PVA-PEG coated pellets can probably be attributed to further gradual polymer particle coalescence upon storage. Even a curing step before storage can not assure complete film formation. This effect is even more pronounced under accelerated conditions. The mobility of macromolecule chains increases with increasing temperature. Additionally, the relative humidity during storage determines the water content of the system. Water acts as a plasticizer for aqueous polymer dispersions and is required for the capillary forces driving the particles together [28, 93, 94].

Increased drug release after storage at 40 °C/75 % rH was observed for uncured pellets (sample D). As mentioned before, the stickiness of the polymer film increased with increasing temperature and humidity. Mechanical forces were necessary to separate the pellets from each other, probably leading to minor damages of the film coat. Thus, injuries in the microstructure of the polymer film eventually compensate reduced permeability of the

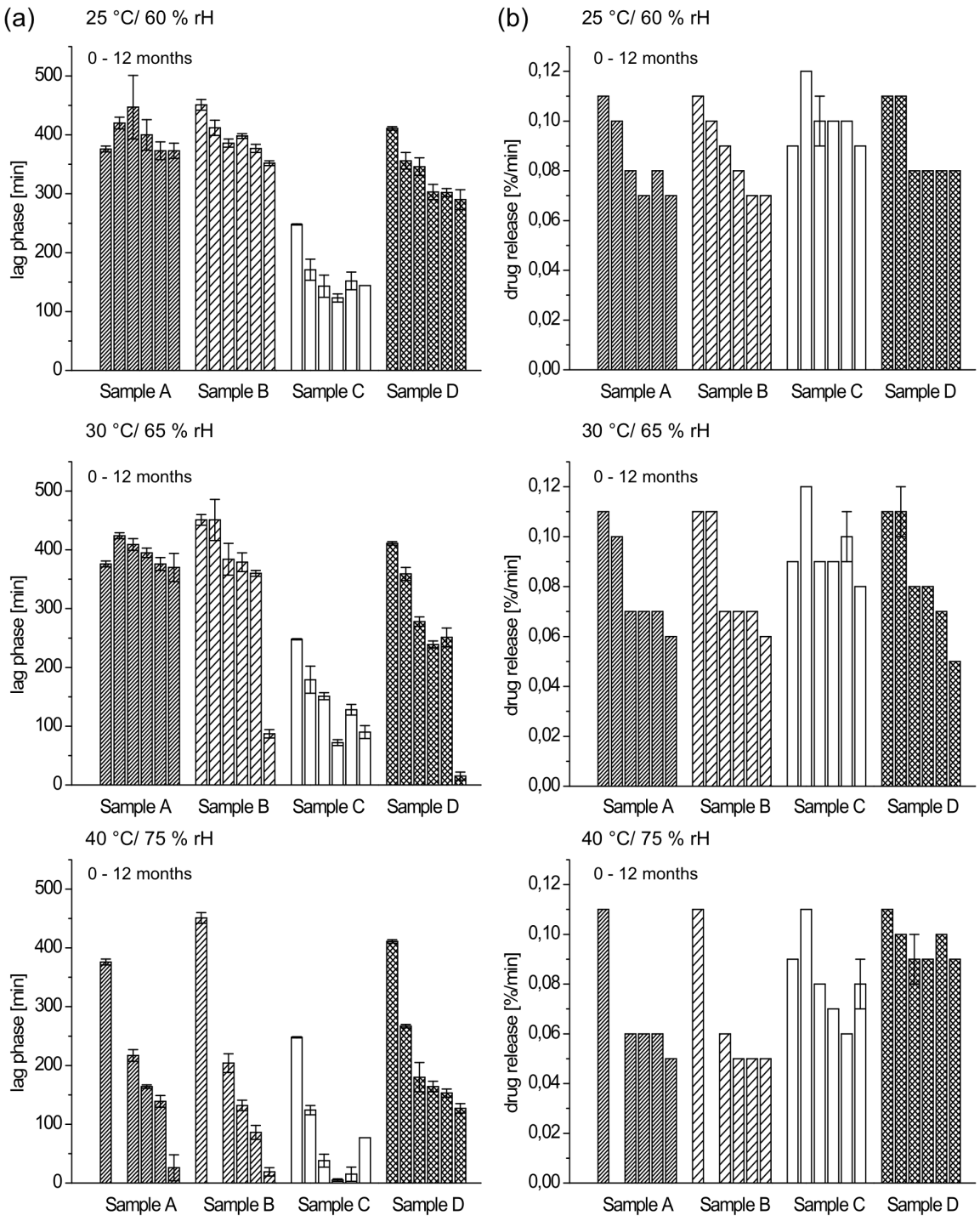


Figure 4.21: The drug release parameters lag phase (a) and drug release rate (b) of different samples after storage at long term, intermediate or accelerated conditions.

polymer film caused by increased polymer interdiffusion.

Environmental scanning electron microscopy (ESEM) was implemented to investigate the pellets surface of sample A and D visually before and after storage. As displayed in [Figure 4.22] all pellets exhibit a smooth surface layer. After storage at 25 °C/60 % rH the surface of sample D appears somewhat more even than prior storage. This effect is even more conspicuous after 12 months storage at 40 °C/75 % rH. These findings confirm the assumption of increased polymer particle coalescence. Though, no damages of the coating surface of sample D could be determined using ESEM, and further investigations have to be accomplished to clarify the faster release after storage from these pellets. An interesting approach to investigate the microstructure of the polymer surfaces more in detail could be the application of confocal laser scanning microscopy (CLSM) [131, 132] or atomic force microscopy (AFM) [133, 134].

Propranolol HCl pellets coated with PVAc/PVA-PEG 9/1 without HPMC sub coat (sample C) exhibited an increased drug release after 12 months storage. Interestingly, this phenomenon was more pronounced after 1.5 months storage than at later times. Syloid® 244 FP was added to sample C as anti-tacking agent before storage to prevent sticking of the pellets. Therefore, injuries of the polymer coat can be excluded as origin of the premature and increased drug release. Besides curing effects, drug migration into the polymer film is often reported as a reason for extended drug release after storage especially for lipophilic drugs [29, 69, 70]. As Propranolol HCl exhibits a lipophilic character the possibility of drug migration into the PVAc/PVA-PEG layer was taken into account.

ESEM pictures of cross sections of coated pellets (sample C) before storage and after 12 months storage are illustrated in [Figure 4.23]. The outer and inner morphology of the analyzed pellets was similar. The cross sections allow for a distinction between matrix core and polymer coating before and after storage. As it is not possible to differentiate divers molecular structures via ESEM energy dispersive X-ray spectroscopy (EDX) was applied to investigate the existence of Propranolol HCl molecules within the polymer film or on its surface. Implementing ESEM-EDX, the emission of X-ray radiation is generated by a high energy electron beam. The X-ray photons emerging from the specimen during the relaxation process have energies specific to the elements in the specimen [135]. Thus, EDX spectroscopy offers the possibility to display the distribution of a specific atom in a sample [136]. Even so, this technique is rarely used in pharmaceutical sciences [42, 137, 138]. The aim of the ESEM-EDX analysis within this thesis was to detect chlorine atoms of Propranolol HCl. No chlorine atoms were detected on the surface of PVAc/PVA-PEG coated pellets after 12 months storage at long term or accelerated conditions respectively. An EDX mapping was performed for a cross section of 25 °C/60 % rH stored pellets but no chlorine atoms were found within the coating layer [Figure 4.24].

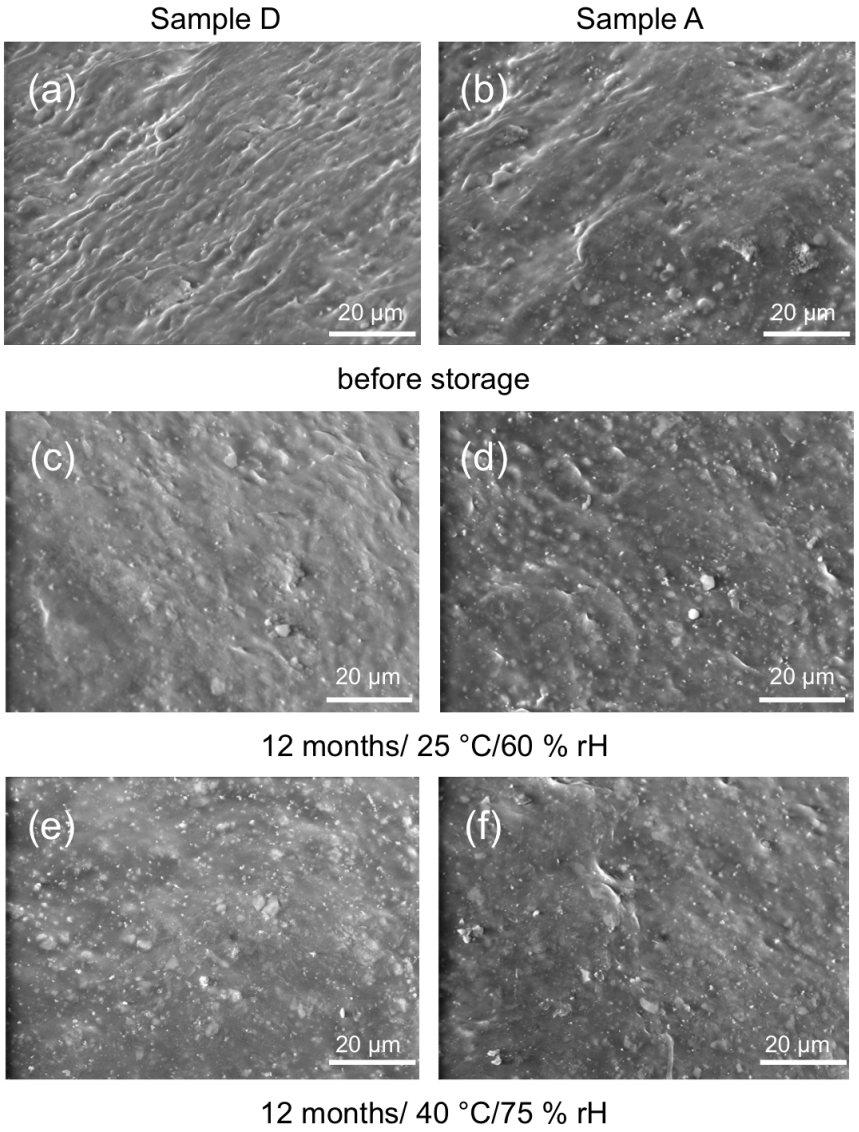


Figure 4.22: ESEM pictures of PVAc/PVA-PEG/ HPMC coated pellet surfaces. Surface of uncured sample D (a) before storage and after 12 months at 25 °C/60 % rH (c) or 40 °C/75 % rH (e) respectively. Surface of sample A (b) prior storage and after 12 months at 25 °C/60 % rH (d) and 40 °C/75 % rH (f).

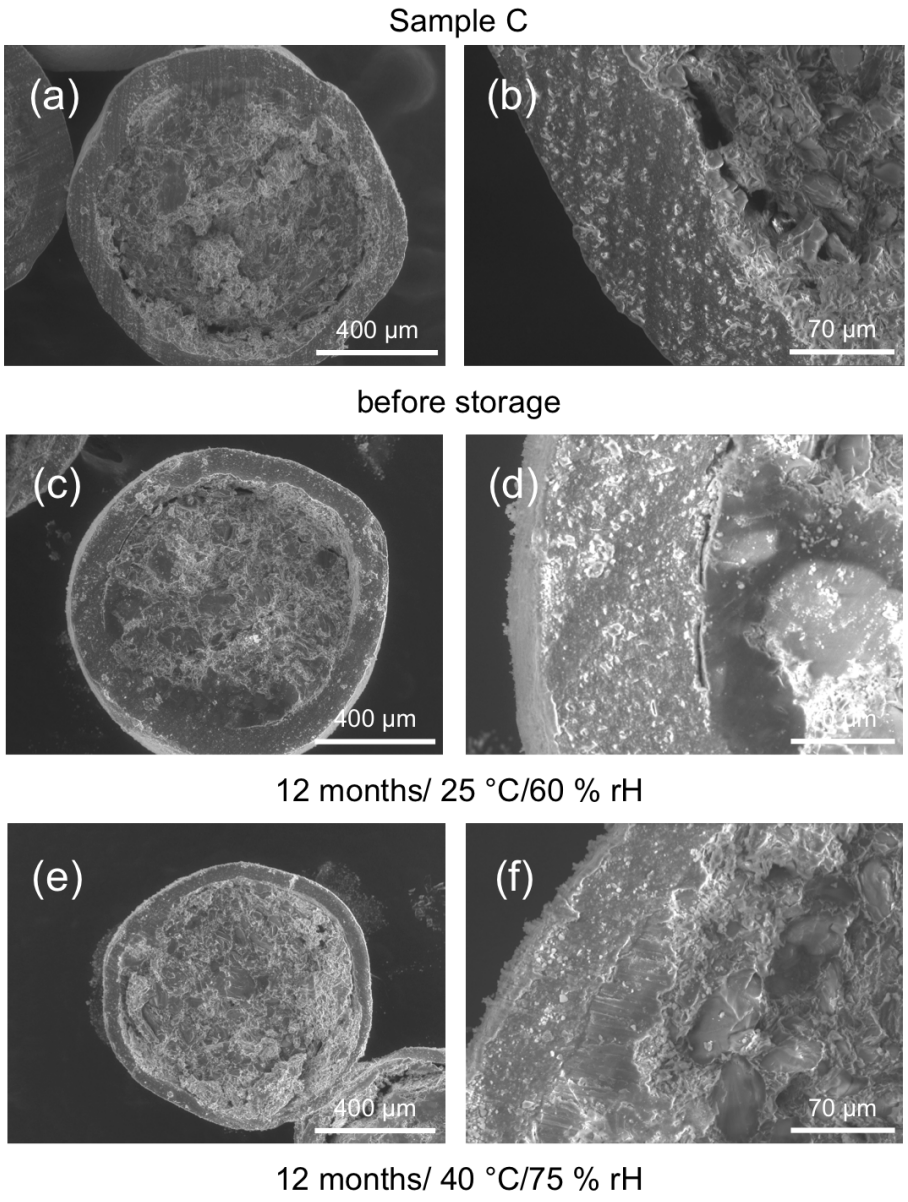


Figure 4.23: ESEM pictures of PVAc/PVA-PEG coated pellet surfaces. Cross sections of sample C before storage (a,b) and after 12 months at 25 °C/60 % rH (c,d) or 40 °C/75 % rH (e,f) respectively.

Using ESEM-EDX it was not possible to examine possible degradation processes of drug or film coating ingredients as well as plasticizer migration. Thus, further investigations are necessary to clarify the phenomenon of increased drug release from PVAc/PVA-PEG coated pellets after storage. Suitable analytical tools for these investigations are confocal raman microscopy (CRM) [44, 134] or nuclear magnetic resonance (NMR).

4.4 Conclusion

Propranolol HCl pellets coated with PVAc/PVA-PEG polymer blends exhibit sigmoid shaped drug release profiles. The drug release is characterized by an initial lag phase followed by a sustained drug liberation. Propranolol HCl release is mainly influenced by the polymer blend ratio of water insoluble PVAc and water soluble PVA-PEG as well as the coating level. The application of a HPMC sub coat slightly decreases the drug release [Figure 4.25]. Further variations of the coating composition as different plasticizer concentrations do not influence the drug liberation. The drug release pattern is not affected by different product temperatures used during the coating process within the investigated range which indicates for a robust formulation.

Comprehensive examinations regarding the stability of PVAc/PVA-PEG coated pellets were accomplished. The drug release is not influenced by the curing conditions or the addition of anti-tacking agent. Though, neither uncured nor cured pellets exhibit sufficient storage stability at long term (25 °C/60 % rH), intermediate (30 °C/65 % rH) or accelerated (40 °C/75 % rH) conditions according to ICH guidelines. The Propranolol HCl release from PVAc/PVA-PEG/ HPMC coated pellets decreases with storage time at all storage conditions. In contrast, drug release increases from pellets comprising no HPMC sub coat upon storage. Further investigations should focus on the effect of curing at accelerated temperature and humidity on PVAc/PVA-PEG coated drug delivery systems. It is often reported that the humidity during the thermal post-treatment is of great importance for the storage stability of coated dosage forms [28, 39, 95].

Osmotic driven drug release was considered for PVAc/PVA-PEG coated pellets. Thus, the influence of ionic (sodium chloride) or non-ionic (polyethylene glycol) additives on drug release was examined. The addition of the osmotically active ingredients to the HPMC sub layer results in decreased lag phases and decreased drug release rates. Further studies should examine the use of osmotically actives within the drug containing matrix cores to investigate an osmotically driven drug release from PVAc/PVA-PEG coated pellets more in detail.

Interestingly, the nature of the surrounding bulk fluid has a great influence on Propranolol HCl release from PVAc/PVA-PEG coated pellets. The pH of the media affects the

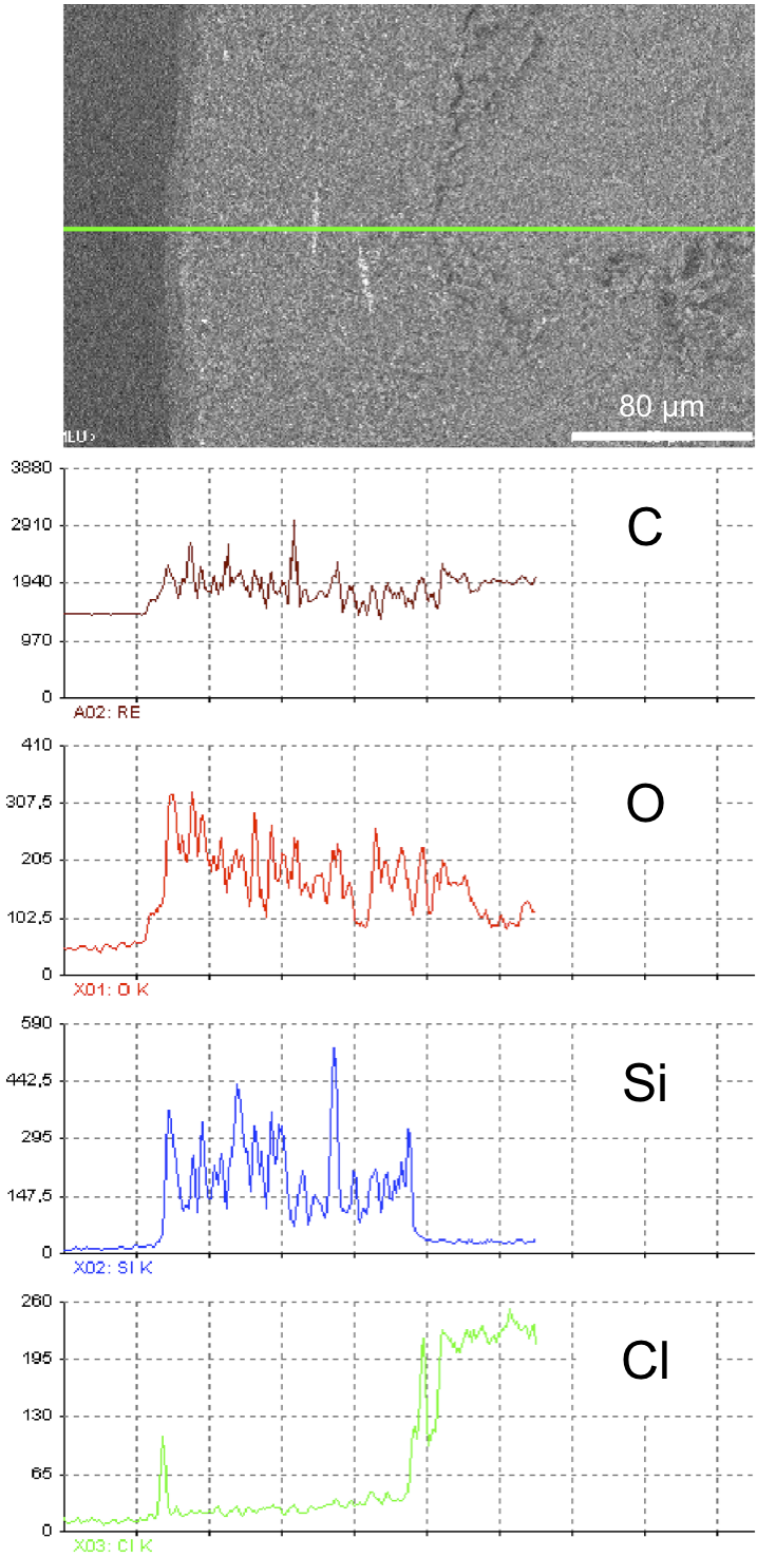


Figure 4.24: EDX scan of PVAc/PVA-PEG 9/1 coated pellets (sample C) after 12 months storage at 25 °C/60 % rH. The EDX signal for chloride atoms was below the detection limit within the film coat layer. At the same time, no silicium atoms were detected in the pellet core.

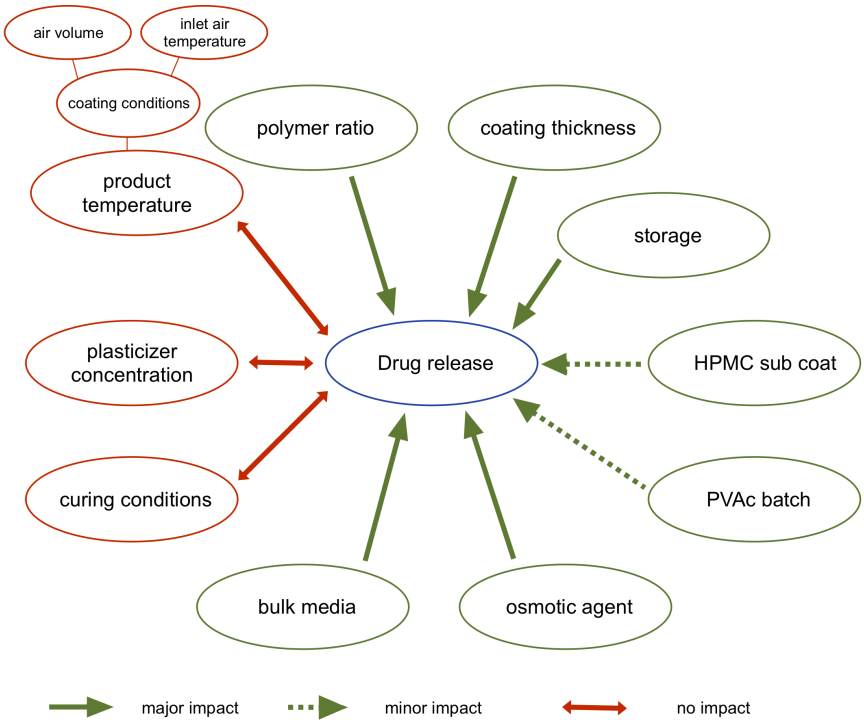


Figure 4.25: Scheme of investigated parameters affecting the drug release from PVAc/PVA-PEG controlled release pellets.

drug release but this phenomenon is most probably not related to the polymer coating. The increase of the osmolality of the dissolution media results in considerable decreased drug release. These findings emphasize the participation of osmotic effects on drug release mechanism of PVAc/PVA-PEG coated pellets.

5

Analysis of the underlying drug release mechanism

5.1 Motivation and objectives

Various effects on drug release characteristics of PVAc/PVA-PEG coated Propranolol HCl pellets were investigated. In addition, the main interest of this thesis is in a more profound understanding of the underlying drug release mechanism. A detailed understanding of the release mechanism is essential for a rational based optimization of the drug release profiles of coated dosage forms. The analysis of the underlying drug release mechanism from coated drug delivery systems is reported frequently in the literature. Siepmann et al. published a multitude of studies concerning the drug release mechanisms from ethylcellulose based coated pellets [25, 37, 38, 93, 139, 140, 141]. Publications concerning the drug release mechanism from PVAc/PVA-PEG coated drug delivery systems were announced by Strübing et al. [32, 40] and Ensslin et al. [42]. The release mechanisms controlling drug release from polymer coated pellets are complex. Several processes can be involved such as water imbibition, drug dissolution and drug diffusion [139].

The drug release is initiated by hydration of the film coat and simultaneous swelling of the membrane [32, 40, 42]. As a second process dissolution of soluble polymer and plasticizer occurs leading to an increased permeability of the film coat [32, 143]. Due to an osmotic pressure difference water will permeate into the pellet core and dissolve drug molecules located in the pellet core. The influx of water into the pellet might also lead to a swelling of the polymer network with increased permeability of the film membrane. When the core is water saturated transport processes through the polymer film become diffusion controlled in both directions [40].

The release mechanism from PVAc/PVA-PEG coated Propranolol HCl pellets is expected to be based on the described approach. The main interests of the present chapter were to study the effect of the PVA-PEG ratio, the influence of osmotically active ingredients and the impact of the nature of the surrounding bulk medium on the underlying drug

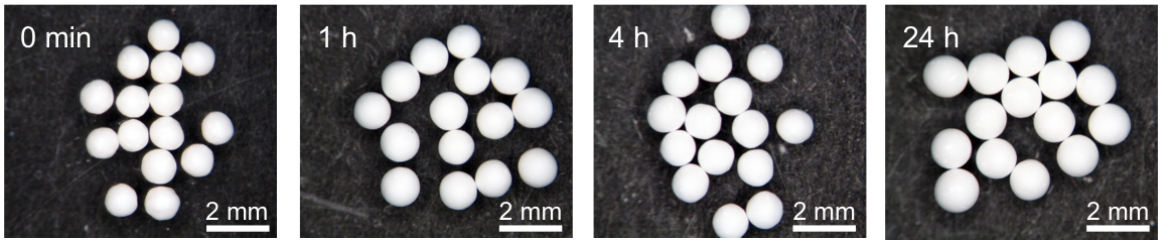


Figure 5.1: Swelling of Propranolol HCl pellets coated with PVAc/PVA-PEG in a ratio of 9/1 in simulated gastric fluid pH 1.2 (coating level 12 mg polymer/cm^2). Swelling of pellets started after only 30 min and continued in course of the experiment.

release mechanism. Therefore, the swelling behaviour of coated pellets within different media was monitored microscopically implementing an optical image analysis software. The swelling of the pellets or the polymer film coat can lead to an expansion of the polymer network resulting in a further increased permeability of the membrane with accelerated drug release. Additionally, low field nuclear magnetic resonance (NMR) relaxometry was implemented to elucidate water penetration and uptake into the delivery system. Electron paramagnetic resonance (EPR) spectroscopy (syn. electron spin resonance, ESR) was applied to monitor solubilization processes within the pellets.

The combination of the results from the mechanistic study should help to explain the underlying drug release mechanism from PVAc/PVA-PEG coated pellets.

5.2 Swelling analysis of coated pellets

To study the impact of water penetration into the pellets on drug release profiles, the swelling of PVAc/PVA-PEG coated Propranolol HCl pellets was investigated in simulated gastric fluid pH 1.2 and phosphate citrate buffer pH 6.8 for 24 h each [Figure 5.1]. Significant swelling behaviour was observed for PVAc/PVA-PEG graft copolymer blends after few minutes contact with the dissolution media. The PVAc based coating demonstrated only a minor swelling which was initiated after 60 min in pH 1.2 and after 120 min in pH 6.8. The swelling kinetics were compared to drug release profiles [Figure 5.2]. The maximum expansion (15.8 % in pH 1.2 and 25.4 % in pH 6.8) of PVAc/PVA-PEG 8/2 coated pellets was achieved after 4 h when 83 % (pH 1.2) or 44 % (pH 6.8) drug were released. Throughout the dissolution process the pellet swelling was reduced. Pellets coated with PVAc/PVA-PEG 9/1 exhibited a maximal expansion of 25.1 % in pH 1.2 or 21.1 % in pH 6.8 after 24 h. The maximum swelling of pellets comprising a PVAc film coat was minor (12.7 % in pH 1.2 or 5.1 % in pH 6.8) after 24 h. In general, swelling was found to be slightly more intense in pH 1.2 than in pH 6.8. This was in good agreement with the

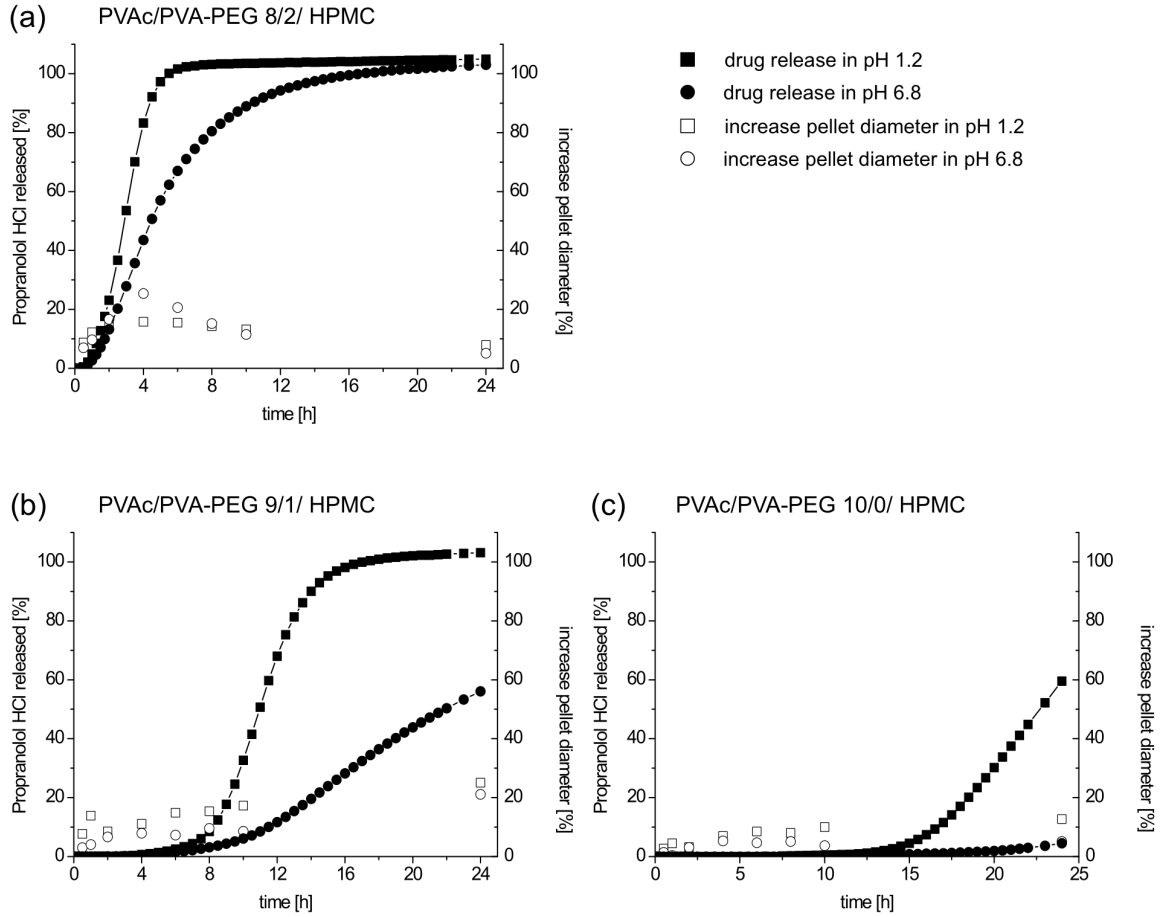


Figure 5.2: Swelling (open symbols) and drug release (closed symbols) of Propranolol HCl pellets coated with PVAc/PVA-PEG in a ratio of 8/2 (a), 9/1 (b) or 10/0 (c) (coating level 12 mg polymer/cm^2) at pH 1.2 (square) and pH 6.8 (circle).

pH dependent drug release which was found to be faster in simulated gastric fluid.

The impact of osmotically active ingredients on drug release was investigated and combined with results from the swelling analysis [Figure 5.3]. All pellets demonstrated significant swelling after 30 min (pH 1.2) or 60 min (pH 6.8) in dissolution medium. The changes of the pellet size upon exposure to the dissolution medium depend on the content of the osmotically active ingredient. Thus, pellets comprising of 7.5 % sodium chloride swell up to 26.8 % (pH 1.2) or up to 27.9 % (pH 6.8) whereas pellets comprising 15 % sodium chloride swell up to 32.8 % (pH 1.2) or up to 30.4 % (pH 6.8) respectively. The maximum expansion is achieved after 24 h in the investigated range for all pellets. The extent of swelling of pellets comprising 15 % PEG 1500 (34.0 % (pH 1.2) or 31.0 % (pH 6.8) was slightly higher than the one of pellets containing 15 % sodium chloride. Probably, water is bound stronger to the hygroscopic PEG molecules than to NaCl. Furthermore, the salt

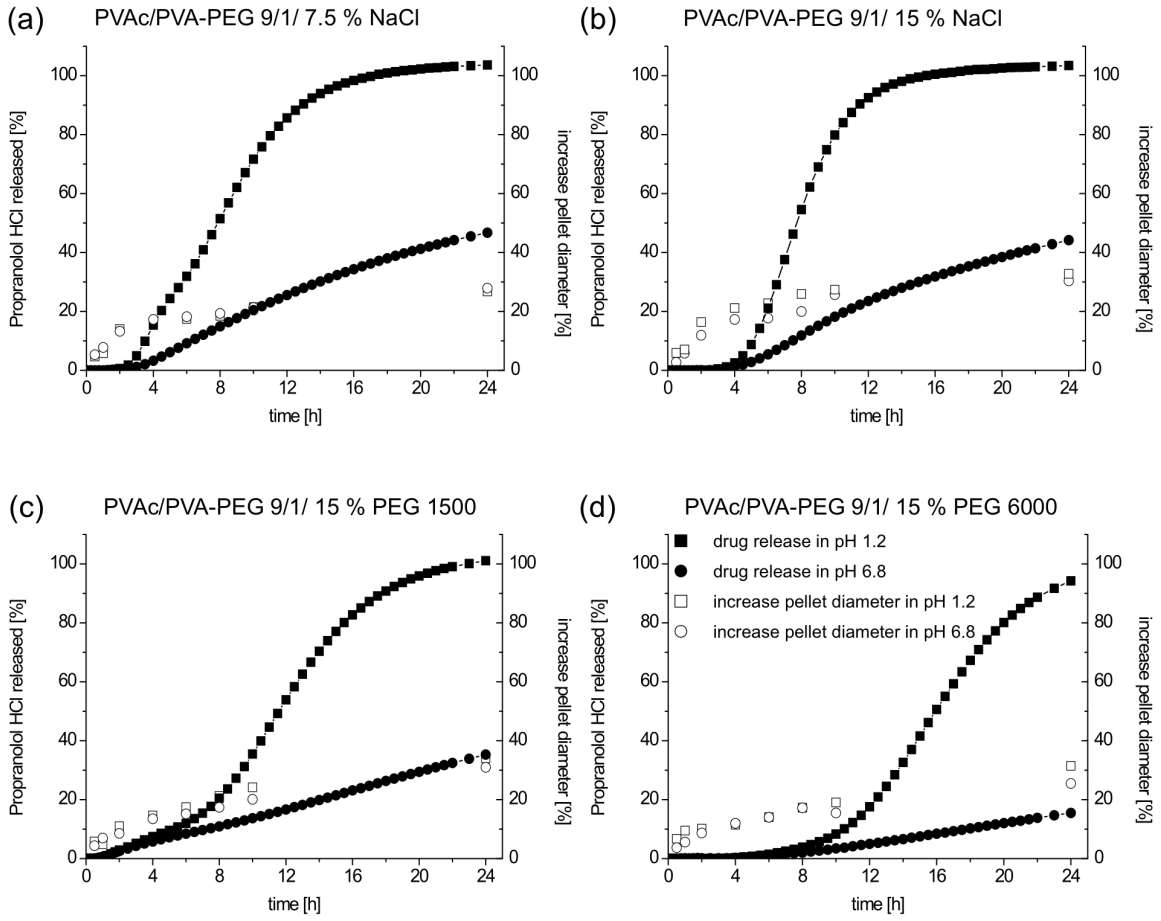


Figure 5.3: Swelling (open symbols) and drug release (closed symbols) of Propranolol HCl pellets coated with PVAc/PVA-PEG 9/1 comprising 7.5 % (a) or 15 % sodium chloride or 15 % PEG 1500 (c) or PEG 6000 (d) respectively. The coating level is 12 mg polymer/cm^2. The measurements were accomplished in pH 1.2 (square) and pH 6.8 (circle).

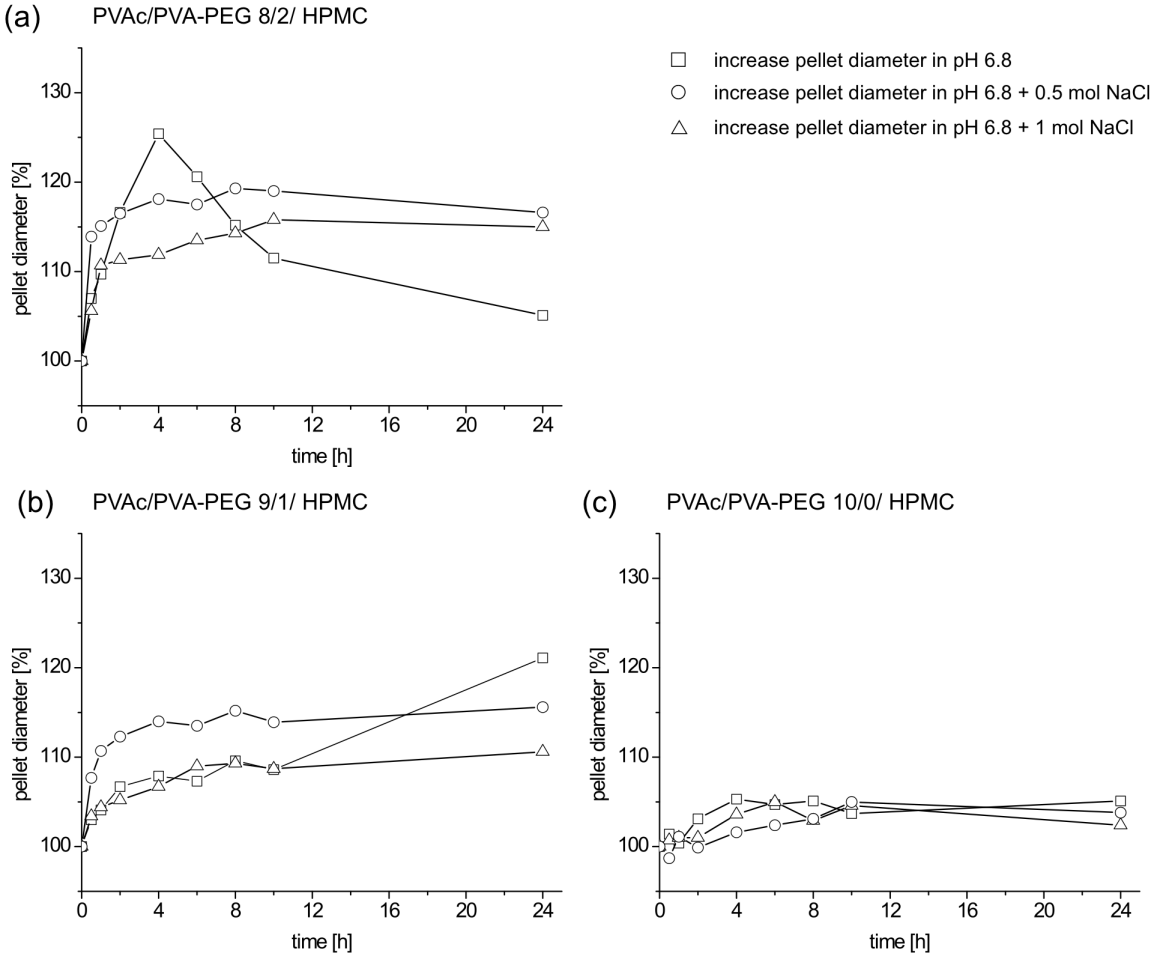


Figure 5.4: Swelling of Propranolol HCl pellets coated with PVAc/PVA-PEG in a ratio of 8/2 (a), 9/1 (b) or 10/0 (c) (coating level 12 mg polymer/cm^2) in buffer pH 6.8 at different osmolality.

is dissolved together with the drug more easily than the longer PEG polymer chains. In contrast, pellets comprising 15 % of higher molecular PEG 6000 exhibited a slightly reduced swelling behaviour (31.5 % (pH 1.2) or 25.5 % (pH 6.8). This phenomenon can be explained by the lower molecular weight of PEG 1500. Due to the lower molecular weight of PEG 1500 compared to PEG 6000, the polymer chains are solubilized more easily leading to a faster imbibing of water. Thus, a greater extend of swelling can be monitored for these pellets. These findings are in good agreement with the drug release which is minor for pellets containing PEG 6000.

Sodium chloride (0.5 mol or 1 mol) was added to phosphate citrate buffer to investigate the influence of the osmolality of the dissolution medium on swelling behaviour [Figure 5.4]. A minor swelling of PVAc/PVA-PEG coated pellets was expected within these media. Interestingly, the swelling was initiated faster in medium with 0.5 mol sodium

chloride than in standard phosphate citrate buffer. Maximum swelling of pellets coated with PVAc/PVA-PEG 8/2 (19.3 % in pH 6.8 with 0.5 mol NaCl and 15.8 % in pH 6.8 with 1 mol NaCl) was achieved after 8 h or 10 h when 42 % or 22 % drug were released. The pellet swelling was reduced throughout the experiment. Though, the extent of swelling was still higher in pH 6.8 with 0.5 mol or 1 mol sodium chloride compared to the standard buffer at the end of the analysis. These results might be due to the slower drug release in media with higher osmolality. Similar observations were made for pellets coated with PVAc/PVA-PEG 9/1. Interestingly, the pellets swell to a greater extend in pH 6.8 with 0.5 mol sodium chloride at the beginning of the analysis and for the first 10 h. When the experiment was finished the maximum swelling was measured (15.6 % in pH 6.8 with 0.5 mol NaCl and 10.6 % in pH 6.8 with 1 mol NaCl). The swelling behaviour of pellets coated with PVAc was similar within the three investigated media. Though, a maximum swelling was achieved after 10 h in dissolution medium with 0.5 or 1 mol sodium chloride. The swelling was reduced in the further course of the study.

The swelling kinetics of pellets comprising osmotically active ingredients in dissolution media with different osmolality are demonstrated in [Figure 5.5]. The swelling of pellets comprising 7.5 % or 15 % sodium chloride started almost identically in pH 6.8 without or with 0.5 mol sodium chloride. A slower swelling behaviour is observed in pH 6.8 with 1 mol NaCl for both samples. The maximal swelling was attained after 6 h for pellets with 7.5 % NaCl (15.8 % or 12.1 %) as well as for pellets with 15 % NaCl (18.5 % or 14.5 %) in both investigated media (pH 6.8 with 0.5 or 1 mol NaCl). Interestingly, the swelling of the pellets was reduced at the end of the analysis in media with different osmolality. PVAc/PVA-PEG 9/1 coated pellets containing PEG 1500 or PEG 6000 swell less in dissolution media pH 6.8 with 1 mol NaCl than in media with 0.5 mol or without sodium chloride. The maximal swelling was determined at the end of the experiment after 24 h. Pellets with PEG 1500 exhibited a higher swelling behaviour (21.7 % in pH 6.8 with 0.5 mol or 18.9 % in pH 6.8 with 1 mol sodium chloride) than pellets comprising PEG 6000 (17.1 % in pH 6.8 with 0.5 or 15.3 % in pH 6.8 with 1 mol NaCl respectively).

To summarize, significant swelling was observed for PVAc/PVA-PEG coated pellets. In contrast, pellets coated with PVAc swell to a lesser extend. Thus, the swelling behaviour is highly depending on the polymer blend ratio. Furthermore, it is significantly influenced by the osmotic activity of the pellet core as well as by the osmolality of the dissolution medium. Finally, the swelling behaviour could be related to the drug release mechanism. The maximum extend of the pellets volume is achieved throughout the drug release phase and is reduced after drug liberation is completed. The decrease of pellet swelling within dissolution media with higher osmolality is probably caused by the high osmotic pressure of the bulk fluid. Thus, the osmotic pressure within the coated pellet is too low to resist

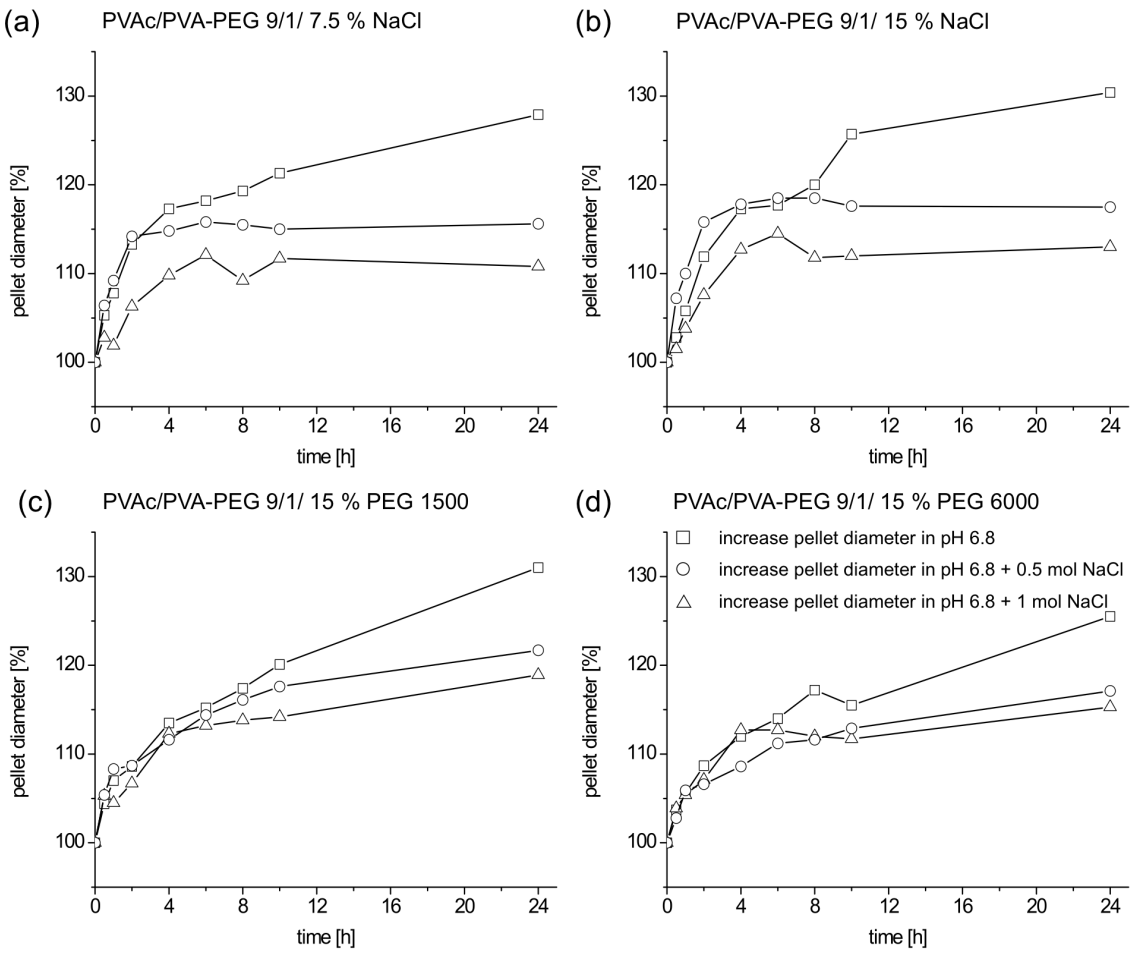


Figure 5.5: Swelling of Propranolol HCl pellets coated with PVAc/PVA-PEG 9/1 comprising 7.5 % (a) or 15 % sodium chloride (b) or 15 % PEG 1500 (c) or PEG 6000 (d) respectively. The coating level is 12 mg polymer/cm^2. The measurements were accomplished in pH 6.8 at different osmolality.

the pressure from outside resulting in minor swelling.

5.3 Monitoring of water diffusion characteristics

Swelling of PVAc/PVA-PEG coated pellets was initiated fast upon contact with dissolution medium. Due to the results from the swelling experiments the water influx through the polymer film is dependent on the polymer ratio as well as on the content and the nature of osmotically active ingredients. Within the current chapter the imbibing of water into the coated drug delivery system should be examined more in detail.

Nuclear magnetic resonance (NMR) spectroscopy is widely used to monitor drug delivery systems in vitro and in vivo. In contrast to the commonly utilized superconducting magnet spectroscopy, low field NMR (syn. Benchtop-NMR) spectroscopy makes use of permanent magnet technology. Thus, low field NMR is less cost intensive and it is commonly used in the food and chemical industry. However, it was rarely applied in the field of pharmaceutical sciences so far [144]. In general, low field NMR spectroscopy is used to detect the total amount of protons and their relaxation times T_1 (spin-lattice) or T_2 (spin-spin) [144]. The relaxation times correspond to different materials like oil and water [145] or water and polymer [146, 147]. Addtionally, different states of one material (molten or solid, free or adsorbed) can be specified by low field NMR relaxometry measurements [148, 149, 150]. For instance, low field NMR can be implemented to determine free or adsorbed water molecules non-invasively [72, 73, 151, 152, 153, 154]. Within this thesis, low field NMR spectroscopy was used to monitor how fast water penetrates into the coated drug delivery system as well as to determine the amount of adsorbed water within the pellets.

In addition, electron paramagnetic resonance (EPR, syn. electron spin resonance ESR) spectroscopy was applied to study the microenvironment within PVAc/PVA-PEG 9/1 coated Propranolol HCl pellets. Electron paramagnetic resonance spectroscopy is a useful tool to provide unique information on solubilization processes [74, 155, 156, 157, 158]. Moreover, the method provides a deeper insight in the drug release mechanism itself as different release mechanisms result in different changes in the spectral intensity and shape [157]. In diffusion controlled release processes water penetration and solubilization lead to remarkable changes in the spectral shape due to the spectral contribution of dissolved, rapidly tumbling radicals [157, 159]. A comprehensive EPR study was accomplished by Strübing et al. [32] to monitor the solubilization process within PVAc/PVA-PEG coated tablets. The results contributed to a deeper understanding of the drug release mechanism of PVAc/PVA-PEG coated monolithic drug delivery systems. A similar study was carried out by Ensslin et al. to define the drug release mechanism from coated pellets [43].

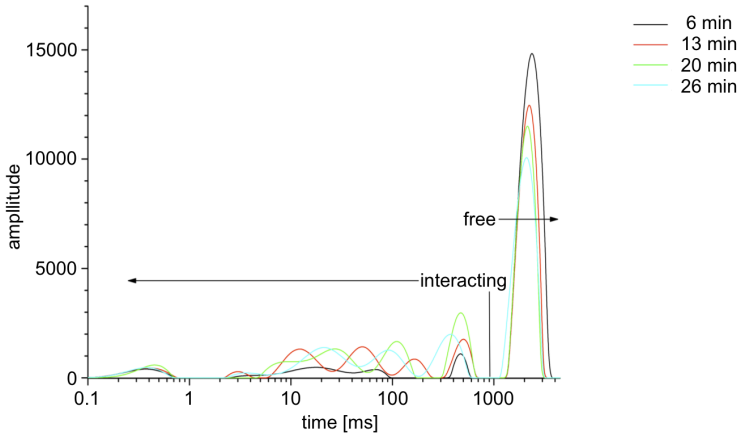


Figure 5.6: Distribution plot of T_2 relaxation times of water for PVAc/PVA-PEG 9/1 coated pellets comprising 15 % NaCl measured in pH 6.8.

Thereby, particular attention was paid to the impact of the polymer blend ratio and the coating thickness on drug release kinetics. The aim of the current study is to elucidate the influence of osmotically active ingredients on the drug liberation process from PVAc/PVA-PEG 9/1 coated Propranolol HCl pellets.

5.3.1 Nuclear magnetic resonance (NMR) studies

The penetration of water into PVAc/PVA-PEG coated pellets was examined by determination of the spin-spin relaxation time T_2. The analysis of relaxation curves by using the inverse Laplace transformation resulted in distribution plots of the spin-spin relaxation time [Figure 5.6].

The T_2 relaxation time represents the time constant that characterizes the signal decay originated in random spin-spin interactions in the transverse plane. Free water molecules exhibit a long T_2 relaxation time of around 2 to 3 s whereas the bound water molecules show shorter relaxation times ($<$ 1000 ms). Therefore, it is possible to detect different states of water within a probe. Based on the distribution plots the fraction of bound water within the coated pellets was calculated according to the following equation:

$$c_b = 100 * (1 - \frac{A_f}{A_0}) \tag{5.1}$$

where c_b stands for the amount of bound water, A_f describes the signal decay of free water and A_0 represents the initial signal amplitude of pure water. Here, the signal amplitude of water is normalized to 100 %. Throughout the experiment the signal amplitude of free water decreases (A_f) as more and more water penetrates into the pellets.

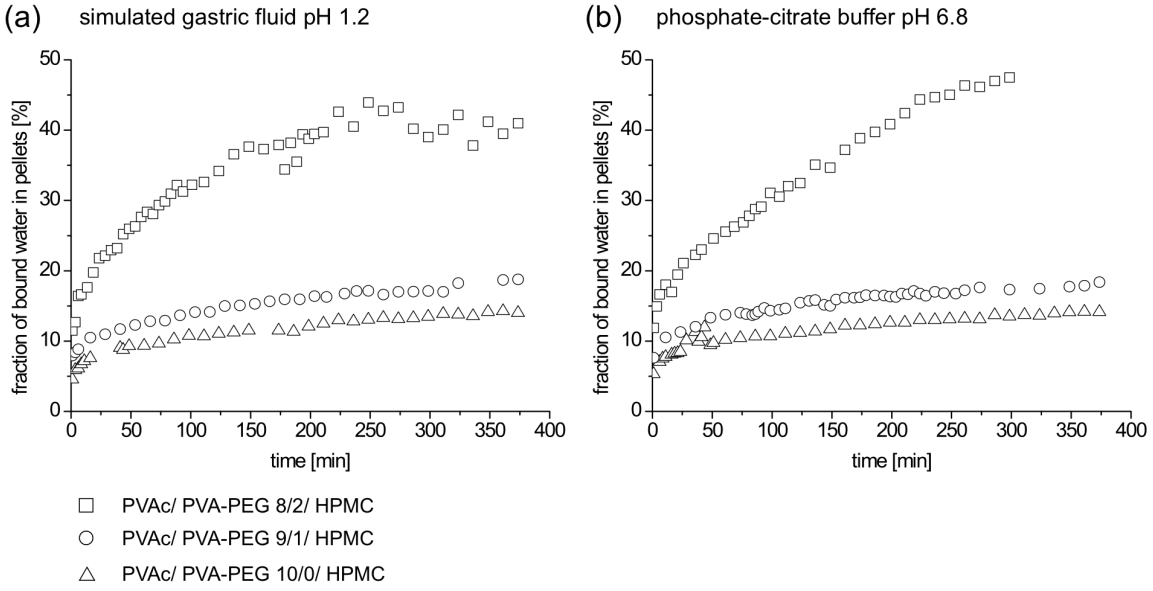


Figure 5.7: The figure demonstrates the fraction of bound water within PVAc/PVA-PEG coated Propranolol HCl pellets as a function of polymer blend ratio and pH of the dissolution medium ((a) in simulated gastric fluid pH 1.2, (b) in phosphate citrate buffer pH 6.8).

In general, NMR spectroscopy is not used as a quantitative method as the filling of the sensitive volume inside the NMR coil influences the NMR responds. This filling factor is determined by the sample volume, the sample shape and sample properties like the dielectric constant or the amount of hydrogen atoms. Thus, an internal standard was used to overcome these problems and allow a quantification of the measurement results. Within this thesis, a constant number of protons given by a constant volume of 2 ml dissolution medium represented the internal standard. Free dissolution medium still covered the pellets at the end of the measurements after several hours. Hence, one can conclude that a saturation state existed within the pellets and free dissolution medium was available outside. In addition, it was observed that the position of free dissolution medium did not change. In this case a swelling of the pellets can be neglected. The initial signal amplitude of the dissolution medium (A_0) was defined as internal standard. Though, the initial signal amplitude increased when some amount of the excipient was dissolved over time. For example, the signal increased up to 4 % in 8 hours for PEG free samples. Still, the effect was more pronounced for pellets comprising PEG in the sub coat layer. The smoothness of these time-dependent increases illustrate the quality of the NMR relaxometry experiment. Time points with strong deviations were removed.

The influence of the polymer blend ratio on increase of bound water within PVAc/PVA-PEG coated pellets measured by NMR relaxometry is monitored in [Figure 5.7]. A con-

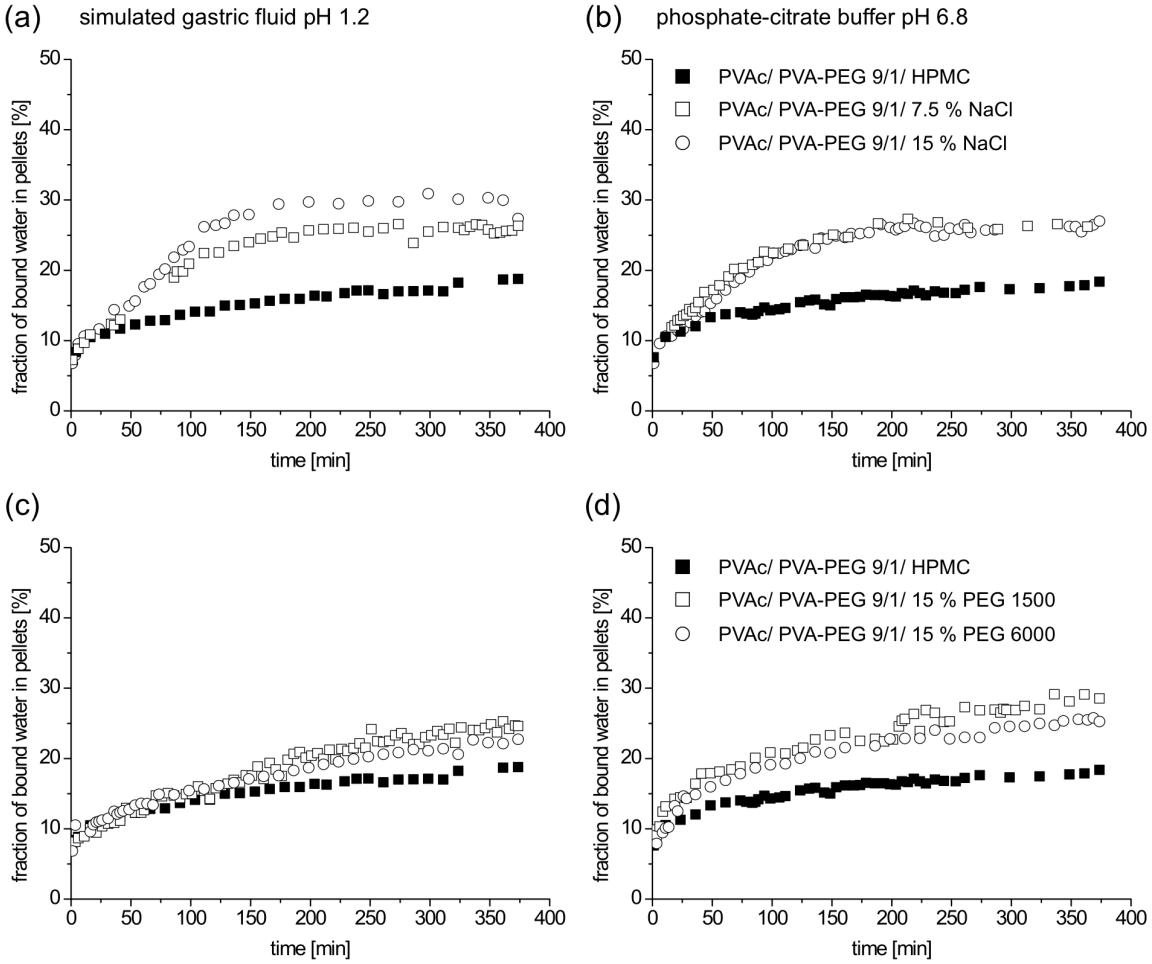


Figure 5.8: The fraction of bound water within PVAc/PVA-PEG 9/1 coated Propranolol HCl pellets is illustrated as a function of osmotic ingredient (NaCl (a, b) or PEG (c, d) within the pellets and pH of the dissolution medium ((a, c) in simulated gastric fluid pH 1.2, (b, d) in phosphate citrate buffer pH 6.8).

siderable increase of bound water was observed for all samples within the first 30 min of the NMR experiment. The fraction of bound water is clearly correlated with the polymer ratio. Thus, the amount of bound water is higher at higher PVA-PEG levels. Propranolol HCl pellets coated with PVAc/PVA-PEG 8/2 comprised a maximum value of around 47 % bound water in pH 6.8. In contrast, around 17 % bound water were detected for PVAc/PVA-PEG 9/1 coated pellets in pH 6.8. A fraction of around 14 % bound water was calculated for the PVAc coated sample in the phosphate citrate buffer. The water influx is terminated after around 4 hours in both dissolution media. Only a minor increase of the bound water fraction could be observed throughout the ongoing experiment.

In a next step, the influence of osmotically active ingredients on the amount of bound water within a sample was investigated [Figure 5.8]. The results of the experiment demon-

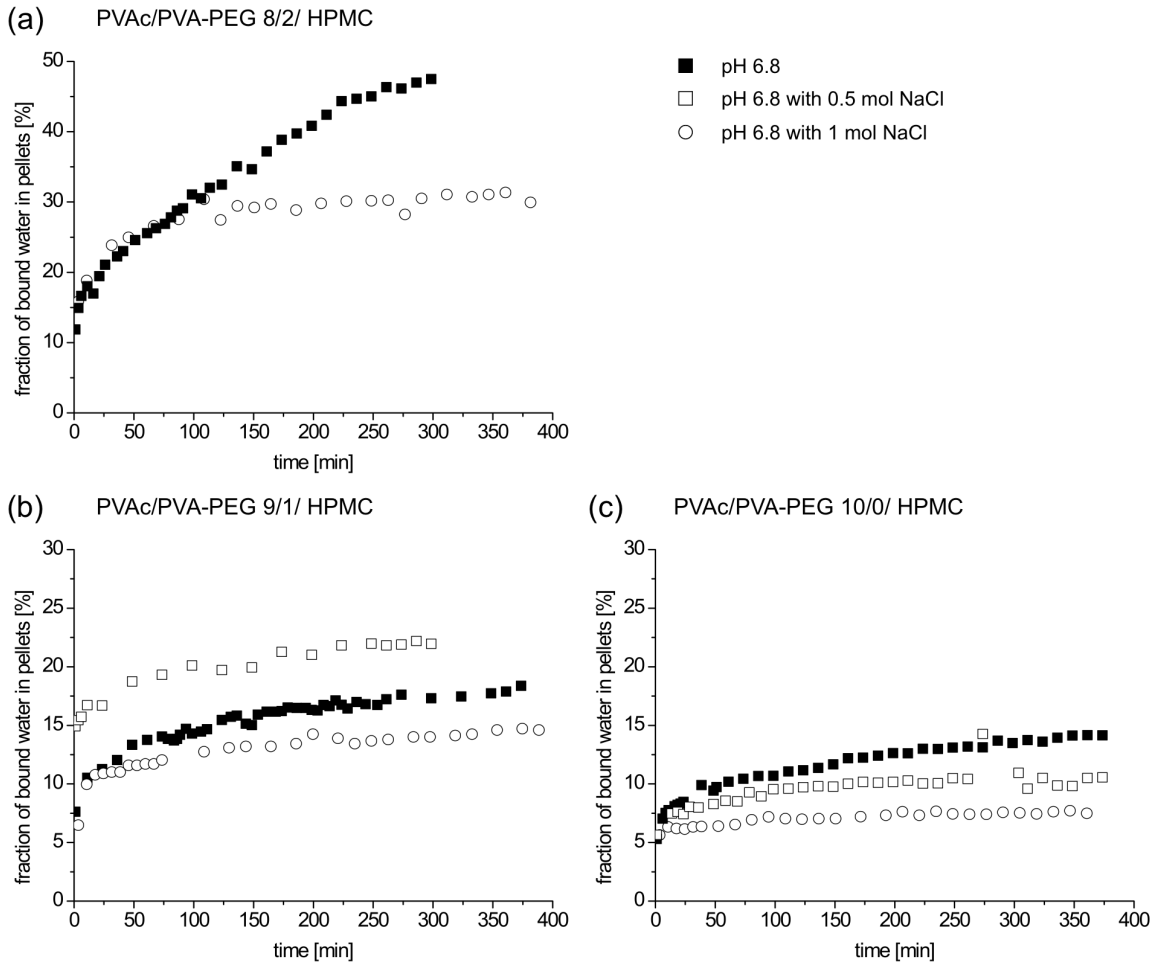


Figure 5.9: The figure displays the fraction of bound water within PVAc/PVA-PEG coated Propranolol HCl pellets as a function of polymer blend ratio and osmotic activity of the dissolution medium ((a) PVAc/PVA-PEG 8/2, (b) PVAc/PVA-PEG 9/1 and (c) PVAc/PVA-PEG 10/0).

strate an explicit influence of the osmotically active compound on the fraction of bound water within PVAc/PVA-PEG coated pellets. A maximum value of 26 % bound water was detected in pH 6.8 for pellets coated with PVAc/PVA-PEG 9/1 comprising 7.5 % sodium chloride. A higher sodium chloride level (15 %) resulted in a fraction of 27 % bound water within the sample. The water influx is finished after around 3 hours. Similar amounts of bound water were discovered within pellets comprising of 15 % PEG 1500 (28 %) or PEG 6000 (26 %) respectively. Although the amount as well as the nature of osmotically active ingredient had a distinct impact on drug release from PVAc/PVA-PEG 9/1 coated pellets, an affect of these parameters on the water influx is not visible.

Sodium chloride (0.5 mol or 1 mol) was added to phosphate citrate buffer pH 6.8 to investigate the influence of osmolality of the dissolution medium on the water binding characteristics of PVAc/PVA-PEG coated pellets [Figure 5.9]. Due to the higher osmotic pressure of the dissolution medium a decreased water influx into the pellets was expected. An amount of 30 % bound water was calculated for PVAc/PVA-PEG 8/2 coated pellets in dissolution medium with 1 mol sodium chloride compared to 47 % in standard buffer. The saturation was achieved after only 3 hours (4 hours in phosphate citrate buffer without sodium chloride). The fraction of bound water determined in phosphate citrate buffer pH 6.8 with 1 mol NaCl added was also reduced for pellets coated with PVAc/PVA-PEG 9/1 (14 % vs. 17 %) or PVAc only (8% vs. 14 %). In addition, the water influx was finished earlier within dissolution medium with higher osmolality. Curiously, the maximum value for bound water in medium with 0.5 mol sodium chloride (22 %) for PVAc/PVA-PEG 9/1 coated pellets was higher than in standard medium. A similar effect was observed during the swelling analysis of PVAc/PVA-PEG 9/1 coated pellets in medium with 0.5 mol sodium chloride. Still the reason for these results is unclear.

The water binding behaviour in media with different osmolality was also investigated for pellets comprising osmotically active ingredients [Figure 5.10]. Less bound water was determined in pellets comprising 7.5 or 15 % sodium chloride in dissolution medium with 0.5 or 1 mol sodium chloride compared to standard medium. Maximum values were measured after 4 h for pellets with 7.5 % NaCl (19 % or 18 %) as well as for pellets with 15 % NaCl (23 % or 22 %) in both media (pH 6.8 with 0.5 or 1 mol NaCl). PVAc/PVA-PEG 9/1 coated pellets containing PEG 1500 or PEG 6000 adsorbed less water in dissolution medium pH 6.8 with 1 mol NaCl (16 % or 14 %) than in media with 0.5 mol (17 % or 13 %) or without sodium chloride (28 % or 26 %).

NMR relaxation measurements were implemented successfully to monitor the absorption of water of PVAc/PVA-PEG coated pellets. Thus, the amount of adsorbed water was highly depend of the polymer blend ratio. Pellets coated with higher PVA-PEG level included considerable higher fractions of bound water. Furthermore, the water uptake

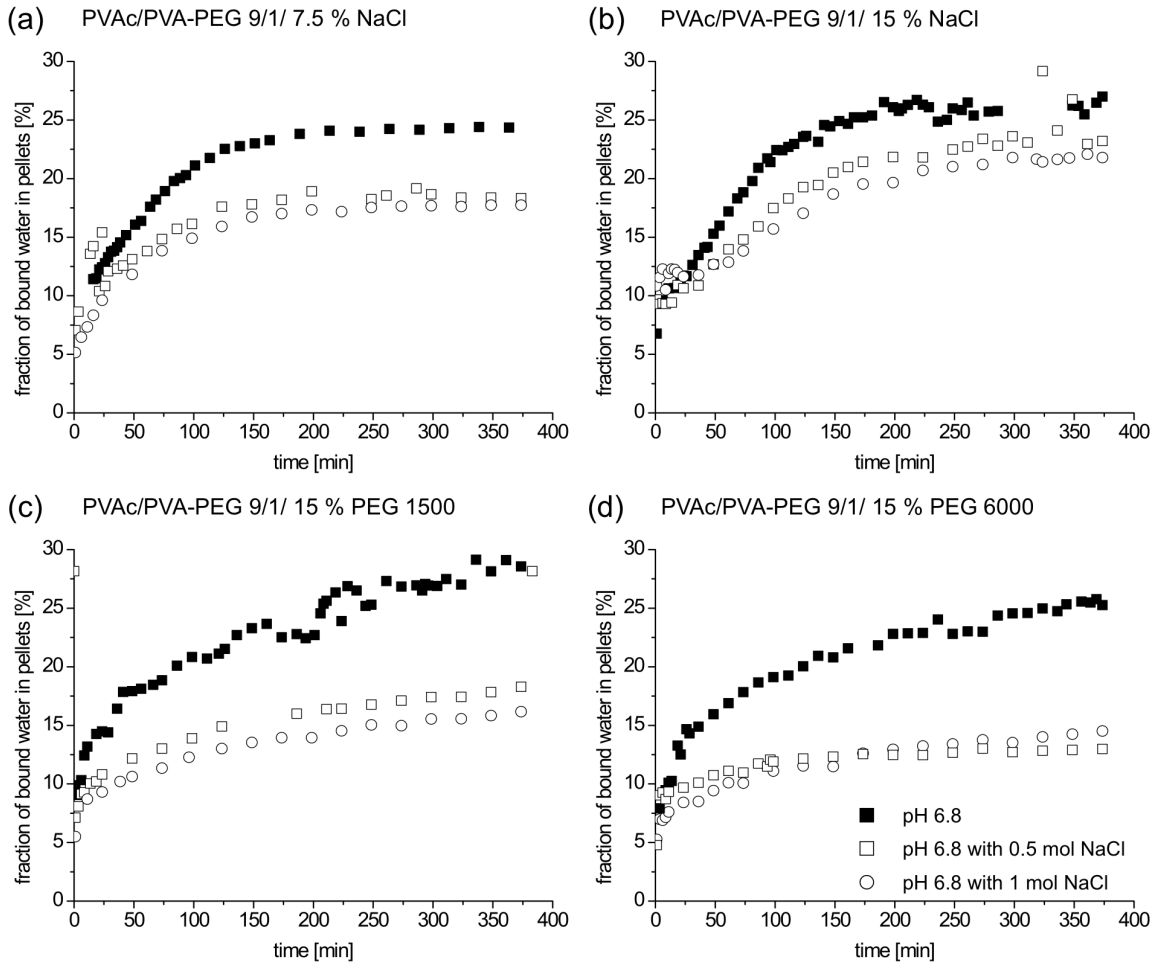


Figure 5.10: The fraction of bound water within PVAc/PVA-PEG 9/1 coated Propranolol HCl pellets is monitored as a function of osmotic ingredient (NaCl (a, b) or PEG (c, d) within the pellets and osmolality of the dissolution medium (phosphate citrate buffer pH 6.8).

behaviour is significantly affected by the osmotic activity of the pellet core. Thereby, the nature of the osmotically active ingredient (sodium chloride vs. polyethylene glycol) played a major role whereas the amount of the incorporated osmotically active compound or its molecular weight were of minor importance.

The influence of the type of dissolution medium on water absorption behaviour was examined. The pH of the dissolution medium did not reveal an influence on the amount of bound water within the pellets. These findings are in good agreement with the results from the swelling study, where the pH showed only a minor impact on the volume expansion of PVAc/PVA-PEG coated pellets. A higher osmolality of the dissolution medium resulted in reduced water absorption. Interestingly, the effect was similar regardless of 0.5 mol or 1 mol sodium chloride were added to the buffer. The water diffusion into the pellets was analyzed by swelling experiments as well as by low field NMR relaxometry. A comparatively fast water uptake behaviour was observed for PVAc/PVA-PEG coated pellets with both methods. Thus, a fast drug solubilization was assumed. The solubilization process within PVAc/PVA-PEG coated Propranolol HCl pellets was examined in a next step.

5.3.2 Electron paramagnetic resonance studies (EPR)

The solubilization of drug inside PVAc/PVA-PEG 9/1 coated pellets was investigated by EPR measurements. EPR is a spectroscopy technique that permits the non-invasive detection of paramagnetic species consisting of an unpaired electron [159]. As Propranolol HCl represents an EPR silent drug, the addition of paramagnetic reporter molecules (spin probe) is required to detect EPR signals. A hydrophilic spin probe, TEMPOL (4-Hydroxy-2,2,6,6,-tetramethylpiperidin-1-oxyl), was selected as a model drug and incorporated into the HPMC sub coat of Propranolol HCl pellets. Exhibiting a logP value of 0.6 [160] TEMPOL demonstrates similar physical properties as Propranolol HCl (logP 0.68) [161].

The mobility of the spin probe is determined by the spectral shape as EPR spectra of nitroxides are sensitive to the microviscosity. Thus, the increasing mobility of TEMPOL indicates its proceeding solubilization and allows to shed light on the dissolution behaviour of the model drug. EPR spectra of dry pellets are anisotropic with low amplitudes and broad lines [Figure 5.11 (a - e, 0 min)]. They demonstrate a high immobilization of the spin probe TEMPOL. Contact with dissolution medium resulted in distinctive changes in spectral shape and signal intensity. After 30 min (PVAc/PVA-PEG 9/1 with 15 % PEG 1500 or PEG 6000 respectively) or 60 min (PVAc/PVA-PEG 9/1/ HPMC or with 7.5 or 15 % sodium chloride) EPR spectra were characterized by three lines. The isotropic spectra indicate the solubilization of spin probe TEMPOL by water molecules which pene-

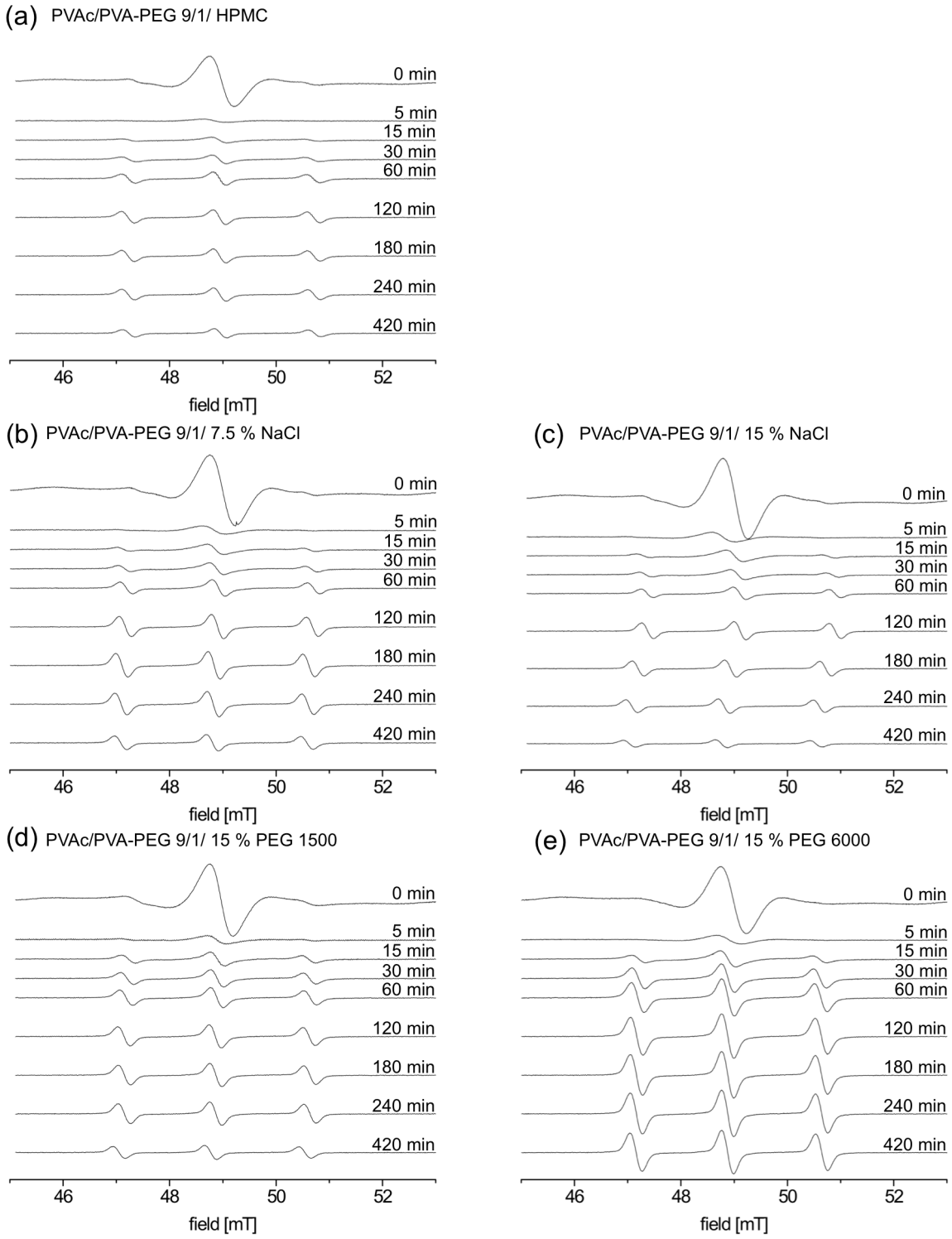


Figure 5.11: EPR spectra of TEMPOL loaded pellets coated with PVAc/PVA-PEG 9/1 (coating level 12 mg polymer/cm^2) after different times in phosphate citrate buffer pH 6.8. The samples are characterized by different amounts and types of osmotically active ingredients.

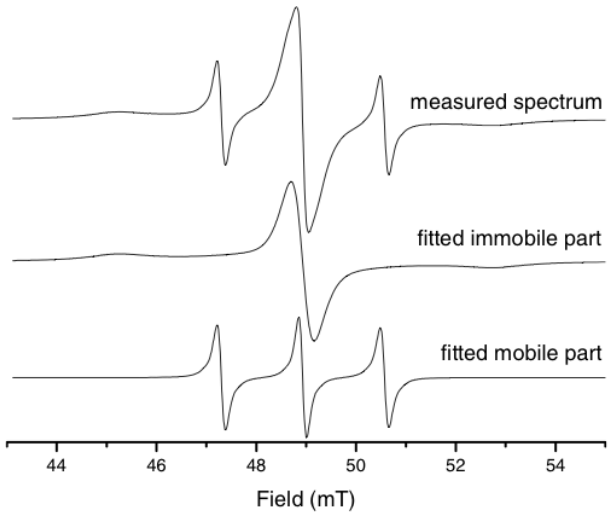


Figure 5.12: EPR spectrum of a tablet comprising spin probe PCM coated with PVAc/PVA-PEG 8/2 (8 mg polymer/cm^2), 5 min after 0.1 N HCl exposure and fits for immobile and mobile part of spin probe by nitroxide spectra simulation. Adapted from [32]

trated the pellets through the polymer coat. The transformation from anisotropic spectra to isotropic spectra was finished after around 120 min for all samples [Figure 5.11 (a - e, 120 min)]. The almost identical amplitude of all three EPR lines demonstrate the formation of a low viscous environment within the pellets; at this time Propranolol HCl is not released from the pellets. It can be assumed that a saturated solution of drug is existent within the cores at this point.

EPR spectra are recorded in the form of the first derivative. Hence, the signal intensity representing the spin probe concentration can be calculated by the double integration of the spectra [157, 159]. In case of proceeding solubilization, the EPR spectrum will be a superposition of an anisotropic ("immobile") and an isotropic ("mobil") spectrum if reporter molecules are localized in two environments with different viscosities (e.g. solid material and water) [32]. The distribution of mobil or immobile spin probe respectively can be evaluated by spectral simulation [Figure 5.12] [32]. However, the quantitative determination of EPR signals is not trivial. Various experimental conditions and instrumental variables can influence the signal shape and intensity and may decrease the accuracy of quantitative calculations [162]. Attempts to determine the concentration of mobile spin probe by double integration or spectral simulation failed due to a low signal-to-noise ratio. Thus, the computed data demonstrated a wide statistical spread. The inferior signal-to-noise ratio might be caused by a too low concentration of spin probe within the investigated material. Furthermore, vibration of the pellets within the flow through cell in the EPR resonator during the measurements can affect the measurements precision. Another possibility to determine the concentration of mobile spin probe is to evaluate the third peak of the signal

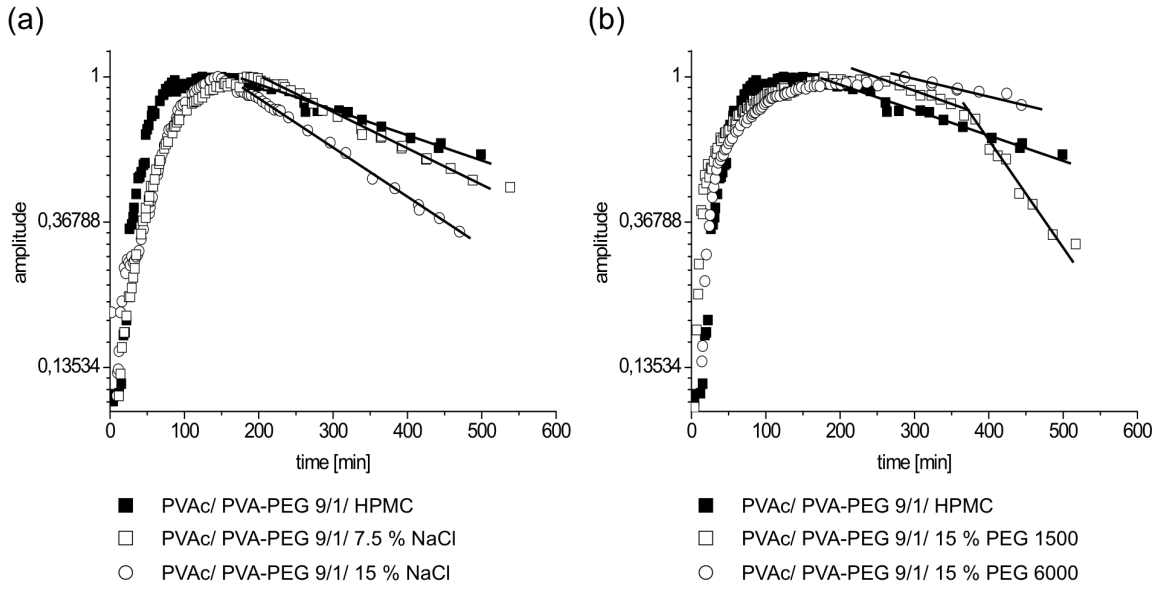


Figure 5.13: Influence of sodium chloride (a) and PEG (b) on the solubilization of the nitroxide TEMPOL in PVAc/PVA-PEG 9/1 coated pellets (coating thickness 12 mg polymer/cm^2).

amplitude. In principle, this method is only consistent when EPR lines of the analysis samples exhibit the same line width and line shape. These conditions are not complied with the measured data within this thesis.

Still, the increasing amount of mobile spin probe TEMPOL within PVAc/PVA-PEG 9/1 coated pellets was detected by analyzing the third peak of the signal amplitude [Figure 5.13]. Therefore, the results must be regarded as an approximation. [Figure 5.13] illustrates the height of the third amplitude as a function of time. The mobility of the spin probe increases as long as solubilization within the pellets proceeds. The decrease of the amplitudes height indicates the release of spin probe from the coated delivery devices. Thus, the liberation of spin probe is initiated after a lag phase. The lag phase before release started could be related to the amount of osmotically active ingredient within the PVAc/PVA-PEG coated pellets as well as to the nature of osmotically active compound. A lag phase of around 150 min was determined for PVAc/PVA-PEG 9/1 coated pellets comprising of 15 % sodium chloride, whereas the lag phase was around 180 min or 240 min for pellets with 7.5 % or without sodium chloride. A longer lag phase of around 360 min was evaluated for pellets containing 15 % PEG 1500. TEMPOL was released slowly after around 400 min from pellets including 15 % PEG 6000. These results are in good agreement with those from the drug release experiments. Thereby, pellets comprising higher concentrations of sodium chloride exhibited a shorter lag phase than those with only 7.5 % NaCl or without osmotically active additive. Additionally, the lag phase prior drug release

was dependent on the nature of osmotically active ingredient. This result was confirmed by the EPR measurements. Decreased lag phases of TEMPOL were defined in comparison to those of Propranolol HCl. This can be explained by the incorporation of spin probe in the HPMC sub layer which is situated above the pellet core. Thus, the diffusion pathway of Propranolol HCl from the core through the HPMC layer and the functional polymer coat is extended leading to a longer lag phase. A linear fit was accomplished for the decay of the signal amplitude [Figure 5.13] to determine the elimination constant k_e of spin probe TEMPOL. The elimination constant is represented by the slope of the regression line. The results are summarized in [Table 5.1].

Table 5.1: Elimination constants k_e of spin probe TEMPOL for PVAc/PVA-PEG 9/1 coated pellets (coating thickness 12 mg polymer/cm^2).

Formulation	**elimination constant** $[\mathbf{min^{-1}}]$
PVAc/ PVA-PEG 9/1/ HPMC	0.0017 ± 0.0001
PVAc/ PVA-PEG 9/1/ 7.5 % sodium chloride	0.0025 ± 0.00004
PVAc/ PVA-PEG 9/1/ 15 % sodium chloride	0.0033 ± 0.00004
PVAc/ PVA-PEG 9/1/ 15 % PEG 1500	0.0017 ± 0.0002
	0.0075 ± 0.0005
PVAc/ PVA-PEG 9/1/ 15 % PEG 6000	0.0011 ± 0.0002

Regarding the results from [Table 5.1] it is obvious that the release velocity depends on the osmotic activity of the pellet core. The liberation of TEMPOL progresses faster from pellets with 15 % sodium chloride incorporated than from pellets comprising 7.5 % or no sodium chloride. In contrast, the spin probe is released more slowly from pellets containing PEG 6000 or PEG 1500. These results agree well with the findings of the Propranolol HCl release studies. Interestingly, the liberation of spin probe from pellets comprising PEG 1500 proceeded in a biphasic mode. The decay of the signal amplitude started after around 240 min and continued in accelerated manner after 360 min.

The mobilization of TEMPOL within PVAc/PVA-PEG 9/1 coated pellets was monitored by EPR spectroscopy. The main interest of the study was to examine the influence of osmotically active ingredients within the pellets on drug release. Although the concentration of mobile spin probe could not be quantified, the results obtained from EPR measurement allow to draw conclusion regarding the drug release characteristics. The solubilization of spin probe was initiated after 30 to 60 min within all pellet samples independent of the osmotic activity of the core. These issues are confirmed by the results of NMR relaxation measurements as well as by the swelling studies. In contrast, the lag

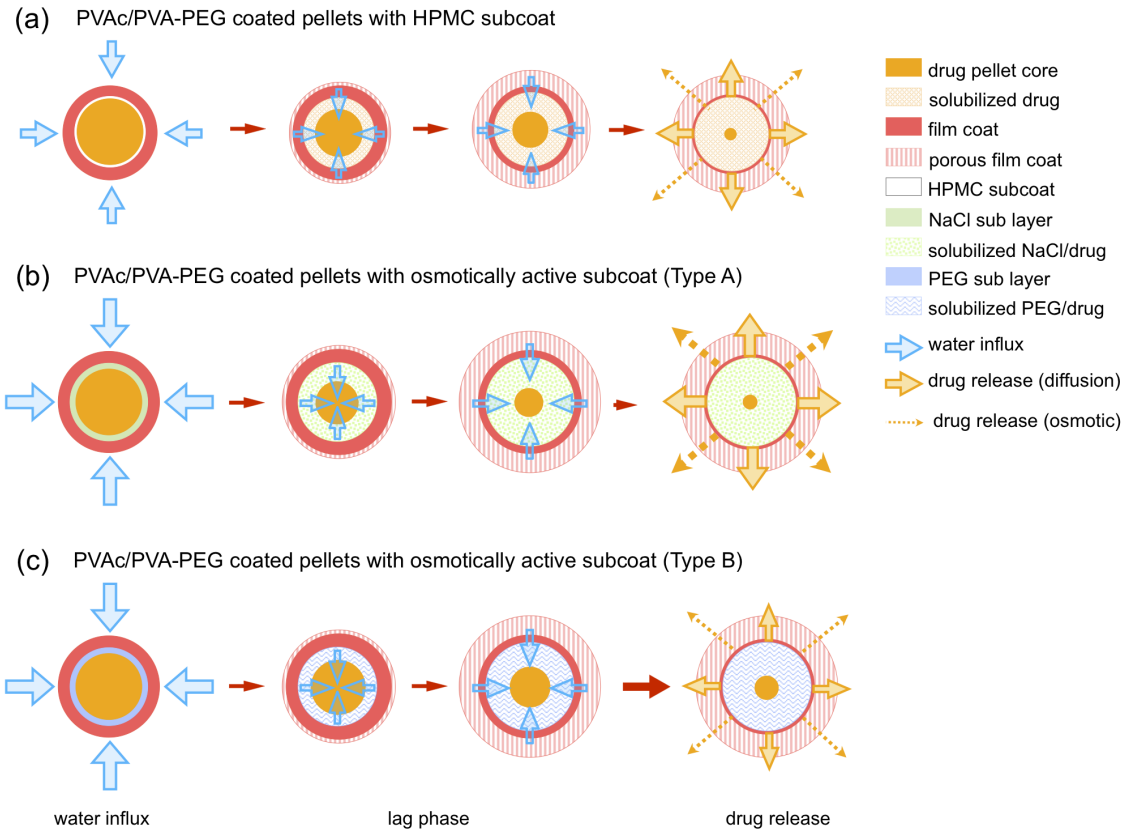


Figure 5.14: Drug release mechanism from PVAc/PVA-PEG coated Propranolol HCl pellets: (a) PVAc/PVA-PEG/ HPMC 9/1, (b) PVAc/PVA-PEG 9/1 with osmotically active sub coat (ionic), (c) PVAc/PVA-PEG 9/1 with osmotically active sub coat (non-ionic).

phase prior spin probe release started as well as the elimination constant of TEMPOL depended on the osmotic activity of the pellets. Thus, it can be assumed that osmotic effects are participating in the drug release mechanism of PVAc/PVA-PEG coated pellets.

5.4 Conclusion

The present study contributes to a more profound understanding of the underlying drug release mechanism of Propranolol HCl from PVAc/PVA-PEG coated pellets. EPR and NMR spectroscopy were implemented as non-invasive techniques to investigate water penetration into and solubilization processes within the pellet core. In addition, the swelling analysis provides further information on water uptake of the drug delivery system. The influence of the polymer blend ratio on drug release mechanism was examined. Furthermore, the main interest of this work was to investigate the influence of osmotically active ingredients within the pellet core on drug release.

Upon contact with dissolution medium water penetration into the coated pellets occurs

rapidly as demonstrated by results from NMR relaxometry measurements. In contrast to drug release, water penetration is only marginally dependent on the polymer blend ratio, the osmotic activity of the pellet core or the osmolality of the surrounding dissolution medium. Though, the amount of permeating water is clearly extended at higher PVA-PEG ratio as well as at higher osmotic activity of the pellet core. On the other hand, a higher osmolality of the bulk medium results in reduced water permeation into all delivery systems. These results are confirmed by the swelling behaviour of the coated pellets.

Penetrating water leads to solubilization of drug inside the pellet core. This can be noticed by changes in molecular mobility of the spin probe TEMPOL within all pellet samples after 30 to 60 min. In the further process, spin probe is released the earlier and the faster the more osmotically active sodium chloride is incorporated within the pellet sub layer. In contrast, the addition of PEG 1500 or PEG 6000 respectively results in extended lag phases and decreased drug release thereafter. The addition of osmotically active substances (sodium chloride or PEG) increased the imbibing of water into the pellet cores as seen by swelling experiments as well as NMR relaxometry. In case of sodium chloride addition a saturated drug/ salt solution is provided leading to extended concentration gradients compared to conventional drug pellets. Thus, the lag phase prior drug release is decreased and drug release is increased [Figure 5.14 (b)].

On the other hand the addition of PEG results in extended lag phases as well as in reduced drug release. This is most probably due to the absorption of water on PEG chains. Thus, the dissolution medium is not available for the solubilization of drug molecules and drug release is initiated at later times [Figure 5.14 (c)]. Simultaneously, the viscosity of the HPMC diffusion layer is most probably increased by the addition of PEG 1500 or PEG 6000 resulting in decreased drug release rates. Moreover, the influence of higher molecular PEGs on the composition of the polymer film coat is still unknown. It is not clarified whether PEG is partially released through the permeable polymer network or if it is integrated into the PVAc/PVA-PEG film coat.

In summary, drug release from PVAc/PVA-PEG coated pellets depends on the coating composition, coating level as well as on the nature and concentration of osmotically active ingredients within the core. Water permeates through the PVAc/PVA-PEG film coat within 30 minutes. Within the pellets Propranolol HCl is solubilized efficiently by penetrating water molecules [Figure 5.14 (a)]. Simultaneously, the water influx continues for around 3 hours and slows down thereafter. At this time diffusion processes are predominantly controlled by the one-way influx of water. This is due to an osmotic pressure difference of the pellet core and the surrounding medium. Pellet swelling continues until the core is water saturated leading to a volume expansion. At the same time water soluble compounds are leached from the polymer coat [40]. This together leads to an increased

permeability of the PVAc/PVA-PEG polymer network. Now the drug release is initiated and the transport processes through the membrane become diffusion controlled in both directions [32]. Thus, drug release from PVAc/PVA-PEG coated Propranolol HCl pellets is controlled by osmotic pumping as well as by diffusion of solubilized drug molecules through the permeable polymer film coat.

6

Summary and perspectives

6.1 English version

Multi particulate sustained release drug delivery systems are of increasing interest at the pharmaceutical market. In contrast to single unit dosage forms, multi particulates like pellets offer several physiological, biopharmaceutical and technological advantages [9]. The application of a modified release membrane film coat facilitates the achievement of constant plasma levels and provides various advantages: less administrations, greater therapeutic effect, reduced side effects and finally a better patience compliance.

The present PhD thesis focused on the development and investigation of multiple unit drug delivery systems coated with poly(vinyl acetate) based polymer films. For this purpose Propranolol HCl pellets were coated with polymer blends based on aqueous polymer dispersion Kollicoat® SR 30D. The polymer dispersion consists of 27 % water insoluble poly(vinyl acetate), 2.7 % poly(vinyl pyrrolidone) and 0.3 % sodium lauryl sulfate. Different amounts of water soluble poly(vinyl alcohol)-poly(ethylene glycol) (Kollicoat® IR) were added to the coating dispersion to control drug release from the coated pellets.

First of all, a stable film coating process for the coating of Propranolol HCl pellets with PVAc/PVA-PEG polymer blends at low product temperature was established. The coating formulations within this thesis based on coating formulations from Strübing et al. [32]. The use of Syloid® 244 FP instead of talc provided an easy-to-process and effective anti-tacking agent resulting in improved coating formulations regarding particle settlement. Moreover, the plasticizer triethyl citrate was introduced to PVAc/PVA-PEG polymer blends within this work. Differential scanning calorimetry (DSC) measurements demonstrated the efficiency of the plasticizer to decrease the glass transition temperatures of PVAc/PVA-PEG blends. In addition, an increased Kollicoat® IR concentration resulted in further reduced glass transition temperatures. This phenomenon was described earlier and was explained by the chemical structure of the water soluble polymer comprising of water soluble poly(vinyl alcohol) with covalently bound plasticizer poly(ethylene glycol) [91].

Propranolol HCl pellets coated with PVAc/PVA-PEG polymer blends revealed sigmoid shaped release profiles. The release pattern was characterized by an initial lag phase without drug release followed by an extended liberation of Propranolol HCl. The drug release characteristics were mainly related to the polymer blend ratio and the coating thickness. The addition of a HPMC sub coat resulted in slightly decreased drug release as imbibing water has to penetrate and dissolve an additional diffusion barrier within the pellets. Further variations of the coating formulation as different plasticizer concentrations did not affect the drug liberation from PVAc/PVA-PEG coated pellets. Moreover, changes of the product temperature used during the coating process did not result in different drug release pattern within the investigated range indicating the robustness of the system.

Due to the sigmoid shape of the drug release profiles an osmotic driven drug release was contemplated. The addition of osmotically active substances (ionic sodium chloride or non-ionic polyethylene glycol) to the HPMC sub layer of PVAc/PVA-PEG 9/1 coated Propranolol HCl pellets led to decreased lag phases and decelerated drug release rates. The nature of the surrounding bulk fluid had a remarkable impact on Propranolol HCl release from PVAc/PVA-PEG coated pellets. Thus, drug release was faster in simulated gastric fluid pH 1.2 than in phosphate citrate buffer pH 6.8. This phenomenon is most probably affected by the pK_a of the drug and independent of the polymer film properties. An increased osmolality of the dissolution media effected substantial reduced drug release emphasizing the participation of osmotic effects on the drug release mechanism.

As the film formation process from aqueous polymer dispersions is a complex process, a time triggered curing step is often necessary to assure complete polymer particle coalescence [67]. To investigate the influence of curing conditions on PVAc/PVA-PEG coated pellets the multi particulates were dried at room temperature or oven-cured directly after the coating step using dry heat (40 °C or 60 °C). The curing step was performed for time periods of 12 or 24 hours with or without anti-tacking agent. The results from this study indicated that drug release from PVAc/PVA-PEG coated pellets was not affected by the curing conditions or the addition of anti-tacking agents. Still, it is difficult even after curing to assure complete film formation and further polymer particle coalescence can occur during storage [39].

The analysis of drug release profiles from PVAc/PVA-PEG coated Propranolol HCl pellets after 12 months storage was another main interest of this thesis. Four samples were stored according to ICH guidelines to examine the storage stability of the coated material. The drug liberation from PVAc/PVA-PEG/ HPMC coated pellets decreased with storage time at long term (25 °C/60 % rH), intermediate (30 °C/65 % rH) or accelerated (40 °C/75 % rH) conditions when pellets were cured prior storage. In contrast, drug release from PVAc/PVA-PEG coated pellets without HPMC sub scoat increased upon

storage at all conditions. Drug liberation from uncured pellets also increased after storage at accelerated conditions.

Another aim of this PhD thesis was to get a deeper understanding of the underlying drug release mechanism from PVAc/PVA-PEG coated Propranolol HCl pellets. The initial step for the liberation of drug is the diffusion of water into the drug delivery system. Within this thesis, NMR relaxometry was implemented as a non-invasive technique to monitor the water penetration into the coated pellets. The swelling analysis contributed further information to the water uptake of the drug delivery system. It was demonstrated that water penetration into the coated pellets occurs rapidly upon contact with dissolution medium nearly independent of the polymer ratio, the osmotic activity of the pellet core or the osmolality of the surrounding bulk. On the other hand, the amount of permeating water considerably depended on the polymer ratio as well as on the osmotic activity of the pellet core or on the osmolality of the dissolution medium. Thus, the amount of penetrating water increased at higher PVA-PEG ratio as well as at higher osmotic activity of the pellet core. In contrast, a higher osmolality of the bulk medium led to minor water permeation in the delivery system.

In a next step the penetrating water solubilizes drug molecules inside the pellets. The solubilization of drug inside the coated multi particulates was studied by means of EPR spectroscopy. As Propranolol HCl represents an EPR silent drug, spin probe 4-Hydroxy-2,2,6,6,-tetramethylpiperidin-1-oxyl (TEMPOL) was incorporated in the HPMC sub coat of PVAc/PVA-PEG 9/1 coated pellets. The non-invasive EPR studies indicated a solubilization of TEMPOL inside the pellets within 30 to 60 min. The release of spin probe was found to be dependent on the osmotic activity of the pellet core as well as on the type of osmotic agent incorporated within the sub layer. Thus, TEMPOL is liberated earlier and faster the more osmotically active sodium chloride is included in the HPMC sub layer. In contrast, the incorporation of PEG 1500 or PEG 6000 led to extended lag phases and reduced release of spin probe thereafter. Combining the results from the drug release studies with those of NMR relaxometry and EPR spectroscopy, we can assume that drug liberation from PVAc/PVA-PEG coated Propranolol HCl pellets is controlled by osmotic pumping as well as by diffusion of solubilized drug molecules through the permeable polymer membrane.

6.1.1 Future perspectives

Even it was demonstrated that Propranolol HCl release from pellets can be controlled efficiently by PVAc/PVA-PEG polymer blends, one of the major challenges associated with this type of coating is to provide long term stability. In most cases, drug release af-

ter storage decreased. Thus, comprehensive investigations regarding the impact of curing conditions on storage stability should be performed in the future. It is reported that not only curing time and temperature can affect the final polymer coalescence but also the relative humidity during the post thermal treatment [94, 95]. In addition, the microstructure of the PVAc/PVA-PEG polymer films after curing and storage should be examined more in detail, for example by means of Confocal Raman Spectroscopy (CRM) or Nuclear Magnetic Resonance (NMR) Spectroscopy studies.

Another interesting question is why coating of pellets with different Kollicoat® SR 30D batches results in dissenting release profiles. The generation of acetic acid within the ready-to-use polymer dispersion might be an explanation for this and should be analyzed in detail by High Performance Liquid Chromatography (HPLC). Hereby, different storage conditions of the investigated material should be taken into account.

Finally, Propranolol HCl release from PVAc/PVA-PEG coated pellets was unequal in simulated gastric fluid pH 1.2 or phosphate citrate buffer pH 6.8. The incorporation of osmotically active agents enforced this phenomenon. Thus, an in-depth analysis of the impact of pH and different ions on PVAc/PVA-PEG polymer blends may be an interesting approach to achieve membrane controlled drug delivery systems providing uniform drug release pattern.

7

Summary and perspectives

7.1 German version

Multipartikuläre Retardarzneiformen sind von immer größerem Interesse für den pharmazeutischen Markt. Im Gegensatz zu monolithischen Darreichungsformen weisen multipartikuläre Arzneiformen wie Pellets etliche physiologische, biopharmazeutische und technologische Vorteile auf [9]. Das Aufbringen eines modifiziert freisetzenden Filmüberzuges erleichtert das Erreichen konstanter Plasmaspiegel und bietet diverse Vorteile: eine geringere Einnahmehäufigkeit, größere therapeutische Effekte, weniger Nebenwirkungen und letztlich eine verbesserte Therapietreue der Patienten.

Im Mittelpunkt dieser Arbeit standen die Entwicklung und Untersuchung multipartikulärer Darreichungsformen, die mit Filmen auf Polyvinylacetatbasis überzogen wurden. Dazu wurden Propranolol HCl Pellets mit Polymermischungen gecoatet, deren Hauptbestandteil die wässrige Polymerdispersion Kollicoat® SR 30D bildete. Diese Polymerdispersion besteht aus 27 % wasserunlöslichem Polyvinylacetat, 2.7 % Polyvinylpyrrolidon und 0.3 % Natriumlaurylsulfat. Verschiedene Mengen an wasserlöslichem Polyvinylalkohol-Polyethylenglykol (Kollicoat® IR) wurden der Coatingdispersion zugesetzt, um die Wirkstofffreisetzung aus den überzogenen Pellets kontrollieren zu können.

Zunächst wurde ein stabiler Filmcoatingprozess für das Überziehen von Propranolol HCl Pellets mit PVAc/PVA-PEG Polymermischungen bei niedrigen Produkttemperaturen eingeführt. Die Coatingformulierungen im Rahmen dieser Arbeit basierten auf den Coatingrezepturen von Strübing et al. [32]. Dabei stellte das anstelle von Talkum verwendete Syloid® 244 FP ein leicht zu verarbeitendes und effektives Formtrennmittel dar, welches besonders im Hinblick auf das Sedimentieren von Pulverpartikeln zu besseren Coatingformulierungen führte. Desweiteren wurde in diesem Kontext Triethylcitrat als Weichmacher für PVAc/PVA-PEG Polymermischungen angewendet. Differential Scanning Kalorimetrische Messungen bewiesen die enorme Fähigkeit des Weichmachers die Glasübergangstemperaturen von PVAc/PVA-PEG Polymermischungen zu senken. Zusätzlich resultierte eine höhere Konzentration an Kollicoat® IR in weiter erniedrigten

Glasübergangstemperaturen. Dieses Phänomen wurde schon früher beschrieben und mit der chemischen Struktur des wasserlöslichen Polymers erklärt, welches sich aus Polyvinylalkohol mit kovalent gebundenem Weichmacher Polyethylenglykol zusammensetzt [91].

Mit PVAc/PVA-PEG Polymermischungen überzogene Propranolol HCl Pellets zeigten sigmoidal geformte Freisetzungsprofile. Das Freisetzungsmuster war durch eine initiale Lagphase ohne Wirkstofffreisetzung charakterisiert, der eine verlängerte Propranolol HCl Freigabe folgte. Die Arzneistofffreigabecharakteristiken waren vor allem dem Polymermischungsverhältnis sowie der Filmdicke zu zuordnen. Das Auftragen eines HPMC Sublayers führte zu einer leichten Abnahme der Wirkstofffreigabe, da einströmendes Wasser eine zusätzliche Diffusionsbarriere innerhalb der Pellets passieren und lösen muss. Weitere Veränderungen der Coatingformulierung wie verschiedene Weichmacherkonzentrationen beeinflussten die Wirkstofffreigabe aus PVAc/PVA-PEG überzogenen Pellets nicht. Darüber hinaus bewirkten Veränderungen der Produkttemperatur, die während des Coatingprozesses gehalten wurden, innerhalb des untersuchten Bereichs keine unterschiedlichen Wirkstofffreisetzungsprofile, was auf die Robustheit des Systems hindeutet.

Wegen der sigmoidalen Form der Freisetzungsprofile wurde eine osmotisch getriebene Wirkstofffreigabe vermutet. Die Zugabe osmotisch aktiver Substanzen (ionisches Natriumchlorid oder nichtionisches Polyethylenglykol) zu dem HPMC Sublayer PVAc/PVA-PEG gecoateter Propranolol HCl Pellets resultierte in verkürzten Lagphasen sowie verlangsamten Freisetzungsraten. Die Art des umgebenden Freisetzungsmediums hatte einen erheblichen Einfluss auf die Propranolol HCl Freigabe aus PVAc/PVA-PEG gecoateten Pellets. So erfolgte die Wirkstofffreigabe in simulierten Magensaft pH 1.2 schneller als in Phosphat-Citrat-Puffer pH 6.8. Dieses Phänomen wird wahrscheinlich vor allem vom pK_s Wert des Arzeistoffes beeinflusst und ist unabhängig von den Polymereigenschaften. Eine erhöhte Osmolalität des Freisetzungsmediums bewirkte eine wesentlich verringerte Wirkstofffreigabe, was die Beteiligung osmotischer Effekte am Freigabemechanismus unterstrich.

Da der Filmbildungsprozess aus wässrigen Polymerdispersionen ein komplexer Vorgang ist, ist häufig ein zeitgesteuerter Curingschritt notwendig, um eine vollständige Polymerpartikelkoaleszenz sicher zu stellen [67]. Dennoch ist es sogar nach dem Curing schwierig, die komplette Filmbildung zu garantieren; somit kann eine weitere Polymerpartikelkoaleszenz auch noch während der Lagerung erfolgen [39].

Die Analyse der Freisetzungsprofile PVAc/PVA-PEG überzogener Pellets nach 12monatiger Lagerung war ein weiteres Hauptanliegen dieser Arbeit. Um die Lagerstabilität des gecoateten Materials zu untersuchen wurden vier Proben gemäß ICH Richtlinien gelagert. Die Wirkstofffreisetzung aus PVAc/PVA-PEG überzogenen Pellets nahm mit der Lagerungsdauer unter Langzeitbedingungen (25 °C/60 % rH), mittelfristigen

(30 °C/65 % rH) und beschleunigten Bedingungen (40 °C/75 % rH) ab, wenn die Pellets vor der Lagerung getempert wurden. Im Gegensatz dazu stieg die Wirkstofffreigabe aus PVAc/PVA-PEG gecoateten Pellets ohne HPMC Subcoat nach der Lagerung unter allen Bedingungen an. Die Wirkstofffreisetzung aus nicht getemperten Pellets war nach der Lagerung unter Stressbedingungen (40 °C/75 % rH) ebenfalls erhöht.

Ein weiteres Ziel dieser Dissertation war es, einen tieferen Einblick in den Wirkstofffreisetzungsmechanismus PVAc/PVA-PEG überzogener Propranolol HCl Pellets zu erlangen. Der initiale Schritt der Wirkstofffreigabe ist die Diffusion von Wasser in die Arzneiform. Im Rahmen dieser Arbeit wurde das Eindringen von Wasser in die gecoateten Pellets mittes nicht-invasiver NMR beobachtet. Die Quellungsanalyse steuerte weitere Informationen zur Wasseraufnahme der Arzneiform bei. Es wurde gezeigt, dass nach Kontakt mit dem Freisetzungsmedium schnell Wasser in die gecoateten Pellets eindringt; nahezu unabhängig von Polymerverhältnis, osmotischer Aktivität des Pelletkerns oder der Osmolalität des Freisetzungsmediums. Auf der anderen Seite hing die Menge des einströmenden Wassers wesentlich vom Polymermischverhältnis als auch von osmotischen Aktivität des Pelletkerns und der Osmolalität des Freisetzungsmediums ab. So nahm die Menge an einströmenden Wasser bei höherem PVA-PEG Anteil und bei größerer osmotischer Aktivität des Pelletkerns zu. Im Gegensatz dazu führte eine höhere Osmolalität des Umgebungsmediums zu einer geringeren Wasserpenetration in die Arzneiform.

In einem weiteren Schritt löst das eindringende Wasser Wirkstoffmoleküle in den Pellets. Die Solubilisierung von Arzneistoff innerhalb der überzogenen Pellets wurde mittels EPR Spektroskopie untersucht. Da Propranolol HCl ein EPR "stummer" Wirkstoff ist, wurde die Spinsonde 4-Hydroxy-2,2,6,6,-tetramethylpiperidin-1-oxyl (TEMPOL) in den HPMC Subcoat PVAc/PVA-PEG 9/1 überzogener Pellets eingebracht. Die nicht-invasiven EPR Analysen wiesen auf eine Solubilisierung des TEMPOLs in den Pellets innerhalb von 30 bis 60 Minuten hin. Die Freisetzung der Spinsonde hing von der osmotischen Aktivität des Pelletkerns sowie von der Art des osmotischen Stoffes, der in das Sublayer eingearbeitet war, ab. So wurde TEMPOL früher und schneller freigesetzt, je mehr osmotisch aktives Natriumchlorid in den HPMC Subcoat eingebracht war. Im Gegensatz dazu resultierte der Einbau von PEG 1500 oder PEG 6000 in erweiterten Lagphasen mit einer sich anschließenden verminderten Freigabe von Spinsonde. Nimmt man die Ergebnisse der Freisetzungsstudien, der NMR Relaxometrie und der EPR Spektroskopie zusammen, kann man annehmen, dass die Wirkstofffreigabe aus PVAc/PVA-PEG gecoateten Propranolol HCl Pellets durch osmotisches Pumpen sowie durch Diffusion gelöster Wirkstoffmoleküle durch die permeable Polymermembran kontrolliert wird.

7.1.1 Ausblick

Obwohl gezeigt wurde, dass die Propranolol HCl Freisetzung aus Pellets effizient mit Hilfe von PVAc/PVA-PEG Polymermischungen kontrolliert werden kann, ist eine der größten mit diesem Coating verbundenen Herausforderungen, Langzeitstabilität zu gewährleisten. In den meisten Fällen nahm die Wirkstofffreigabe nach der Lagerung ab. Daher sollten in Zukunft umfassende Untersuchungen durchgeführt werden, die den Einfluss der Curingbedingungen auf die Lagerstabilität berücksichtigen. Verschiedene Publikationen berichten [94, 95], dass nicht nur die Curingdauer und -temperatur sondern auch die relative Feuchtigkeit während des Temperns die finale Polymerkoaleszenz beeinflussen können. Außerdem sollte die Mikrostruktur der PVAc/PVA-PEG Polymerfilme nach dem Curing und der Lagerung detaillierter untersucht werden, zum Beispiel mittels Confokaler Raman Spektroskopie (CRM) oder Nuklear Magnetischer Resonanz (NMR) Spektroskopie.

Eine weitere interessante Frage ist, warum das Überziehen von Pellets mit verschiedenen Kollicoat® SR 30D Chargen voneinander abweichende Freisetzungsprofile zur Folge hat. Die Bildung von Essigsäure in der zur direkten Verarbeitung vorgesehenen Polymerdispersion könnte eine Erklärung dafür sein und sollte eingehender mittels Hochleistungsflüssigkeitschromatographie (HPLC) analysiert werden. Dabei sollten verschiedene Lagerungsbedingungen des untersuchten Material mit betrachtet werden.

Schließlich war die Propranolol HCl Freisetzung aus PVAc/PVA-PEG gecoateten Pellets in simuliertem Magensaft pH 1.2 oder Phosphat-Citrat-Puffer pH 6.8 unterschiedlich. Diese Beobachtung wurde durch den Zusatz osmotisch aktiver Stoffe zusätzlich verstärkt. Daher stellt eine tiefgehende Analyse des Einflusses von pH und verschiedenen Ionen auf PVAc/PVA-PEG Polymermischungen einen interessanten Ansatz dar, Darreichungsformen mit membrankontrollierter Wirkstofffreisetzung zu erhalten, die einheitliche Arzneistofffreisetzungsprofile bereitstellen.

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Erklärung an Eides statt

Hiermit erkläre ich, die vorliegende Dissertation

Development and investigation of Propranolol HCl pellets coated with poly(vinyl acetate) based polymer films for sustained release applications

selbständig und ohne fremde Hilfe verfasst und keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt zu haben. Die den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen sind als solche kenntlich gemacht. Die Ergebnisse der vorliegenden Arbeit habe ich, unter Anleitung von Herrn Prof. Dr. Karsten Mäder selbständig erarbeitet bzw. im Rahmen der angegebenen Kooperationen erhalten.

Eggenstein-Lepoldshafen, Februar 2012

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