POLYMERIC COATINGS FOR SOLID DOSAGE FORMS: CHARACTERIZATION AND OPTIMIZATION

Susanne Muschert

UNIVERSITE DE LILLE II
FACULTE DES SCIENCES PHARMACEUTIQUES ET BIOLOGIQUES

POLYMERIC COATINGS FOR SOLID DOSAGE FORMS : CHARACTERIZATION AND OPTIMIZATION

--

ENROBAGES POLYMÉRIQUES POUR DES FORMES ORALES SOLIDES : CARACTÉRISATION ET OPTIMISATION

THÈSE

pour l'obtention du

DOCTORAT D'UNIVERSITÉ

Susanne Muschert

Lille 2008

Premier rapporteur : Pr. K. Amighi

Deuxième rapporteur : Pr. M.-C. Venier-Julienne

Date de la soutenance : 04. 12. 2008

inoubliée : Anaïs, notre soleil du Nord

Remerciements

Je remercie le Pr. Karim Amighi et le Pr. Marie-Claire Venier-Julienne d’avoir accepté d’être les rapporteurs de ce travail.

Merci au Dr. Bruno Leclercq et au Dr. Brian Carlin d’avoir toujours eu un oeil critique et constructif sur mes travaux et surtout de m’avoir donné l’inspiration pour ce projet.

J'offre mes sincères remerciements au Dr. Florence Siepmann pour l'aide qu'elle m'a apportée au cours de cette recherche. Son intérêt et ses précieux conseils m'ont été d'un grand profit.

Je remercie également le personnel du laboratoire « Pharmacotechnie industrielle » et de la Faculté de Pharmacie de l’Université Lille 2 pour leur accueil. Merci aussi aux autres doctorants et stagiaires pour leurs conseils et réponses utiles.

Je désire remercier le Pr. Juergen Siepmann, mon directeur de thèse, pour l'aide et les encouragements prodigués tout au long de ce travail de recherche.

Je veux exprimer ma gratitude à Ruth Muschert, la meilleure secrétaire privée, guide et mère que je puisse imaginer.

Merci à mon grand-père et mon frère pour leur soutien et leur énorme patience.

Spécialement je veux remercier Steffi, Hugues, Muriel et Yvonne pour être plus que des collègues et pour l'atmosphère détendu au laboratoire qu'ils savent créer et pour leur confiance.

Un grand merci à Cécile, Florian, Vincent, Emma, Yannick, Clémentine et tous les autres membres de la « Dream Ch'team » pour m'avoir bien accueillie après mon arrivée en France et de m'avoir fait découvrir plein des choses ici en France, que ce soit sois des activités sportives, des endroits exceptionnellement beaux ou la finesse de la langue française. J'ai surtout trouvé des très bons amis en eux et je leur suis infiniment reconnaissante de m'avoir soutenu pendant les moments très durs et pour beaucoup d'heures inoubliables.

Le dernier et non le moindre des mercis, je le dis aux amis qui m'accueillent avec une telle chaleur à chaque retour au pays : Steffi & René, Melanie & Sebastian, Christian & Uta, Markus, Kirsten et tous les autres.

TABLE OF CONTENTS

1. INTRODUCTION

In order to provide optimal drug concentrations at the site of action and, thus, improved therapeutic effects, the release of the drug out of its dosage form can be time controlled. This can be achieved via matrix systems, in which the drug is embedded within an excipient matrix and drug release is controlled by diffusion through the matrix, swelling of the matrix forming excipient and/or erosion [1]. On the other hand a drug containing core can be surrounded by a membrane barrier which controls the release rate. This is particularly important when potent drugs with a small therapeutic window are used in order to ensure drug levels below the minimum toxic and above minimum effective concentration. Furthermore, the patient's compliance can be improved by reducing the number of drug administrations [2].

1.1. Multiparticulate controlled oral drug delivery

During the last two decades multiparticulates, comprising pellets, minitablets and granules significantly gained in importance in the pharmaceutical industry [3]. These multi-unit dosage forms offer major therapeutic advantages over single units, in dispersing freely over the gastrointestinal tract after administration and maximizing absorption [4]. Thus, side effects can be reduced and the therapy becomes less affected by patient variability [5]. *Pellets* as a spherical multiparticulate dosage form, offer many advantages. Neutral cores (consisting of different types of material, such as sugar, microcrystalline cellulose, starch and many more) can be loaded with a broad variety of drugs by layering or preparation of matrix spheres exhibiting various sizes and drug loadings. Pellets can be coated to allow for controlled release, compressed into tablets or simply filled into hard gelatine capsules to facilitate oral administration. Due to their spherical form pellets show better flow behavior for filling processes [6] and the coating layer which might be applied can be expected to be of higher uniformity compared to cylindrical minitablets due to the absence of edges. To control the drug release from pellets, coatings can be applied to form a film barrier around drug

loaded cores. A broad variety of polymers can be used for pellet coating, including acrylates [7] and ethylcellulose. Due to additional functional groups, enteric film coatings with slower release at low pH and triggered release at higher pH can be obtained [8].

1.2. Coated pellets for controlled drug release

1.2.1. Drug release mechanisms

Drug release from coated pellets is affected by several factors such as the thickness of the polymeric film coating [9], physicochemical properties of the starter core material [10], solubility of the drug and the polymer [11]. Upon exposure to the release media, water penetrates into the system and depending on the drug loading and the drug's solubility, the latter is dissolved (completely or partially) [12, 13]. The type of polymer and type of core material can have a major influence on the velocity of water diffusion into the system. The overall drug release rate controlling mechanisms can be more or less complex [14].

Diffusion is often of major importance [15]. This can include drug diffusion through a continuous, flexible polymer film surrounding the drug loaded core [16]. Upon water penetration into the pellet core, the drug is dissolved. Due to the concentration gradient "inside of the pellet (c_i) versus outside of the pellet", drug is released. In the case of perfect sink conditions the amount of drug released (dM) within a certain time period (dt) can be calculated as follows (according to Fick's law of diffusion):

$$\frac{dM}{dt} = D_m \cdot A \cdot K \cdot \frac{c_i}{d} \qquad (1.1)$$

Where D_m is the apparent diffusion coefficient of the drug in the polymeric film, A the surface available for diffusion, K the partition coefficient of the drug (aqueous phase – polymeric phase), and d denotes the thickness of the film coating [17, 18].

In the case of pseudo-steady-state conditions (initial excess of drug leading to saturated drug concentration within the pellet and perfect sink conditions outside), zero-order release kinetics

result. In the case of a non-constant active source (initial concentration in the pellet < saturation concentration) and perfect sink conditions, first-order release kinetics result [1].

In addition, drug release through **water filled channels** might be of importance [19]. This is the case if the film coatings contain pores or cracks, which are either initially present or created due to the leaching of water soluble compounds into the bulk fluid or due to the hydrostatic pressure generated within the system upon water penetration into the devices. Thus, blending two types of polymers [17] or adding salts or other soluble molecules [20] to insoluble polymers might be used to alter drug release. In the case of perfect sink conditions drug release from the pellets into the bulk fluid can be described as follows:

$$\frac{dM}{dt} = D_p \cdot A \cdot \frac{\varepsilon}{\tau} \cdot \frac{c_i}{d} \qquad (1.2)$$

Where D_p is the diffusion coefficient of the drug in the aqueous phase present in the channels and pores, ε the volume fraction of the pores, τ the tortuosity of the channels [17]. The volume fraction and the form of the in situ formed pores needs to be known [21].

Furthermore, **osmotic effects** might contribute to the control of drug release from coated pellets, a well known process for devices containing an osmotic active core material (for instance sugar cores) surrounded by a semipermeable polymer wall. In these cases, an osmotic gradient is created across the polymer wall [22]. Osmotically driven release depends on the porosity of the polymeric membrane and the osmotic pressure of the sugar core and the drug [14]. Water imbibes into the system as soon as the coated pellet gets into contact with the aqueous environment and the drug is pushed out via pores. The water influx depends on the properties and composition of the polymeric barrier and can be quantified as follws:

$$\frac{dV}{dt} = \frac{A\theta\Delta\pi}{l} \qquad (1.3)$$

Where dV/dt denotes the water flow, A the membrane surface area, l the membrane thickness, θ the permeability of the polymeric membrane, and Δπ the difference in osmotic pressure (neglecting the counteracting hydrostatic pressure) [22].

1.2.2. Coating process

Pellets can be coated using conventional sugar coating machines, commonly used for coating dosage forms with sugar syrups. The pellets are tumbling in a rotating kettle and the coating dispersion is poured or sprayed with a spray gun onto the moving beads. Due to the non-continuous application of the polymeric formulation, often insufficient air flow and the existence of dead-zones (in which no movement of the pellets occurs), inhomogeneous film coatings with wet, swollen cores might be obtained. The fluid bed coating process, where particles are fluidized and the coating formulation sprayed onto the pellets (which are in permanent movement due to a strong air flow), assures an efficient drying of the devices [23]. Small droplets and a low viscosity of the sprayed formulation ensure a homogeneous film coating thickness. Several techniques can be used in fluidized bed coatings: **Batch fluid bed coating**, where the coating suspension is sprayed via the *top spray* method with turbulent, random movement of the pellets [24]. The **Wurster process**, where the spray nozzle is fitted in the base plate resulting in a spray pattern that is concurrent with the air feed. As demonstrated in Figure 1.1, by using a Wurster cylinder and a base plate with different perforations, the particles to be coated are accelerated inside the Wurster tube and fed through the spray cone concurrently. As the particles continue traveling upwards, they dry and fall outside the Wurster tube back towards the base plate. They are guided from the outside back to the inside of the tube where they are once again accelerated by the airflow. This allows preparing very homogeneous films [25]. Due to the fact that the nozzle is immersed within the air flow, droplets of the coating formulation travel only short distances before striking the pellet surface, so films will be applied more evenly [24]. In the **tangential spray method** the

spray nozzle is arranged tangentially to the rotor disc and spraying into the same direction as the moving particles. Very thick film layers can be applied by means of the rotor method [25].

All processes have in common essential coating steps: (i) the formation of suitable droplets from the coating formulation, (ii) contact and adhesion of the droplets onto the particles' surface and subsequently (iii) spreading and coalescence [26].

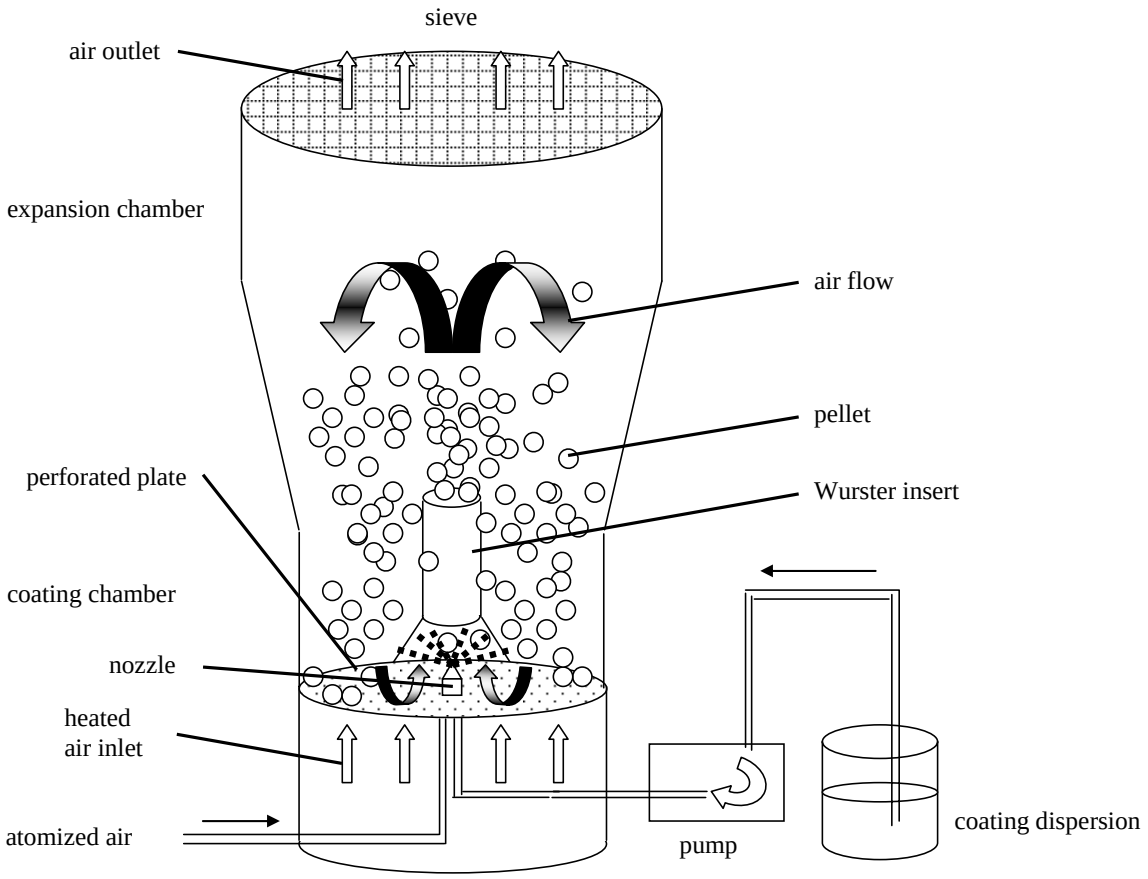


Figure 1.1: Schematic presentation of a fluidized bed coater with Wurster insert.

Polymeric film coatings can be administered from organic polymer solutions or aqueous dispersions. Due to environmental and production safety, some important disadvantages of organic solvents, aqueous dispersions are generally preferred.

Important process parameters for applications of *aqueous* polymer formulations for manufacturing controlled release dosage forms by using the Wurster process include:

- The solids content of the dispersion, as high solid contents can lead to strong variations with respect to the reproducibility of a coating process and the homogeneity of the film coating [26].
- The product temperature, which can be adjusted by varying the inlet air temperature, has a direct effect on film formation due to polymer particle coalescence [27]. Generally, the temperature of the fluidized bed should be set to 10 °C to 20 °C above the minimum film formation temperature of the polymer dispersion [28, 29].
- The air flow setting, which is of importance to assure sufficient movement of the beads.
- The spray rate, because too slow application of the coating formulations leads to porous films due to partial drying on the pellets' surface and film formation comparable to spray drying of the polymeric dispersion. On the other hand, too high spraying rates lead to sticking and agglomeration of the pellets.
- The atomization air pressure affects the droplet size [30] of the coating formulation and has an impact on the particle temperature distribution [31].

1.2.3. Film forming mechanisms

The film formation mechanisms essentially depend on the type of coating formulation (aqueous versus organic) [32]. If **organic polymer solutions** are used, the macromolecules are dissolved, which can lead to high viscosity of the solution depending on the molecular weight and the affinity of the polymer to the solvent. During the coating process the solvent evaporates and a highly viscous gel is formed around the pellet core (Figure 1.2). Upon complete solvent evaporation, a continuous polymeric film is formed [32].

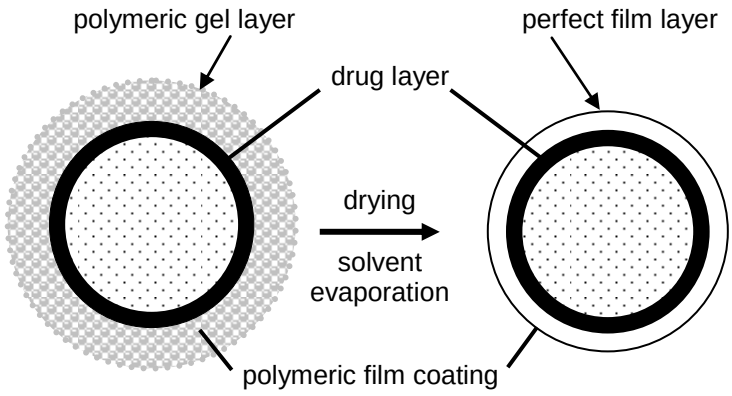


Figure 1.2: Schematic presentation of the film forming mechanism from organic polymer solutions.

Film formation from **aqueous dispersions** is more complex [3]. Several theories to explain the formation of a continuous polymeric film from discrete polymer particles have been presented [33-36]. Upon water evaporation during the coating process the polymer particles get into contact with each other and form a layer of closed packed polymer spheres with water filled cavities [37]. Polymer spheres are pulled closer together as water further evaporates due to surface tension (water-air interfacial tension) [24]. Finally, particle coalescence occurs when the capillary forces are sufficiently strong (Figure 1.3) [38].

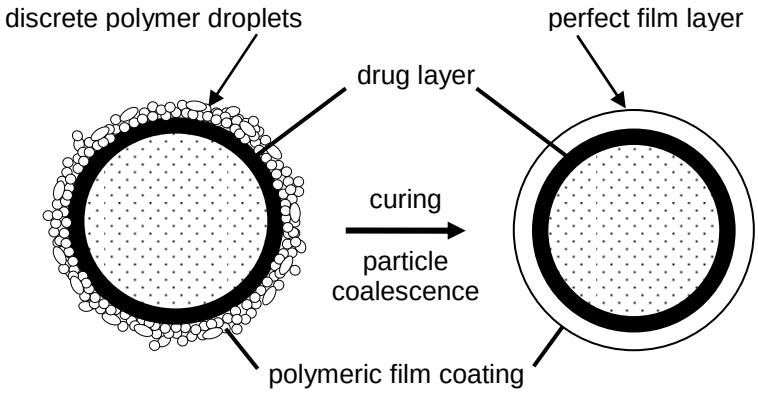


Figure 1.3: Schematic presentation of the film forming mechanism from aqueous polymer dispersions.

To assure sufficient softness of the discrete polymer particles the coating process generally needs to be performed at elevated temperatures. The softening is related to the glass transition temperature of the polymer (section 1.3.1.) expressed by a sharp increase in polymer chain mobility [39].

Further gradual coalescence upon storage might occur [35], due to incomplete film formation during the coating process. In order to avoid this phenomenon, a curing step is recommended [40-42].

1.3. Ethylcellulose based coatings

Ethylcellulose is a hydrophobic coating material often used [43] for controlled release, taste masking and moisture barrier applications [42]. It is generally regarded as nontoxic, nonallergenic and nonirritant and widely used in oral drug delivery devices as polymeric film former. It is insoluble throughout the gastro-intestinal tract [44], and due to its neutral side-chains assures pH-independent drug release [32].

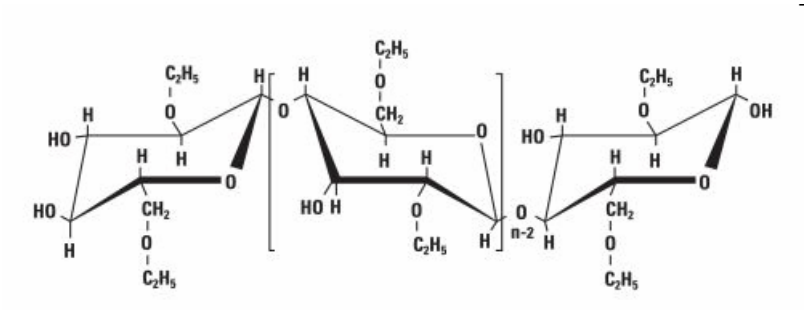


Figure 1.4: Chemical structure of ethylcellulose.

Ethylcellulose coatings can be applied from organic solutions of methanol, ethanol, isopropanol, acetone and dichloromethane or from aqueous dispersions. Polymeric coatings based on ethylcellulose, applied from organic solutions do not require a curing step and show pH *in*dependent drug release behavior [45]. However, due to the above described potential

concerns, aqueous dispersions might be preferred. In this case care needs to be taken to provide long term stability [38, 46, 47].

1.3.1. Aquacoat ECD

Aquacoat ECD is a commercially available ethylcellulose dispersion with 30 % solids content (27 % ethylcellulose) with polymer droplets of around 200 nm and a viscosity of 150 cP. Further additives to stabilize the pseudolatex suspension are sodium lauryl sulfate (SLS) (4 % w/w of total solids), an anionic surfactant, and cetyl alcohol (9 % w/w of total solids) [42].

The glass transition temperature (T_g) of ethylcellulose is within the range of 125-130 °C [48], Above this temperature the polymer is in a rubbery state, while below the T_g the polymeric chains are immobilized for the most part forming a glassy state of the polymer.

Aquacoat ECD is a pseudolatex produced by the direct emulsification – solvent evaporation method [28, 38, 42], where the polymer solution (non water miscible, volatile solvent) is emulsified in water, this emulsion being stabilized by surfactants. Upon evaporation of the organic compound, polymer particles are formed in the aqueous phase.

1.3.2. Plasticizers for aqueous ethylcellulose dispersions

In order to decrease the T_g of ethylcellulose, plasticizers can be added. These are generally high-boiling organic compounds, which reduce the cohesive intermolecular forces of the polymer chains, thus, leading to higher flexibility of the polymeric materials [28]. For ethylcellulose aqueous dispersion the T_g can be lowered for example to 32 °C or 36 °C by adding 30 % w/w triethyl citrate (TEC) or dibutyl sebacate (DBS), respectively [49]. The addition of plasticizers to Aquacoat ECD is necessary to allow for appropriate film formation (section 1.2.3.).

The choice of a plasticizer depends on several aspects. Generally, the plasticizer should show no or little tendency of migration and be compatible with the polymer [50]. Incompatibilities might lead to poor film formation and instable drug release rates upon storage [51]. When adding a plasticizer to an aqueous dispersion it should be taken into consideration that the dissolution of the plasticizer in water, the convection through the aqueous phase and finally the diffusion into the discrete polymeric particles is a time dependent process [38, 52]. Not only the chemical properties [28], but also the amount of added plasticizer has an impact on film formation from the (pseudo)latexes [53]. Incomplete film formation has been reported for coatings based on aqueous polymeric dispersions [35, 53] expressed by release rates that decrease upon storage due to further particle coalescence into a continuous film [54].

1.3.3. Polymer blends with Aquacoat ECD

The drug release from ethylcellulose coated pellets might be very low [55]. In order to accelerate drug release, hydroxypropyl methylcellulose (HPMC) has been proposed to be added to aqueous dispersions of ethylcellulose [56-58]. But it was reported that adding HPMC to an Aquacoat ECD dispersion can lead to physical instability of the coating dispersion [59]. For instance, the addition of 2-20 % [44] of HPMC was reported to result in flocculation [60]. This can lead to inhomogeneous film formation [61] with ethylcellulose rich areas and HPMC rich areas [62]. Furthermore, ethylcellulose:HPMC based film coatings might show instability upon storage expressed by decreasing drug release rates [63].

Alternative hydrophilic additives with increased ethylcellulose compatibility have been proposed [44, 64]. Carrageenan for example which is used in the food industry, is a highly sulphated type of carrageenan (Figure 1.5) that does not gel and shows good solubility in hot and cold water.

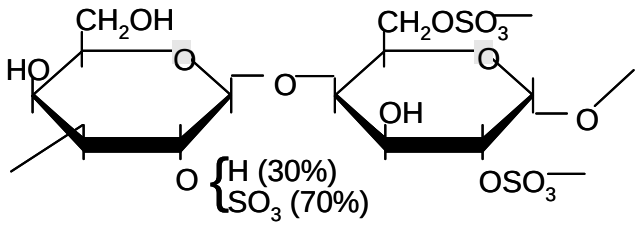
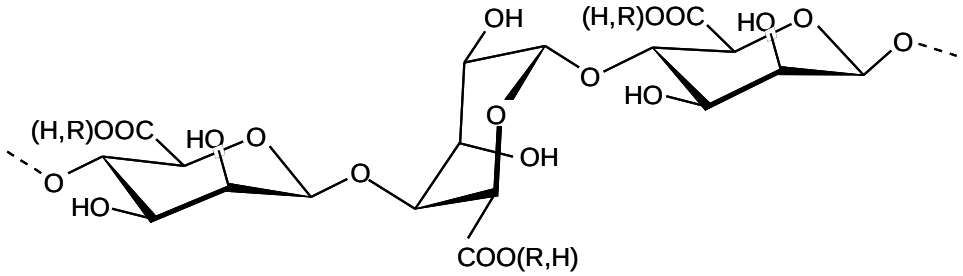


Figure 1.5: Chemical structure of λ-Carrageenan.

Another hydrophilic polymer used in food industries as stabilizer, thickener, emulsifier is propylene glycol alginate (Figure 1.6) a partially 1,2-propandiol esterified alginate. It is soluble in water yielding a viscous, colloidal solution.



(PG)M (PG)G (PG)M

(PG)M = (Propylene glycol) Mannuronate

(PG)G = (Propylene glycol) Guluronate

R = -CH 2 -CH(OH)-CH 3 (40-90 %)

H = -H (10-60 %)

Figure 1.6: Chemical structure of PG alginate.

Poly(vinyl-alcohol)-poly(ethylene glycol) (PVA-PEG) graft copolymer is a hydrophilic polymer very soluble in water. It is mainly used for the production of instant release coatings for tablets [65].

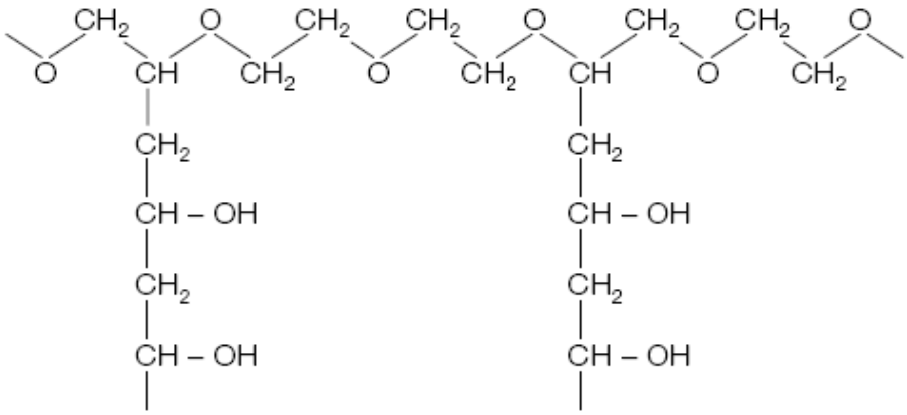


Figure 1.7: Chemical structure of PVA-PEG graft copolymer.

1.4. Process and formulation parameters affecting drug release from coated pellets

Several factors can significantly affect the resulting drug release kinetics from polymer coated pellets.

1.4.1. Curing conditions

A major process parameter for aqueous coated pellets is the curing of the devices after coating. This step should be performed at a temperature above the glass transition temperature, to assure sufficient polymer chain mobility. During curing, remaining discrete polymer particles are intended to merge, resulting in long term stable and smooth polymeric films [66]. The curing process can be performed in an oven, where samples are stored at about 10 °C above the MFT [55] or in the fluidized bed coater immediately after the coating process. But excessive curing temperatures can cause agglomeration and tackiness of the coated beads.

1.4.2. Type of starter core

The nature of the starter core material can significantly affect the resulting drug release kinetics [67, 68]. A very hygroscopic core material, e.g. sugar can increase the water influx

into the coated system. The continuous water penetration into the pellets is likely to generate a monotonically increasing hydrostatic pressure within the pellets. This can lead to steadily increasing device dimensions until a critical threshold value is reached at which crack formation is induced [10]. In contrast, inert core materials such as microcrystalline cellulose are considered as osmotically neutral and do not induce significant water penetration into the pellets upon contact with aqueous media.

1.4.3. Type of drug

The physicochemical properties of the drug present in the formulation can have a major impact on the release behavior [69]. The drug's water solubility is of importance, since only the dissolved drug can diffuse through the intact polymeric film or through water filled pores [70]. For this reason highly water-soluble drugs are generally released more rapidly than poorly water-soluble compounds [69]. But not only the drug's solubility in the release media, also their solubility in the polymeric film coating can be of fundamental importance for the release behavior [28].

1.5. Research objectives

Due to the complexity of the underlying drug release mechanisms in ethylcellulose coated dosage forms, the optimization of this type of advanced drug delivery systems is challenging. Generally, time- and cost-intensive series of trial and error experiments are required to adjust desired release profiles. Despite of their steadily increasing practical importance, the respective dosage forms are often treated as black-boxes.

The major objective of this work was to better understand the underlying drug release mechanisms from aqueous ethylcellulose coated pellets and to provide easy tools to allow for the optimization of the resulting drug release kinetics and to increase the long term stability of the systems. Specific objectives included:

- The identification of a second compatible, hydrophilic, polymeric compound to adjust drug release profiles and to improve film formation during coating and curing.
- The adjustment of drug release profiles from ethylcellulose based film coating to achieve suitable drug release profiles from coated pellets containing different types of drugs and core materials.
- The elucidation of the drug release mechanisms from pellets coated with aqueous ethylcellulose dispersion blended with a second hydrophilic polymeric compound.
- The stabilization of the film coatings even upon open long term storage under stress conditions.

1.6. References

1. Siepmann, J., *Neue Arzneiformen - Seminar*, F.U. Berlin, Editor. 2002: Berlin.
2. Rowland, M. and T.N. Tozer, *Clinical Pharmacokinetics: Concepts and Applications*. 3 ed, ed. M. Rowland and T.N. Tozer. 1995, Baltimore: Lippincott Williams & Wilkins. 601.
3. Fukumori, Y., *Coating of Multiparticulates Using Polymeric dispersions*, in *Multiparticulate Oral Drug Delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 79-111.
4. Hardy, J.G., S.S. Davis, and C.G. Wilson, *Drug delivery to the gastrointestinal tract*. 1989, Chichester: Ellis Horwood
5. Ghebre-Sellassie, I., *Multiparticulate oral drug delivery*. 1997, New York: Marcel Dekker.
6. Lightfood, D.K., *Multiparticulate Encapsulation equipment and process*, in *Multiparticulate Oral Drug Delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 159-180.
7. Lehmann, K., *Chemistry and application properties of polymethacrylate coating systems*, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York. p. 101-176.
8. Stafford, J.W., *Enteric film coating using completely aqueous dissolved hydroxypropyl methyl cellulose phtalate spray solutions.* Drug Dev. Ind. Pharm., 1982. **8**(4): p. 513-530.
9. Munday, D.L. and A.R. Fassihi, *Controlled release delivery: Effect of coating composition on release characteristics of mini-tablets.* International Journal of Pharmaceutics, 1989. **52**(2): p. 109-114.

10. Lecomte, F., et al., *pH-Sensitive Polymer Blends used as Coating Materials to Control Drug Release from Spherical Beads: Importance of the Type of Core.* Biomacromolecules, 2005. **6**(4): p. 2074-2083.
11. Frohoff-Hülsmann, M.A., B.C. Lippold, and J.W. McGinity, *Aqueous ethyl cellulose dispersion containing plasticizers of different water solubility and hydroxypropyl methyl-cellulose as coating material for diffusion pellets II: properties of sprayed films.* Eur. J. Pharm. Biopharm., 1999. **48**(1): p. 67-75.
12. Strübing, S., H. Metz, and K. Mäder, *Mechanistic analysis of drug release from tablets with membrane controlled drug delivery.* European Journal of Pharmaceutics and Biopharmaceutics, 2007. **66**(1): p. 113-119.
13. Ensslin, S., et al., *New insight into modified release pellets - Internal structure and drug release mechanism.* Journal of Controlled Release, 2008. **128**(2): p. 149-156.
14. Ozturk, A.G., et al., *Mechanism of release from pellets coated with an ethylcellulose-based film.* Journal of Controlled Release, 1990. **14**(3): p. 203-213.
15. Fan, L.T. and S.K. Singh, *Controlled Release: A Quantitative Treatment.* 1989, Berlin: Springer-Verlag.
16. Dressman, J.B., et al., *Mechanisms of release from coated pellets,* in *Multiparticulate Oral Drug delivery,* I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 285-306.
17. Lecomte, F., *pH-sensitive polymer blends used as coating materials in controlled drug delivery systems*. 2004, Freie Universität Berlin: Berlin.
18. Siepmann, J. *Understanding drug release mechanisms*. in *Coating Workshop*. 2008. Lille, France.
19. Hoffman, A., M. Donbrow, and S. Benita, *Direct measurements on individual microcapsule dissolution as a tool for determination of release mechanism.* J Pharm Pharmacol. , 1986. **38**(10): p. 764-766.

20. Rohera, B.D. and N.H. Parikh, *Influence of type and level of water-soluble additives on drug release and surface and mechanical properties of Surelease films.* Pharm Dev Technol. , 2002. **7**(4): p. 421-432.

21. Vidmar, V., I. Jalsenjak, and T. Kondo, *Volume of waterfilled pores in the ethyl cellulose membrane and the permeability of microcapsules.* J. Pharm. Pharmacol, 1982. **34** (7): p. 411-414.

22. Schmidt, C., *Multiparticulate Oral Drug Delivery Systems*. 2000, Freie Universität Berlin: Berlin.

23. Bauer, K.H., K.-H. Froemming, and C. Fuehrer, *Lehrbuch der Pharmazeutischen Technologie*. 7 ed. 2002, Stuttgart: Wissenschaftliche Verlagsgesellschaft.

24. Wheatley, T.A. and C.R. Steuernagel, *Latex emulsion for controlled drug delivery*, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York.

25. Glatt. *Fluid Bed Coating*. Technologies 2004-2008 [cited; Available from: http://www.glatt.com/e/01_technologien/01_04_08.htm.

26. Naelapää, K., et al. *Dealing with complex interactions in experimental data*. in *2nd Pharmaceutical Solid State Research Cluster (PSSRC) Symposium*. 2008. Gent, Belgium.

27. Naelapää, K., et al., *Coating of potassium chloride with ethylcellulose aqueous dispersion--Effects of processing parameters on film formation and film properties.* European Journal of Pharmaceutical Sciences, 2007. **32**(1, Supplement 1): p. S20-S20.

28. Bodmeier, R., X. Guo, and O. Paeratakul, *Process and formulation factors affecting the drug release from pellets coated with the ethylcellulose-pseudolatex Aquacoat*, in *Aqueous polymeric coatings for pharmaceutical dosage forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York.

29. Schultz, R.K. and R.R. Myers, *Acrylic latex film formation in the critical temperature range.* Journal of Applied Polymer Science, 1964. **8**(2): p. 755 - 764.

30. Wagner, K., *Aqueous ppolymer dispersions for extended release dosage forms*. 2002, Freie Universitaet Berlin: Berlin.

31. Ronsse, F., J.G. Pieters, and K. Dewettinck, *Modelling heat and mass transfer in batch, top-spray fluidised bed coating processes.* Powder Technology, 2008. **in press**.

32. Lehmann, K., *Coating of multiparticulates using organic solutions - Formulation and process considerations*, in *Multiparticulate drug delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 51-78.

33. Dillon, R.E., L.A. Matheson, and E.B. Bradford, *Sintering of synthetic latex particles.* Journal of Colloid Science, 1951. **6**(2): p. 108-117.

34. Brown, G., *Formation of films from polymer dispersions.* J. Polymer Sci., 1956. **22**(102): p. 423-434.

35. Vanderhoff, J.W., et al., *Theoretical consideration of the interfacial forces involved in the coalescence of latex particles.* Macromol. Chem. , 1966. **1**: p. 361-397.

36. Nagakami, H., et al., *Application of aqueous suspensions and latex dispersions of water-insoluble polymers for tablets and granule coatings.* . Chem. Pharm. Bull., 1991. **39** p. 1837-1842.

37. Onions, A., *Films from water-based colloidal dispersions.* Manuf. Chem., 1986. **57**(4): p. 66-67.

38. Paeratakul, O., *Pharmaceutical applications of aqueous colloidal polymer dispersions.* 1993, University of Texas: Austin.

39. Okhamafe, A.O. and P. York, *Studies of interaction phenomena in aqueous-based film coatings containing soluble additives using thermal analysis techniques.* J. Pharm. Sci., 1988. **77**(5): p. 438-443.

40. Harris, M.R. and I. Ghebre-Sellassie, *Aqueous polymeric coating for modified release oral dosage forms*, in *Aqueous polymeric film coatings for pharmaceutical dosage forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York.

41. Bodmeier, R. and O. Paeratakul, *Process and formulation variables affecting the drug release from chlorpheniramine maleate-loaded beads coated with commercial and self-prepared aqueous ethyl cellulose pseudolatexes.* International Journal of Pharmaceutics, 1991. **70**(1-2): p. 59-68.

42. FMC, *Aquacoat ECD sales brochure*. 2008, FMC Biopolymer.

43. Wallace, J.W., *Cellulose derivatives and natural products utilized in pharmaceutics*, in *Encyclopedia of Pharmaceutical Technology*, J.S.a.J.C. Boylan, Editor. 1990, Marcel Dekker: New York. p. 319-339.

44. Siepmann, F., et al., *How to adjust desired drug release patterns from ethylcellulose-coated dosage forms.* Journal of Controlled Release, 2007. **119**(2): p. 182-189.

45. Wesseling, M. and R. Bodmeier, *Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat(R), or an organic ethylcellulose solution.* European Journal of Pharmaceutics and Biopharmaceutics, 1999. **47**(1): p. 33-38.

46. Buscall, R. and R.H. Ottewill, *The stability of polymer latices*, in *Polymer Colloids*, T.C. R. Buscall, J.F. Stageman, Editor. 1985, Elsevier: London.

47. Zimehl, R. and G. Lagaly, *Coagulation of latex dispersions in the presence of some organic compounds.* Colloids and Surfaces, 1987. **22**(2): p. 215-224.

48. Keshikawa, T. and H. Nakagami, *Film formation with coating systems of aqueous susoensions and latex dispersions of ethylcellulose.* Chemical Pharmaceutical Bulletin, 1994. **42**(3): p. 656-662.

49. Morflex, *Influence of plasticizers on the dissolution and physical properties of ethylcellulose films and coated beads*, in *Pharmaceutical Coatings Bulletin*. 1995, Morflex Inc.

50. Pearnchob, N., *Evaluation of new film coating processes and materials*. 2002, Freie Universitaet Berlin: Berlin.

51. Kucera, S., *Physical and chemical properties of acrylic polymers influencing physical aging*. 2007, University of Texas: Austin.

52. Siepmann, J., *Polymeric controlled drug delivery systems : Elucidation of transport mechanisms and optimization of release patterns*. 1999, Freie Universitaet Berlin: Berlin.

53. Amighi, K. and A.J. Moes, *Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit RS 30D film-coated sustained-release theophylline pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42**(1): p. 29-35.

54. Wu, C. and J.W. McGinity, *Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer.* European Journal of Pharmaceutics and Biopharmaceutics, 2000. **50**(2): p. 277-284.

55. Lippold, B.r.H., B.K. Sutter, and B.C. Lippold, *Parameters controlling drug release from pellets coated with aqueous ethyl cellulose dispersion.* International Journal of Pharmaceutics, 1989. **54**(1): p. 15-25.

56. Gunder, W., B.H. Lippold, and B.C. Lippold, *Release of drugs from ethyl cellulose microcapsules (diffusion pellets) with pore formers and pore fusion.* European Journal of Pharmaceutical Sciences, 1995. **3**(4): p. 203-214.

57. Tang, L., et al., *Drug Release from Film-Coated Chlorpheniramine Maleate Nonpareil Beads: Effect of Water-Soluble Polymer, Coating Level, and Soluble Core Material.* Pharmaceutical Development and Technology, 2000. **5**(3): p. 383 - 390.

58. Frohoff-Hülsmann., M.A., A. Schmitz, and B.C. Lippold, *Aqueous ethyl cellulose dispersions containing plasticizers of different water solubility and hydroxypropyl*

methylcellulose as coating material for diffusion pellets I. Drug release rates from coated pellets. Int. J. Pharm., 1999. **177**(1): p. 69-82.

59. Wong, D. and R. Bodmeier, *The impact of the use of flocculated colloidal dispersions on the drug release from drug-containing films and coated tablets.* Pharm. Res., 1994. **11**: p. S-185.
60. Wong, D. and R. Bodmeier, *Flocculation of an aqueous colloidal ethyl cellulose dispersion (Aquacoat) with a water-soluble polymer, hydroxypropyl methyl cellulose.* Eur. J. Pharm. Biopharm., 1996. **42**(1): p. 12-15.
61. Sakellariou, P., R.C. Rowe, and E.F.T. White, *Polymer/polymer interaction in blends of ethyl cellulose with both cellulose derivatives and polyethylene glycol 6000.* International Journal of Pharmaceutics, 1986. **34**(1-2): p. 93-103.
62. Sakellariou, P. and R.C. Rowe, *The morphology of blends of ethylcellulose with hydroxypropyl methylcellulose as used in film coating.* International Journal of Pharmaceutics, 1995. **125**(2): p. 289-296.
63. Hoffart, V., et al., *Storage stability of pellets coated with the aqueous ethylcellulosee dispersion Aquacoat® ECD at elevated temperature and humidity,* in *Annual Meeting and Exposition, American Association of Pharmaceutical Scientists*. 2005: Nashville, USA.
64. Chan, L.W., K.T. Ong, and P.W.S. Heng, *Novel Film Modifiers to Alter the Physical Properties of Composite Ethylcellulose Films.* Pharmaceutical Research, 2005. **22**(3): p. 476-489.
65. BASF, *Kollicoat IR,* in *Technical Information*. 2001, BASF Aktiengesellschaft.
66. Lippold, B.C. and R. Monells Pages, *Film formation, reproducibility of production and curing with respect to release stability of functional coatings from aqueous polymer dispersions.* Pharmazie, 2001, Pages 5-17. **56**(1): p. 5-17.

67. Porter, S.C., *Controlled-Release Film Coatings Based on Ethylcellulose.* Drug Development and Industrial Pharmacy, 1989. **15**(10): p. 1495 - 1521.

68. Ragnarsson, G., et al., *In vitro release characteristics of a membrane-coated pellet formulation -- influence of drug solubility and particle size.* International Journal of Pharmaceutics, 1992. **79**(1-3): p. 223-232.

69. Sadeghi, F., J.L. Ford, and A. Rajabi-Siahboomi, *The influence of drug type on the release profiles from Surelease-coated pellets.* International Journal of Pharmaceutics, 2003. **254**(2): p. 123-135.

70. Ghebre-Sellassie, I., et al., *Characterization of a new water-based coating for modified-release preparations.* Pharm. Technol., 1988. **12**: p. 96-106.

2. PARTIE BIBLIOGRAPHIQUE

Afin d'atteindre des concentrations optimales du principe actif au site d'action et d'améliorer les effets thérapeutiques, il est possible de contrôler dans le temps la libération du principe actif hors de sa forme galénique. Ceci peut être obtenu via des systèmes matriciels, dans lesquels le principe actif est piégé dans réseau de chaînes de l'agent matriciel. La libération du principe actif est alors contrôlée par diffusion à travers la matrice et/ou gonflement et/ou érosion de cette dernière [1]. On peut également avoir recours à des systèmes réservoirs dans lesquels un noyau renfermant le principe actif est recouvert d'une membrane qui contrôle la vitesse de libération du principe actif. Ceci est particulièrement important dans le cas de principes actifs puissants à fenêtre thérapeutique étroite afin d'assurer une concentration en principe actif inférieure à la concentration minimale toxique et supérieure à la concentration minimale efficace. De plus, les formes à libération contrôlée permettent de réduire le nombre de doses administrées et facilitent ainsi la compliance du patient [2].

2.1. Systèmes multiparticulaires à libération contrôlée pour administration orale

Au cours des vingt dernières années les systèmes multiparticulaires, notamment les minigranules, les mini-comprimés et les granules ont gagnés beaucoup d'importance dans l'industrie pharmaceutique [3]. Ces formes multiparticulaires offrent de grands avantages comparé aux systèmes unitaires. Ils se dispersent facilement après administration dans le tractus gastro-intestinal et optimisent ainsi l'absorption du principe actif [4]. Ainsi, les effets secondaires peuvent être minimisés et la thérapie devient moins sensible à la variabilité d'un sujet à l'autre [5]. En tant que systèmes multiparticulaires sphériques, les minigranules présentent des nombreux avantages. Des noyaux neutres (de différentes natures, tel que le sucre, la cellulose microcristalline, l'amidon et de nombreux autres) peuvent être chargés avec une grande variété de principes actifs par montage ou par préparation de sphères matricielles

de taille et de teneur en principe actif très variable. Les minigranules peuvent être pelliculés pour contrôler la libération du principe actif, compressés en des comprimés ou tout simplement conditionnés dans des gélules afin de faciliter leur administration. Du fait de leur forme sphérique, les minigranules montrent une meilleure fluidité pour le remplissage [6] et si pelliculage a lieu ce dernier devrait être d'une plus grande uniformité que s'il était réalisé sur des mini-comprimés cylindriques du fait de l'absence d'arrêtes. Afin de contrôler la libération du principe actif à partir de minigranules, on peut avoir recours au pelliculage qui consiste à déposer un film « barrière » autour des noyaux de principe actif. Un large éventail de polymère peut être utilisé, notamment les dérivés acryliques [7] et l'éthyle cellulose. Grâce à l'ajout de groupements fonctionnels supplémentaires, il est possible d'obtenir des pelliculages dits entériques qui ne libèrent pas le principe actif à pH acide et libèrent entièrement le principe actif à pH élevé [8].

2.2. Minigranules pelliculés à libération contrôlée du principe actif

2.2.1. Mécanismes de libération du principe actif

Les cinétiques de libération d'un principe actif à partir de minigranules pelliculés sont affectés pas plusieurs facteurs tel que l'épaisseur du film polymérique [9], les propriétés physico-chimiques du matériau utilisé pour le noyau [10], la solubilité du principe actif et du polymère [11]. Une fois exposé au milieu de libération, l'eau pénètre dans le système et selon la teneur du noyau en principe actif et la solubilité du principe actif, ce dernier se dissout (complètement ou partiellement) [12, 13]. Le type de polymère et la nature du noyau peuvent fortement influencer la vitesse à laquelle l'eau diffuse dans le système. Les mécanismes contrôlant les cinétiques de libération peuvent être plus ou moins complexes [14].

La diffusion joue souvent un rôle majeur [15]. Il peut notamment s'agir de la diffusion du principe actif à travers un film polymérique continu et flexible qui recouvre le noyau de principe actif [16]. Après pénétration de l'eau au sein du minigranule, le principe

actif se dissout. Du fait des gradients de concentration entre l'intérieur (c_i) et l'extérieur du minigranule, le principe actif est libéré. Dans le cas de conditions sink parfaites, la quantité de principe actif libéré (dM) pendant un intervalle de temps (dt) peut être calculée, selon la loi de diffusion de Fick, comme suivant :

$$\frac{dM}{dt} = D_m \cdot A \cdot K \cdot \frac{c_i}{d} \qquad (2.1)$$

Où D_m est le coefficient de diffusion apparent du principe actif dans le film polymérique. A est la surface disponible pour la diffusion, K est le coefficient de partition du principe actif (phase aqueuse – phase polymérique) et d représente l'épaisseur du pelliculage [17, 18].
Dans le cas de conditions pseudo équilibrées (un excès initial de principe actif assurant une concentration saturée en principe actif et des conditions sink dans le milieu de libération), on obtient des cinétiques d'ordre zéro. Dans le cas où il n'y a pas une source active constante (concentration initiale en principe actif < solubilité du principe actif) et de conditions sink parfaites, on obtient des cinétiques de libération d'ordre 1 [1].

De plus, la libération du principe actif peut également avoir lieu à travers **des canaux remplis d'eau** [19]. Ceci est notamment le cas, lorsque le pelliculage présente des pores ou des fissures, qui sont soient initialement présents ou soient créées par dissolution de composés solubles dans le milieu de libération ou du fait de la pression hydrostatique générée dans le système après pénétration de l'eau dans la forme pelliculée. Ainsi, le mélange de deux types de polymères [17] ou l'addition de sels ou autres molécules solubles [20] à des polymères insolubles peut être utilisé pour modifier les cinétiques de libération. Dans le cas de conditions sink parfaites, la vitesse de libération du principe actif peut être décrite comme suivant :

$$\frac{dM}{dt} = D_p \cdot A \cdot \frac{\varepsilon}{\tau} \cdot \frac{c_i}{d} \qquad (2.2)$$

Où D_p est le coefficient de diffusion du principe actif dans la phase aqueuse présente dans les canaux et les pores, ε est la proportion volumique des pores, τ est la tortuosité des canaux [17]. La proportion volumique et la forme des pores formés in situ doivent être connus [21].

Les effets osmotiques peuvent également jouer un rôle essentiel dans le contrôle des cinétiques de libération à partir de minigranules pelliculés. Ce processus est très bien connu pour des systèmes comportant un noyau osmotiquement actif (par exemple des noyaux de sucre) et recouverts d'une membrane semi-perméable. Dans ce cas, un gradient osmotique se crée à travers le film polymérique [22]. Les cinétiques contrôlées osmotiquement dépendent de la porosité de la membrane polymérique, de la pression osmotique du noyau de sucre et du principe actif [14]. Dès que les minigranules entre en contact avec le milieu aqueux environnant, l'eau pénètre dans le système, et le principe actif est expulsé via les pores. Le flux d'eau entrant dépend des propriétés et de la composition de la barrière polymérique et peut être quantifié comme suivant :

$$\frac{dV}{dt} = \frac{A\theta\Delta\pi}{l} \qquad (2.3)$$

Où dV/dt représente le flux d'eau, A est la surface de la membrane, l l'épaisseur du film, θ la perméabilité de la membrane polymérique et $\Delta\pi$ la différence de pression osmotique [22].

2.2.2. Procédés de pelliculage

Les minigranules peuvent être pelliculés en utilisant des turbines à dragéifier conventionnelles, communément utilisés pour enrober des formes solides avec des sirops de sucre. Les minigranules sont en mouvement dans une turbine en rotation et la dispersion d'enrobage est pulvérisée dessus. Du fait de l'application non-continue de la formulation polymérique, un débit d'air insuffisant et l'existence d'angles morts (dans lesquels les minigranules ne sont pas en mouvement), il peut en résulter des pelliculages inhomogènes avec des noyaux humides et gonflés. Le pelliculage en lit d'air fluidisé ou les minigranules

sont mis en suspension dans l'air et la formulation pulvérisée dessus assure quant à lui un séchage efficace des noyaux [23]. Des gouttelettes de petite taille et une faible viscosité de la formulation pulvérisée assurent un pelliculage homogène. Différentes techniques peuvent être utilisées en lit d'air fluidisé : La méthode dite du « **Top spray** » où la suspension est pulvérisée par dessus les minigranules [24]. La méthode dite du « **Bottom Spray** » fait appel à un insert appelé **Wurster.** Dans ce cas de figure, la buse de pulvérisation est fixée à la base de la cuve. Comme illustré en Figure 2.1, les particules sont aspirées à l'intérieur de Wurster et sont donc forcées à travers le cône de pulvérisation. En continuant leur ascension, les particules sèchent et retombent à l'extérieur du Wurster pour être de nouveau aspirées à sa base. Cette technique permet d'obtenir des films très homogènes [25]. Du fait que la buse est immergée dans le flux d'air, les gouttelettes de la formulation d'enrobage ne parcourent que de très courtes distance avant d'atteindre la surface des particules, ainsi les films sont appliqués de manière plus homogène [24]. Dans la **méthode par spray tangentiel**, la buse est orientée tangentiellement à un disque qui tourne et entraîne les particules. Ainsi, la pulvérisation se fait dans la même direction que le mouvement des particules. Des pelliculages très épais peuvent être obtenus par cette méthode [25].

Tous ces procédés ont en commun les étapes suivantes: (i) la formation de gouttelettes de la formulation d'enrobage, (ii) contact et adhésion des gouttelettes à la surface des particules puis (iii) étalement et coalescence [26].

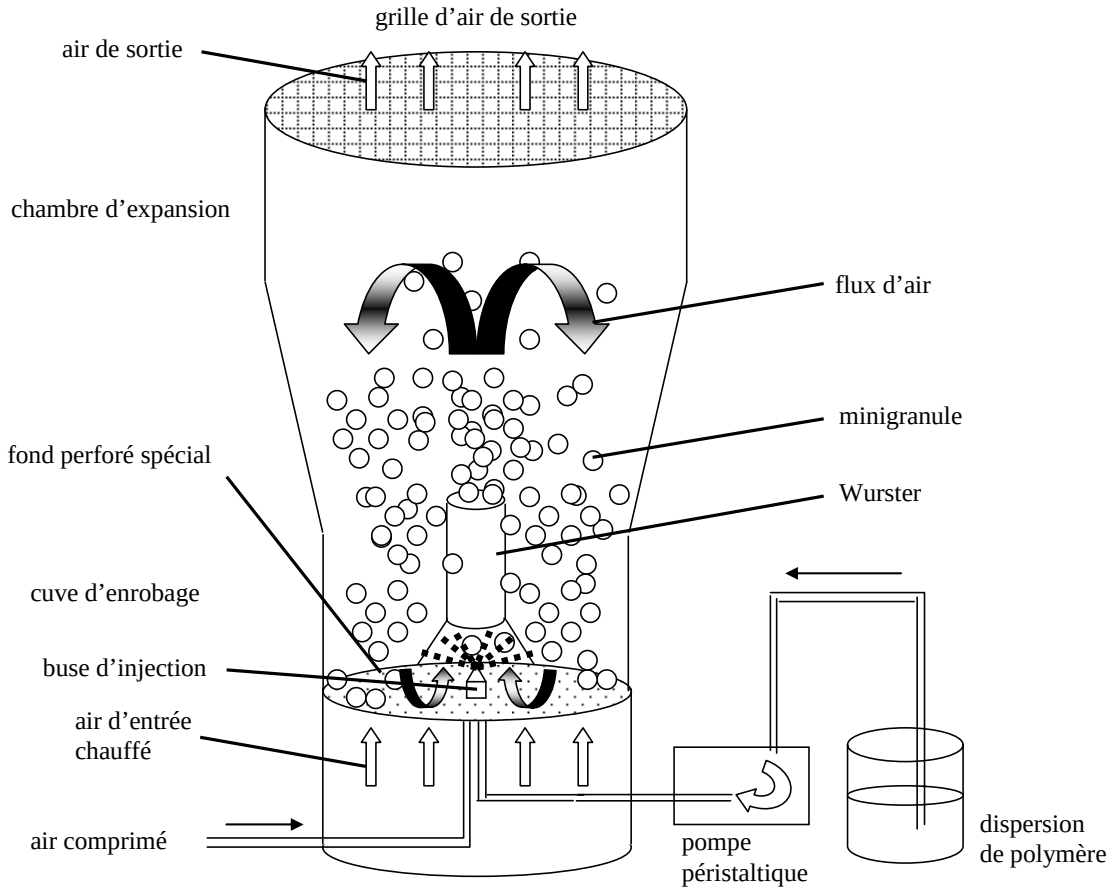


Figure 2.1: Représentation schématique d'un lit d'air fluidisé équipé d'un Wurster.

Les pelliculages polymériques peuvent être réalisés soit à partir de solutions organiques polymériques, soit à partir de dispersions aqueuses polymériques. Du fait des problèmes environnementaux et de sécurité associés aux solutions organiques, les dispersions aqueuses sont généralement préférées. Les principaux paramètres à considérer lors du pelliculage de formes solides par la technique du Wurster sont :

- Le taux de matière sèche de la dispersion, étant donné qu'une haute teneur en matière sèche peut conduire à de grandes variations au niveau de la reproductibilité et de l'homogénéité du pelliculage [26].
- La température produit, qui est ajustée en variant la température de l'air d'entrée. Cette dernière affecte directement la formation du film du fait de la coalescence des particules polymériques [27]. Généralement, la température du lit d'air fluidisé doit

être réglée 10 à 20 °C au dessus de la température minimale de formation du film (MFT) [28, 29].

- Le réglage du débit d'air. Il est important pour assurer un mouvement suffisant des minigranules.
- Le débit de pulvérisation. Un débit trop faible de la dispersion aqueuse de polymère peut conduire à la formation de films poreux due à un séchage partiel de la surface des minigranules et une formation du film comparable au spray drying de la dispersion polymérique. A l'opposé, un débit trop élevé peut entraîner à l'agglomération des minigranules entre elles.
- Le débit d'air de pulvérisation affecte quant à lui la taille des gouttelettes de la dispersion [30] et la température de distribution des particules [31].

2.2.3. Mécanismes de formation des films

Les mécanismes de formation des films dépend essentiellement du type de formulation (dispersion aqueuse versus solution organique polymérique) [32]. Dans le cas de **solutions organiques polymériques**, les macromolécules sont dissoutes, ce qui peut conduire à de fortes viscosités suivant le poids moléculaire et l'affinité du polymère pour le solvant. Durant le procédé de pelliculage, le solvant s'évapore et un gel très visqueux se forme à la surface des minigranules (Figure 2.2). Après évaporation complète du solvant, un film continu se forme [32].

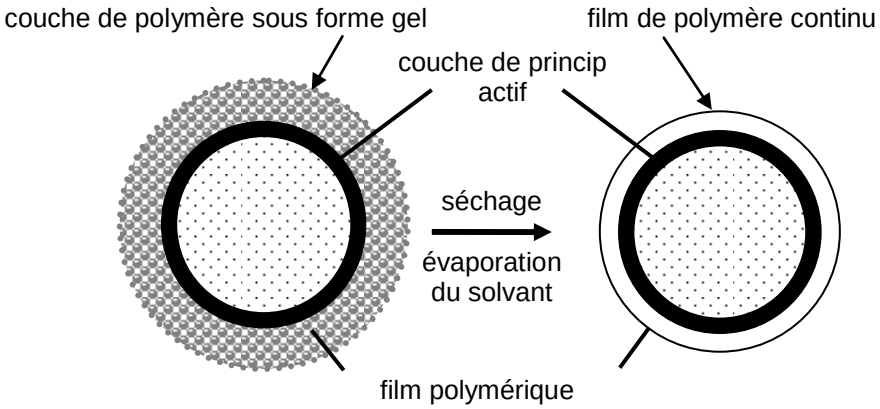


Figure 2.2: Représentation schématique du mécanisme de formation du film à partir de solutions organiques polymériques.

La formation de film à partir de **dispersion aqueuse** est quant à lui plus complexe [3]. Plusieurs théories ont été rapportées [33-36]. Après évaporation du solvant au cours du procédé de pelliculage, les particules polymériques entre en contact les unes avec les autres et sont intimement empilées les une sur les autres avec des cavités interstitielles remplies d'eau [37]. Les particules de polymère se rapprochent de plus en plus au fur et à mesure que l'eau s'évapore du fait de la tension de surface (tension interfaciale eau-air) [24]. Finalement la coalescence des particules intervient lorsque les forces capillaires sont suffisamment fortes (Figure 2.3) [38].

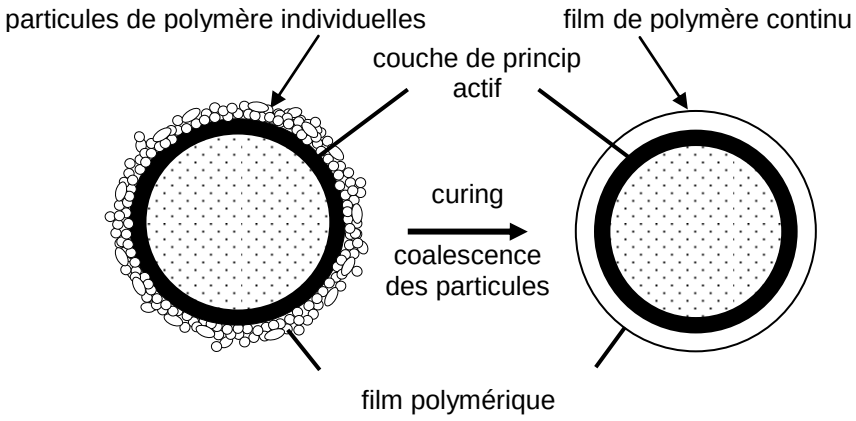


Figure 2.3: Représentation schématique du mécanisme de formation du film à partir de dispersions aqueuses polymériques.

Pour assurer une déformabilité suffisante des particules de polymère, le procédé de pelliculage doit généralement être réalisé à température élevée. Cette capacité à se déformer est directement lié à la température de transition vitreuse (section 2.3.1.) qui se traduit par une augmentation brutale de la mobilité des chaînes polymériques [39].

Si le film n'est pas complètement formé, il est possible que la coalescence continue à se poursuivre au cours du temps [35]. Afin d'éviter ce phénomène, une étape de traitement thermique est fortement recommandée [40-42].

2.3. Pelliculages à base d'éthyle cellulose

L'éthyle cellulose est un matériau hydrophobique [43] fréquemment utilisé pour contrôler la libération de principes actifs, masquer le goût et protéger de l'humidité [42]. Il est considéré comme non toxique, non allergénique et non irritant et est de ce fait largement utilisé pour le pelliculage de formes solides destinées à la voie orale. Il est insoluble dans le tractus gastro-intestinal [44] et du fait de ses groupements neutres il permet d'obtenir des cinétiques de libération pH-indépendantes [32].

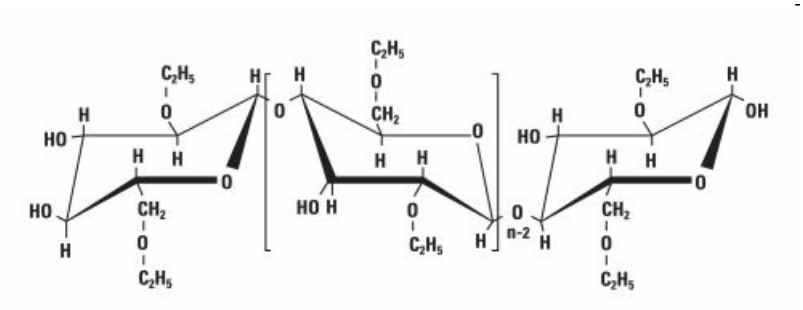


Figure 2.4: Structure chimique de l'éthyle cellulose.

Les pelliculages d'éthyle cellulose peuvent être appliqués à partir de solutions organiques de méthanol, éthanol, isopropanol, acétone et dichlorométhane ou à partir de dispersions aqueuses de polymères. Les pelliculages à base d'éthyle cellulose réalisés à partir de solutions aqueuse ne requièrent pas d'étape de traitement thermique et montrent des cinétiques de libération pH-indépendantes [45]. Cependant du fait des problèmes cités précédemment, les dispersions aqueuses sont préférées. Dans ce cas il est important de faire attention à assurer une stabilité sur le long terme [38, 46, 47].

2.3.1. Aquacoat ECD

L'Aquacoat ECD est une dispersion commerciale d'éthyle cellulose avec 30 % de matière sèche (dont 27 % d'éthyle cellulose). Les particules de polymère font de l'ordre de 200 nm et une viscosité de 150cP. La suspension de pseudolatex est stabilisée à l'aide d'un tensioactif anionique, le lauryl sulfate de sodium (SLS) (4 % w/w basé sur le taux de matière sèche total) ainsi que de d'alcool cétylique (9 % w/w basé sur le taux de matière sèche total) [42].

La température de transition vitreuse (T_g) de l'éthyle cellulose est de l'ordre de 125 à 130 °C [48]. Au-delà de cette température, le polymère est à l'état caoutchouteux et au-

dessous de cette température les chaînes de polymère sont très peux mobiles, on dit que le polymère est à l'état vitreux.

L'Aquacoat ECD est un pseudolatex produit par méthode d'émulsion - évaporation de solvant [28, 38, 42]. La solution de polymère (non miscible à l'eau, solvant volatile) est émulsifiée dans l'eau et est stabilisée par des tensions actives. Après évaporation du solvant, les particules de polymère se forment dans la phase aqueuse.

2.3.2. Plastifiants utilisés pour les dispersions aqueuses d'éthyle cellulose

Afin de diminuer le T_g de l'éthyle cellulose, des plastifiants peuvent être ajoutés. Ces derniers sont généralement des composés organiques avec un point d'ébullition élevé, qui permettent de réduire les forces de cohésion intermoléculaires et apportent donc une plus grande flexibilité aux matériaux polymériques [28]. Le T_g de la dispersion aqueuse d'éthyle cellulose peut être réduit à 32 ou 36 °C en ajoutant 30 % m/m de triéthyle citrate (TEC) ou de dibutyle sébaçate (DBS), respectivement [49]. L'addition de plastifiants à l'Aquacoat ECD est nécessaire pour assurer une bonne formation du film polymérique (section 2.2.3.).

Le choix du plastifiant relève de différentes considérations. Généralement le plastifiant ne doit pas ou peu montrer de tendance à migrer et être compatible avec le polymère [50]. Les incompatibilités peuvent mener à une formation de film médiocre qui vont résulter en des cinétiques de libération instables au cours du stockage [51]. Lorsque l'on ajoute un plastifiant à une dispersion aqueuse polymérique, il est important de prendre en compte le fait que la dissolution du plastifiant dans l'eau, la convection à travers la phase aqueuse et finalement la diffusion dans les particules de polymère est un processus qui est dépendant du temps [38, 52].

Non seulement les propriétés chimiques [28], mais aussi la quantité de plastifiant ajouté a un impact sur la formation du film à partir de (pseudo) latex [53]. Une formation incomplète du film a été reportée pour des pelliculages formés à partir de dispersions

aqueuses de polymère [35, 53]. Ceci se traduit par une diminution des taux de principe actif libérés au cours du stockage et s'explique par une poursuite de la coalescence des particules de polymère en un film continu [54].

2.3.3. Mélanges de polymère avec l'Aquacoat ECD

Les cinétiques de libération à partir de minigranules pelliculés avec de l'éthyle cellulose peuvent être très lentes [55]. Afin d'obtenir des profiles plus rapides, il a été proposé d'ajouter de l'hydroxypropyle méthyle cellulose (HPMC) à des dispersions aqueuses d'éthyle cellulose [56-58]. Mais il a été rapporté que l'ajout d'HPMC à l'Aquacoat ECD peut générer une instabilité physique de la dispersion [59]. Par exemple, il a été noté que l'addition de 2-20 % [44] d'HPMC résultait en une floculation de la dispersion [60]. Ceci peut avoir comme conséquence la formation de films inhomogènes [61] avec des régions plus riches en éthyle cellulose et d'autres en HPMC [62]. De plus, les pelliculages à base d'éthyle cellulose et d'HPMC peuvent se montrer instables au cours du stockage comme le montre une baisse des taux de libération [63].

D'autres additifs hydrophiles montrant une meilleure compatibilité avec l'éthyle cellulose ont été proposés [44, 64]. Par exemple le carraghénane de type λ, utilisé dans l'industrie alimentaire, est un type de carraghénane fortement sulfaté (Figure 2.5) qui ne forme pas de gel et montre une très bonne solubilité dans l'eau froide et l'eau chaude.

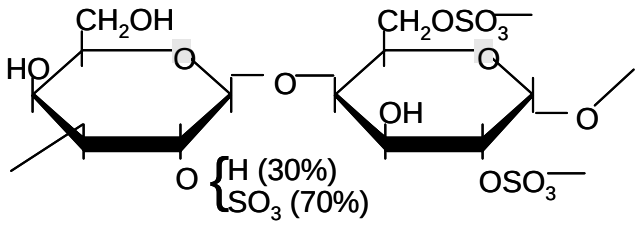
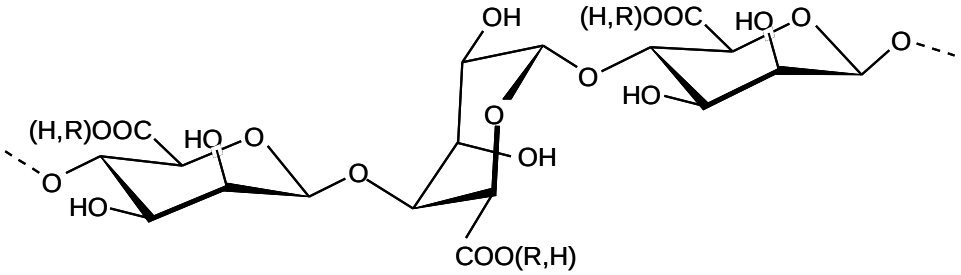


Figure 2.5: Structure chimique du carraghénane de type λ.

Un autre polymère hydrophile utilisé dans l'industrie alimentaire en tant que stabilisateur, épaississant, émulsifiant est l'alginate de propylène glycol (Figure 2.6), un alginate partiellement estérifié avec du 1,2-propandiol. Il est soluble dans l'eau et donne une solution colloïdale visqueuse.



(PG)M (PG)G (PG)M

(PG)M = (Propylene glycol) Mannuronate

(PG)G = (Propylene glycol) Guluronate

R = -CH $_2$ -CH(OH)-CH $_3$ (40-90 %)

H = -H (10-60 %)

Figure 2.6: Structure chimique de l'alginate de propylène glycol.

Le copolymère d'acide polyvinylique et de polyéthylène glycol (PVA-PEG) est un autre polymère hydrophile très soluble dans l'eau. Il est principalement utilisé comme agent de pelliculage à libération immédiate [65].

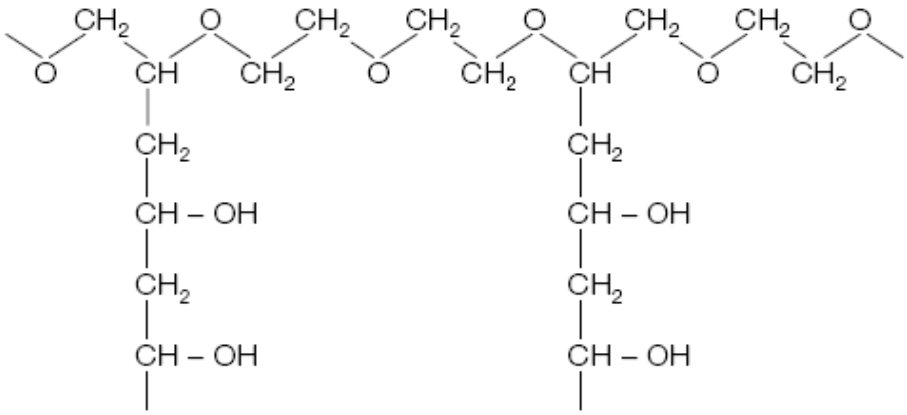


Figure 2.7: Structure chimique du copolymère d'acide polyvinylique et de polyéthylène glycol.

2.4. Procédés et paramètres de formulation affectant les cinétiques de libération de minigranules pelliculés

Plusieurs facteurs peuvent significativement influencer les cinétiques de libération à partir de minigranules pelliculés.

2.4.1. Conditions de traitement thermique

L'étape de traitement thermique est un important paramètre à prendre en compte après le pelliculage de formes solides avec des dispersions aqueuses polymériques. Cette étape doit être réalisée à une température supérieure à la température de transition vitreuse, afin d'assurer une mobilité suffisante des chaînes polymériques. Au cours de cette étape, les particules qui n'avaient pas encore fusionnées fusionnent ce qui permet de garantir la formation de films bien lisses et d'assurer la stabilité à long terme [66]. Ce traitement thermique peut être réalisé dans un four, où les échantillons sont stockés au moins 10 °C au-dessus de la MFT [55] ou dans un lit d'air fluidisé immédiatement après l'étape de pelliculage proprement dite. Mais des températures trop élevées peuvent entraîner l'agglomération des minigranules entre eux

2.4.2. Type de noyau

La matériau utilisé pour le noyau peut significativement influencer les cinétiques de libération résultantes [67, 68]. Un noyau très hygroscopique tel que le sucre peut augmenter le flux entrant d'eau dans le système pelliculé. La pénétration continue d'eau à l'intérieur des minigranules a de grande chance de générer une augmentation continue de la pression hydrostatique dans les minigranules. Ceci peut avoir pour conséquence une augmentation des dimensions du système jusqu'à ce qu'une valeur critique soit atteinte à laquelle la formation de fissures est induite [10]. En revanche, des noyaux en matériaux inertes tel que la cellulose microcristalline sont considérés comme osmotiquement neutres et n'induisent pas une

pénétration significative d'eau dans les minigranules une fois en contact avec des milieux aqueux.

2.4.3. Type de principe actif

Les propriétés physicochimiques du principe actif présent dans la formulation peuvent avoir une grande influence sur les profils de libération [69]. La solubilité des principes actifs est d'importance, car seul le principe actif dissout peut diffuser à travers le film polymérique intact ou à travers les pores remplis d'eau [70]. Pour cette raison, des principes actifs fortement solubles dans l'eau sont généralement plus rapidement libérés que des composés peu solubles [69]. En plus de la solubilité du principe actif dans le milieu de libération, la solubilité du principe actif dans le film polymérique joue également un rôle clé [28].

2.5. Objectifs des travaux

Du fait de la complexité des mécanismes de libération sous-jacents pour les formes pelliculées avec l'éthyle cellulose, l'optimisation de ce type de système représente un véritable challenge. Généralement, on a recours à de longues séries d'expériences qui coûtent beaucoup de temps et d'effort pour ajuster les cinétiques de libération. Malgré l'intérêt de plus en plus croissant portés à ce type de systèmes, ces derniers sont encore trop souvent traités comme des « boîtes noires ».

Le principal objectif de ce travail était de mieux comprendre les mécanismes sous-jacents aux cinétiques de libération à partir de minigranules pelliculés avec de l'éthyle cellulose et de proposer des outils pour l'optimisation des cinétiques de libération résultantes et d'augmenter la stabilité à long terme de ces systèmes. Les objectifs spécifiques incluaient :

- L'identification d'un second polymère hydrophile, compatible pour ajuster les profils de libération et améliorer la formation du film pendant le pelliculage et l'étape de traitement thermique.

- L’ajustement des cinétiques de libération de minigranules pelliculés avec de l’éthyle cellulose et ce pour différents types de principes actifs et de matériaux pour le noyau.
- L’élucidation des mécanismes de libération à partir de minigranules pelliculés avec un mélange de dispersion aqueuse d’éthyle cellulose et un second polymère
- La stabilisation des pelliculages pendant le stockage à long terme ainsi que dans des « conditions stress ».

2.6. Références

1. Siepmann, J., *Neue Arzneiformen - Seminar*, F.U. Berlin, Editor. 2002: Berlin.
2. Rowland, M. and T.N. Tozer, *Clinical Pharmacokinetics: Concepts and Applications*. 3 ed, ed. M. Rowland and T.N. Tozer. 1995, Baltimore: Lippincott Williams & Wilkins. 601.
3. Fukumori, Y., *Coating of Multiparticulates Using Polymeric dispersions*, in *Multiparticulate Oral Drug Delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 79-111.
4. Hardy, J.G., S.S. Davis, and C.G. Wilson, *Drug delivery to the gastrointestinal tract*. 1989, Chichester: Ellis Horwood
5. Ghebre-Sellassie, I., *Multiparticulate oral drug delivery*. 1997, New York: Marcel Dekker.
6. Lightfood, D.K., *Multiparticulate Encapsulation equipment and process*, in *Multiparticulate Oral Drug Delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 159-180.
7. Lehmann, K., *Chemistry and application properties of polymethacrylate coating systems*, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York. p. 101-176.
8. Stafford, J.W., *Enteric film coating using completely aqueous dissolved hydroxypropyl methyl cellulose phtalate spray solutions.* Drug Dev. Ind. Pharm., 1982. **8**(4): p. 513-530.
9. Munday, D.L. and A.R. Fassihi, *Controlled release delivery: Effect of coating composition on release characteristics of mini-tablets.* International Journal of Pharmaceutics, 1989. **52**(2): p. 109-114.

10. Lecomte, F., et al., *pH-Sensitive Polymer Blends used as Coating Materials to Control Drug Release from Spherical Beads: Importance of the Type of Core.* Biomacromolecules, 2005. **6**(4): p. 2074-2083.

11. Frohoff-Hülsmann, M.A., B.C. Lippold, and J.W. McGinity, *Aqueous ethyl cellulose dispersion containing plasticizers of different water solubility and hydroxypropyl methyl-cellulose as coating material for diffusion pellets II: properties of sprayed films.* Eur. J. Pharm. Biopharm., 1999. **48**(1): p. 67-75.

12. Strübing, S., H. Metz, and K. Mäder, *Mechanistic analysis of drug release from tablets with membrane controlled drug delivery.* European Journal of Pharmaceutics and Biopharmaceutics, 2007. **66**(1): p. 113-119.

13. Ensslin, S., et al., *New insight into modified release pellets - Internal structure and drug release mechanism.* Journal of Controlled Release, 2008. **128**(2): p. 149-156.

14. Ozturk, A.G., et al., *Mechanism of release from pellets coated with an ethylcellulose-based film.* Journal of Controlled Release, 1990. **14**(3): p. 203-213.

15. Fan, L.T. and S.K. Singh, *Controlled Release: A Quantitative Treatment.* 1989, Berlin: Springer-Verlag.

16. Dressman, J.B., et al., *Mechanisms of release from coated pellets,* in *Multiparticulate Oral Drug delivery,* I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 285-306.

17. Lecomte, F., *pH-sensitive polymer blends used as coating materials in controlled drug delivery systems*. 2004, Freie Universität Berlin: Berlin.

18. Siepmann, J. *Understanding drug release mechanisms*. in *Coating Workshop*. 2008. Lille, France.

19. Hoffman, A., M. Donbrow, and S. Benita, *Direct measurements on individual microcapsule dissolution as a tool for determination of release mechanism.* J Pharm Pharmacol. , 1986. **38**(10): p. 764-766.

20. Rohera, B.D. and N.H. Parikh, *Influence of type and level of water-soluble additives on drug release and surface and mechanical properties of Surelease films.* Pharm Dev Technol. , 2002. **7**(4): p. 421-432.

21. Vidmar, V., I. Jalsenjak, and T. Kondo, *Volume of waterfilled pores in the ethyl cellulose membrane and the permeability of microcapsules.* J. Pharm. Pharmacol, 1982. **34** (7): p. 411-414.

22. Schmidt, C., *Multiparticulate Oral Drug Delivery Systems*. 2000, Freie Universität Berlin: Berlin.

23. Bauer, K.H., K.-H. Froemming, and C. Fuehrer, *Lehrbuch der Pharmazeutischen Technologie*. 7 ed. 2002, Stuttgart: Wissenschaftliche Verlagsgesellschaft.

24. Wheatley, T.A. and C.R. Steuernagel, *Latex emulsion for controlled drug delivery*, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York.

25. Glatt. *Fluid Bed Coating*. Technologies 2004-2008 [cited; Available from: http://www.glatt.com/e/01_technologien/01_04_08.htm.

26. Naelapää, K., et al. *Dealing with complex interactions in experimental data*. in *2nd Pharmaceutical Solid State Research Cluster (PSSRC) Symposium*. 2008. Gent, Belgium.

27. Naelapää, K., et al., *Coating of potassium chloride with ethylcellulose aqueous dispersion--Effects of processing parameters on film formation and film properties.* European Journal of Pharmaceutical Sciences, 2007. **32**(1, Supplement 1): p. S20-S20.

28. Bodmeier, R., X. Guo, and O. Paeratakul, *Process and formulation factors affecting the drug release from pellets coated with the ethylcellulose-pseudolatex Aquacoat*, in *Aqueous polymeric coatings for pharmaceutical dosage forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York.

29. Schultz, R.K. and R.R. Myers, *Acrylic latex film formation in the critical temperature range.* Journal of Applied Polymer Science, 1964. **8**(2): p. 755 - 764.

30. Wagner, K., *Aqueous ppolymer dispersions for extended release dosage forms*. 2002, Freie Universitaet Berlin: Berlin.

31. Ronsse, F., J.G. Pieters, and K. Dewettinck, *Modelling heat and mass transfer in batch, top-spray fluidised bed coating processes.* Powder Technology, 2008. **sous presse**.

32. Lehmann, K., *Coating of multiparticulates using organic solutions - Formulation and process considerations*, in *Multiparticulate drug delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 51-78.

33. Dillon, R.E., L.A. Matheson, and E.B. Bradford, *Sintering of synthetic latex particles.* Journal of Colloid Science, 1951. **6**(2): p. 108-117.

34. Brown, G., *Formation of films from polymer dispersions.* J. Polymer Sci., 1956. **22**(102): p. 423-434.

35. Vanderhoff, J.W., et al., *Theoretical consideration of the interfacial forces involved in the coalescence of latex particles.* Macromol. Chem. , 1966. **1**: p. 361-397.

36. Nagakami, H., et al., *Application of aqueous suspensions and latex dispersions of water-insoluble polymers for tablets and granule coatings.* . Chem. Pharm. Bull., 1991. **39** p. 1837-1842.

37. Onions, A., *Films from water-based colloidal dispersions.* Manuf. Chem., 1986. **57**(4): p. 66-67.

38. Paeratakul, O., *Pharmaceutical applications of aqueous colloidal polymer dispersions.* 1993, University of Texas: Austin.

39. Okhamafe, A.O. and P. York, *Studies of interaction phenomena in aqueous-based film coatings containing soluble additives using thermal analysis techniques.* J. Pharm. Sci., 1988. **77**(5): p. 438-443.

40. Harris, M.R. and I. Ghebre-Sellassie, *Aqueous polymeric coating for modified release oral dosage forms*, in *Aqueous polymeric film coatings for pharmaceutical dosage forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York.

41. Bodmeier, R. and O. Paeratakul, *Process and formulation variables affecting the drug release from chlorpheniramine maleate-loaded beads coated with commercial and self-prepared aqueous ethyl cellulose pseudolatexes.* International Journal of Pharmaceutics, 1991. **70**(1-2): p. 59-68.

42. FMC, *Aquacoat ECD sales brochure*. 2008, FMC Biopolymer.

43. Wallace, J.W., *Cellulose derivatives and natural products utilized in pharmaceutics*, in *Encyclopedia of Pharmaceutical Technology*, J.S.a.J.C. Boylan, Editor. 1990, Marcel Dekker: New York. p. 319-339.

44. Siepmann, F., et al., *How to adjust desired drug release patterns from ethylcellulose-coated dosage forms.* Journal of Controlled Release, 2007. **119**(2): p. 182-189.

45. Wesseling, M. and R. Bodmeier, *Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat(R), or an organic ethylcellulose solution.* European Journal of Pharmaceutics and Biopharmaceutics, 1999. **47**(1): p. 33-38.

46. Buscall, R. and R.H. Ottewill, *The stability of polymer latices*, in *Polymer Colloids*, T.C. R. Buscall, J.F. Stageman, Editor. 1985, Elsevier: London.

47. Zimehl, R. and G. Lagaly, *Coagulation of latex dispersions in the presence of some organic compounds.* Colloids and Surfaces, 1987. **22**(2): p. 215-224.

48. Keshikawa, T. and H. Nakagami, *Film formation with coating systems of aqueous susoensions and latex dispersions of ethylcellulose.* Chemical Pharmaceutical Bulletin, 1994. **42**(3): p. 656-662.

49. Morflex, *Influence of plasticizers on the dissolution and physical properties of ethylcellulose films and coated beads*, in *Pharmaceutical Coatings Bulletin*. 1995, Morflex Inc.

50. Pearnchob, N., *Evaluation of new film coating processes and materials*. 2002, Freie Universitaet Berlin: Berlin.

51. Kucera, S., *Physical and chemical properties of acrylic polymers influencing physical aging*. 2007, University of Texas: Austin.

52. Siepmann, J., *Polymeric controlled drug delivery systems : Elucidation of transport mechanisms and optimization of release patterns*. 1999, Freie Universitaet Berlin: Berlin.

53. Amighi, K. and A.J. Moes, *Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit RS 30D film-coated sustained-release theophylline pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42**(1): p. 29-35.

54. Wu, C. and J.W. McGinity, *Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer.* European Journal of Pharmaceutics and Biopharmaceutics, 2000. **50**(2): p. 277-284.

55. Lippold, B.r.H., B.K. Sutter, and B.C. Lippold, *Parameters controlling drug release from pellets coated with aqueous ethyl cellulose dispersion.* International Journal of Pharmaceutics, 1989. **54**(1): p. 15-25.

56. Gunder, W., B.H. Lippold, and B.C. Lippold, *Release of drugs from ethyl cellulose microcapsules (diffusion pellets) with pore formers and pore fusion.* European Journal of Pharmaceutical Sciences, 1995. **3**(4): p. 203-214.

57. Tang, L., et al., *Drug Release from Film-Coated Chlorpheniramine Maleate Nonpareil Beads: Effect of Water-Soluble Polymer, Coating Level, and Soluble Core Material.* Pharmaceutical Development and Technology, 2000. **5**(3): p. 383 - 390.

58. Frohoff-Hülsmann., M.A., A. Schmitz, and B.C. Lippold, *Aqueous ethyl cellulose dispersions containing plasticizers of different water solubility and hydroxypropyl*

methylcellulose as coating material for diffusion pellets I. Drug release rates from coated pellets. Int. J. Pharm., 1999. **177**(1): p. 69-82.

59. Wong, D. and R. Bodmeier, *The impact of the use of flocculated colloidal dispersions on the drug release from drug-containing films and coated tablets.* Pharm. Res., 1994. **11**: p. S-185.

60. Wong, D. and R. Bodmeier, *Flocculation of an aqueous colloidal ethyl cellulose dispersion (Aquacoat) with a water-soluble polymer, hydroxypropyl methyl cellulose.* Eur. J. Pharm. Biopharm., 1996. **42**(1): p. 12-15.

61. Sakellariou, P., R.C. Rowe, and E.F.T. White, *Polymer/polymer interaction in blends of ethyl cellulose with both cellulose derivatives and polyethylene glycol 6000.* International Journal of Pharmaceutics, 1986. **34**(1-2): p. 93-103.

62. Sakellariou, P. and R.C. Rowe, *The morphology of blends of ethylcellulose with hydroxypropyl methylcellulose as used in film coating.* International Journal of Pharmaceutics, 1995. **125**(2): p. 289-296.

63. Hoffart, V., et al., *Storage stability of pellets coated with the aqueous ethylcellulosee dispersion Aquacoat® ECD at elevated temperature and humidity,* in *Annual Meeting and Exposition, American Association of Pharmaceutical Scientists*. 2005: Nashville, USA.

64. Chan, L.W., K.T. Ong, and P.W.S. Heng, *Novel Film Modifiers to Alter the Physical Properties of Composite Ethylcellulose Films.* Pharmaceutical Research, 2005. **22**(3): p. 476-489.

65. BASF, *Kollicoat IR,* in *Technical Information*. 2001, BASF Aktiengesellschaft.

66. Lippold, B.C. and R. Monells Pages, *Film formation, reproducibility of production and curing with respect to release stability of functional coatings from aqueous polymer dispersions.* Pharmazie, 2001, Pages 5-17. **56**(1): p. 5-17.

67. Porter, S.C., *Controlled-Release Film Coatings Based on Ethylcellulose.* Drug Development and Industrial Pharmacy, 1989. **15**(10): p. 1495 - 1521.

68. Ragnarsson, G., et al., *In vitro release characteristics of a membrane-coated pellet formulation -- influence of drug solubility and particle size.* International Journal of Pharmaceutics, 1992. **79**(1-3): p. 223-232.

69. Sadeghi, F., J.L. Ford, and A. Rajabi-Siahboomi, *The influence of drug type on the release profiles from Surelease-coated pellets.* International Journal of Pharmaceutics, 2003. **254**(2): p. 123-135.

70. Ghebre-Sellassie, I., et al., *Characterization of a new water-based coating for modified-release preparations.* Pharm. Technol., 1988. **12**: p. 96-106.

3. CARRAGEENAN AS A DRUG RELEASE MODIFIER IN ETHYLCELLULOSE-BASED FILM COATINGS

Abstract. Ethylcellulose-based film coatings offer a promising potential to control drug release from orally administered pharmaceutical dosage forms. However, continuous ethylcellulose films are poorly permeable for most drugs, resulting in too low release rates within the gastro-intestinal tract. To overcome this restriction, small amounts of carrageenan were added to the film coatings. Importantly, the presence of this hydrophilic biomacromolecule effectively increased the water uptake rate and extent as well as the dry mass loss of the polymeric membranes upon exposure to simulated gastric and intestinal fluids. Both phenomena significantly increased the resulting drug permeability of the coatings and, consequently, the release rates from pharmaceutical dosage forms. In practice, desired release patterns (leading to optimal therapeutic effects) can easily be obtained by varying the amount of added carrageenan. Importantly, this biomacromolecule does not cause flocculation in aqueous ethylcellulose dispersions used for film coating.

3. Carrageenan as a drug release modifier in ethylcellulose-based film coatings

3.1. Introduction

Pharmaceutical dosage forms (e.g., tablets, capsules) are frequently coated with polymeric films for various reasons, such as, to facilitate swallowing, to protect the drug during storage against moisture or oxygen, to protect the stomach from the drug, or to control the resulting drug release kinetics. In the latter case, the aim is to optimize the drug concentration–time profile at the site of action in the human body: Each drug has a characteristic "minimum effective concentration" (below which no therapeutic effects occur) and a "minimum toxic concentration" (above which toxic side effects occur). The range in-between is called the therapeutic window. If the drug is administered using a conventional immediate release dosage form (e.g., standard tablet), the entire dose may be rapidly dissolved within the stomach. On absorption into the blood stream a high maximum plasma concentration (peak) results, with the risk of toxic side effects for drugs with a narrow therapeutic window. Subsequent elimination of the drug reduces the plasma concentration, limiting the time periods with therapeutic concentrations. To overcome these restrictions, the time course of drug release from the dosage form can be controlled, using for instance polymeric drug delivery systems [1-7]. The drug can either be directly embedded within a polymeric matrix (monolithic systems) [8], or a drug depot is surrounded by a rate-limiting polymeric shell (reservoir systems) [9]. Different physicochemical processes may be involved in the control of the resulting drug release rate, e.g., dissolution, diffusion, crack formation within the polymeric shell (coating), osmotic effects and polymer swelling [10, 11].

For the preferred oral route of administration, water-insoluble film coatings are frequently used to control drug release within the gastro-intestinal tract. Common water-insoluble polymers are either synthetic acrylate derivatives, such as poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) and poly(ethyl acrylate-co-methyl methacrylate) [9], or ethylcellulose (a partial ether of the biomacromolecule cellulose) which is a good film former and generally regarded as nontoxic,

nonallergenic and nonirritant [12]. Ethylcellulose-based films can either be applied from organic solutions or aqueous dispersions [13]. The use of aqueous systems is advantageous because of: (i) environmental concerns, (ii) the risk of toxicity of organic solvent residues for the patient, and (iii) the reduced processing times (aqueous dispersions generally contain higher polymer amounts than organic solutions for film coating because their viscosity is lower: the formulations need to be sprayable). However, if pharmaceutical dosage forms are surrounded by a continuous ethylcellulose film, the resulting drug release rates may be too low to allow sufficient drug release within the gastro-intestinal transit time.

To overcome this restriction, the addition of hydroxypropyl methylcellulose (HPMC) to the film coatings has been proposed [14, 15]. However, HPMC destabilizes colloidal ethylcellulose dispersions [16, 17], resulting in flocculation and inhomogeneous film formation. It has recently been shown that synthetic poly(vinylalcohol)-poly(ethyleneglycol) graft copolymer is an efficient drug release modifier for ethylcellulose-based film coatings, which does not cause flocculation in the coating formulations [18]. But this is a synthetic polymer. Also propylene glycol alginate has been shown to be suitable, but with pH-dependent drug release kinetics [19]. Thus, the drug release rate depends on the location within the gastro-intestinal tract.

The aim of the present study was to identify a biomacromolecule which allows effective pH-independent modification of drug release from ethylcellulose-coated pharmaceutical dosage forms without causing flocculation of the coating dispersion.

3.2. Experimental Section

3.2.1. Materials

Theophylline anhydrous (BASF, Ludwigshafen, Germany), theophylline pellets (70 % drug content; FMC, Philadelphia, PA), aqueous ethylcellulose dispersion (Aquacoat ECD; FMC), lambda carrageenan (Viscarin GP 209; FMC), propylene glycol alginate (PG alginate,

Protanal ester SD-LB; FMC), poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer, Kollicoat IR; BASF, Ludwigshafen, Germany), triethyl citrate (TEC; Morflex, Greensboro, NC).

3.2.2. Preparation of thin, free films

Thin, polymeric films were prepared by casting aqueous dispersions of ethylcellulose (Aquacoat ECD), plasticized with 25 % w/w (based on the polymer mass) triethyl citrate (being listed in the Food Chemical Codex and included in the FDA Inactive Ingredients Guide). The systems were stirred overnight to allow for plasticization (magnetic stirrer, 600 rpm, room temperature). Optionally, carrageenan was added (as aqueous solution; the blended systems were stirred for 30 min prior to casting). The respective aqueous dispersions were cast onto Teflon plates and subsequently dried in an oven (for 24 h at 60 °C). The following ethylcellulose:carrageenan blend ratios were investigated: 90:10, 95:5, 97.5:2.5 and 100:0 (w/w). Drug-containing films were prepared similarly by adding theophylline to the aqueous dispersions. In all cases, the drug loading (0.25 % w/w, based on the total dry polymer mass) was below the solubility of theophylline within the polymeric systems (clear films, monolithic solutions). The thickness of the films (around 200 μm) was measured using a thickness gauge (Minitest 600; Erichsen, Hemer, Germany).

3.2.3. Evaluation of the stability of the aqueous dispersions

The stability of the aqueous dispersions was evaluated after 24 h stirring (magnetic stirrer, 600 rpm, room temperature) by visual observation with a light microscope (Nikon Eclipse E400; Elvetec, Templemars, France) equipped with a Sony camera (Hyper HAD model SSC-DC38DP; Elvetec, Templemars, France) and the Optimas 6.0 software (Media Cybernetics, Silver Spring, MD).

3.2.4. Water uptake and dry mass loss of thin, free films

Thin, polymeric films were cut into pieces of 2 x 2 cm, which were placed into 50 mL plastic flasks filled with 40 mL pre-heated 0.1 N HCl or phosphate buffer pH 7.4 (USP XXIX), followed by horizontal shaking for 8 h (37 °C, 80 rpm; GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). At pre-determined time intervals, samples were withdrawn, accurately weighed [wet mass (t)] and dried to constant mass at 60°C [dry mass (t)]. The water content (%) and dry film mass (%) at time t were calculated as follows:

$$\text{water content (\%) (t)} = \frac{\text{wet mass (t)} - \text{dry mass (t)}}{\text{wet mass (t)}} \cdot 100\ \% \qquad (3.1)$$

$$\text{dry film mass (\%) (t)} = \frac{\text{dry mass (t)}}{\text{dry mass (0)}} \cdot 100\ \% \qquad (3.2)$$

3.2.5. Drug release from thin, free films

Drug release from thin, drug-containing films was measured by placing film pieces (2 x 2 cm) into 50 mL plastic flasks filled with 40 mL pre-heated 0.1 N HCl or phosphate buffer pH 7.4 (USP XXIX), followed by horizontal shaking for 80 h (37 °C, 80 rpm; GFL 3033; n = 3). To avoid film folding and/or floating during the experiments (resulting in potential variations of the surface area exposed to the release medium), the films were fixed within the plastic flasks. At pre-determined time intervals, 3 mL samples were withdrawn (replaced with fresh medium) and analyzed UV-spectrophotometrically (λ = 271 nm; Anthelie Advanced; Secomam, Domont, France).

3.2.6. Preparation of coated pellets

Theophylline pellets (70 % w/w drug loading) were coated with aqueous ethylcellulose dispersion (Aquacoat ECD) containing various levels of carrageenan (for details on the preparation procedure see *Preparation of thin, free films*), in a fluidized bed

coater equipped with a Wurster insert (Strea 1; Niro Inc., Aeromatic-Fielder AG, Bubendorf, Switzerland). The coating dispersions were sprayed onto theophylline pellets until a weight gain of 5, 10, 15 and 20 % (w/w) was achieved. The process parameters were as follows: inlet temperature = 40 °C, product temperature = 38 ± 2 °C, spray rate = 3 g/min, atomization pressure = 1.2 bar, air volume = 100 m³/h, nozzle diameter = 1.2 mm. After coating the pellets were further fluidized for 10 min and subsequently cured for 24/48 h at 60°C & ambient relative humidity (RH) or for 24/48 h at 40 °C & 75 % RH (followed by an additional drying step of 24 h at 60 °C & ambient RH).

3.2.7. Drug release from coated pellets

Theophylline release from the pellets was measured in 0.1 N HCl and phosphate buffer pH 7.4 (USP XXIX) using the paddle apparatus (USP XXIX; Sotax, Basel, Switzerland) (900 mL; 37 °C, 100 rpm; n = 3). At pre-determined time intervals, 3 mL samples were withdrawn and analyzed UV-spectrophotometrically (λ = 271 nm; Anthelie Advanced).

3.3. Results and discussion

3.3.1. Compatibility of the coating components

When adding a new compound to an aqueous colloidal polymer dispersion used for film coating, the stability of the novel system needs to be evaluated. For instance bridging effects can lead to polymer particle agglomeration and, thus, unstable coating formulations. In practice, this can lead to inconsistent or inhomogeneous film formation, resulting in poorly reproducible drug release profiles. Figure 3.1 shows an optical microscopy picture of a 90:10 blends of Aquacoat ECD (an aqueous ethylcellulose dispersion) and carrageenan after 24 h stirring at room temperature. Clearly, no signs of polymer particle agglomeration or other incompatibilities are visible. This is true for all the investigated blend ratios (data not shown). Importantly, derivatives of other biomacromolecules (e.g., hydroxypropyl methylcellulose) lead to significant flocculation [16, 17]. Thus, carrageenan fulfills the first pre-requisite for an efficient release modifier for ethylcellulose film coatings: It is compatible with the aqueous coating formulation. Next it is important to see whether small amounts of carrageenan are able to effectively alter the physicochemical properties of ethylcellulose films.

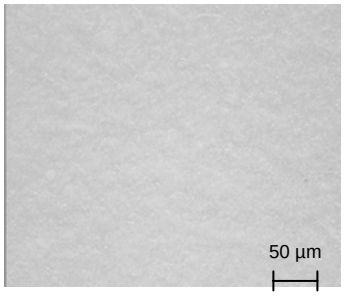


Figure 3.1: Microscopic picture of a 90:10 Aquacoat ECD (a colloidal aqueous ethylcellulose dispersion):carrageenan blend after 24 h stirring at room temperature.

3.3.2. Water uptake of thin, free films

As it can be seen in Figure 3.2, the rate and extent of water uptake in pure (plasticized) ethylcellulose films (filled squares) is limited in simulated gastric as well as in simulated intestinal fluids (0.1 N HCl and phosphate buffer pH 7.4, respectively). This can at least partially explain why ethylcellulose is poorly permeable for many drugs: With increasing water content the mobility of the macromolecules increases and, thus, the free volume available for drug diffusion increases. Importantly, both the rate and extent of water uptake in these films tremendously increases with only a few percent of carrageenan, irrespective of the type of release medium (Figure 3.2). This clearly indicates the ability of this biomacromolecule to significantly alter the properties of ethylcellulose film coatings. For instance, the addition of only 5 % (w/w) carrageenan results in a water content of around 65 % (instead of 13 %) upon film swelling in 0.1 N HCl. Thus, more than half of the film consists of water. This can be expected to significantly affect the mobility of drug molecules in these polymeric networks and, thus, the resulting drug release kinetics from coated pharmaceutical dosage forms.

To better understand which mass transport phenomena (e.g., diffusion, polymer chain relaxation, dissolution) are of importance once the polymeric films are exposed to the release media, the experimentally measured water uptake kinetics (symbols in Figure 3.2) were analyzed using an appropriate analytical solution of Fick' second law. The mathematical model quantifies diffusional mass transport in one dimension into a plane sheet [20]:

$$\frac{\partial c}{\partial t} = D \cdot \frac{\partial^2 c}{\partial x^2} \tag{3.3}$$

where c denotes the water concentration within the polymeric system, being a function of time t and position x; D represents the apparent diffusion coefficient of water.

The model takes into account that the films are initially dry:

$$t=0 \qquad c=0 \qquad -L \leq x \leq +L \tag{3.4}$$

(with L being the half-thickness of the films), and that edge effects are negligible (because the films' surface is very large in relation their thickness: ~ 8 cm² versus ~ 200 µm). Furthermore, the theory considers that the water concentration in the bulk fluids (0.1 N HCl or phosphate buffer pH 7.4) remains constant throughout the experiments:

$$t>0 \qquad c=\text{constant} \qquad x =+/- L \tag{3.5}$$

(a) (b)

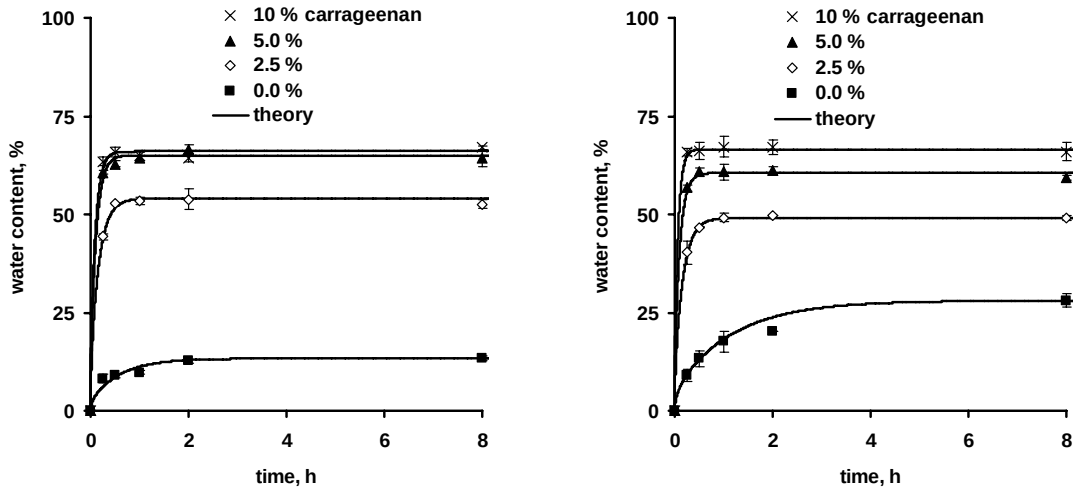


Figure 3.2: Water uptake behavior of ethylcellulose-based films containing different amounts of carrageenan (indicated in the figures) upon exposure to: (a) 0.1 N HCl; (b) phosphate buffer pH 7.4. The symbols represent the experimentally measured values, the curves the fitted theory (Equation 3.6).

This initial value problem (Equations 3.3-3.5) can be solved using the method of Laplace transform, leading to [21, 22]:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2 \cdot n + 1)^2 \cdot \pi^2} \cdot \exp\left(- \frac{(2 \cdot n + 1)^2 \cdot \pi^2}{4 \cdot L^2} \cdot D \cdot t \right) \tag{3.6}$$

where M_t and M_∞ are the absolute cumulative amounts of water taken up at time t and t=∞, respectively, and n is a dummy variable running from 0 to ∞.

As it can be seen in Figure 3.2, fitting this equation to the experimentally measured water uptake kinetics results in good agreement between theory (curves) and experiment (symbols) in all cases. This clearly indicates that the water influx into the film coatings is predominantly controlled by pure diffusion. Importantly, the addition of small amounts of carrageenan (leading to a significant increase in the rates and extents of water uptake) does not alter the relative importance of the involved mass transport phenomena. If polymer chain relaxation was the dominant mass transport mechanism, zero order uptake kinetics would have been observed under the given experimental conditions. If both polymer chain relaxation and water diffusion simultaneously governed the water influx kinetics, significant deviations between theory and experiment would have been observed in Figure 3.2.

Based on these calculations the apparent diffusion coefficient of water in the polymeric film coatings can be determined. Figure 3.3 shows the water diffusivity in ethylcellulose films upon exposure to simulated gastric and intestinal fluids as a function of the carrageenan content (filled triangles). Clearly, the water permeability significantly increases upon addition of only 2.5-10 % (w/w) carrageenan. This can be explained by the high hydrophilicity of this biomacromolecule. For comparison, the results obtained with two other polymers, poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer) and propylene glycol alginate (PG alginate) are also shown in Figure 3.3 (filled squares and open diamonds, respectively). Importantly, the synthetic copolymer was much

less efficient in altering the ethylcellulose film properties than the two biomacromolecules. Thus, much smaller amounts of the latter are necessary to achieve equivalent effects. In contrast to PG alginate, carrageenan-containing films have relatively pH-independent properties, e.g. drug permeabilities [19]. pH changes within the human gastro-intestinal tract can be expected to lead to significant alterations in release from pH-dependent film coatings. Such "environmentally triggered" coating properties can be advantageous for certain types of drugs. However, for the large majority of therapeutic treatments dosage forms with pH-independent drug release kinetics are desirable. Thus, based on the water diffusivities shown in Figure 3.3 carrageenan can be expected to be the most efficient pH-independent drug release modifier for ethylcellulose film coatings.

(a) (b)

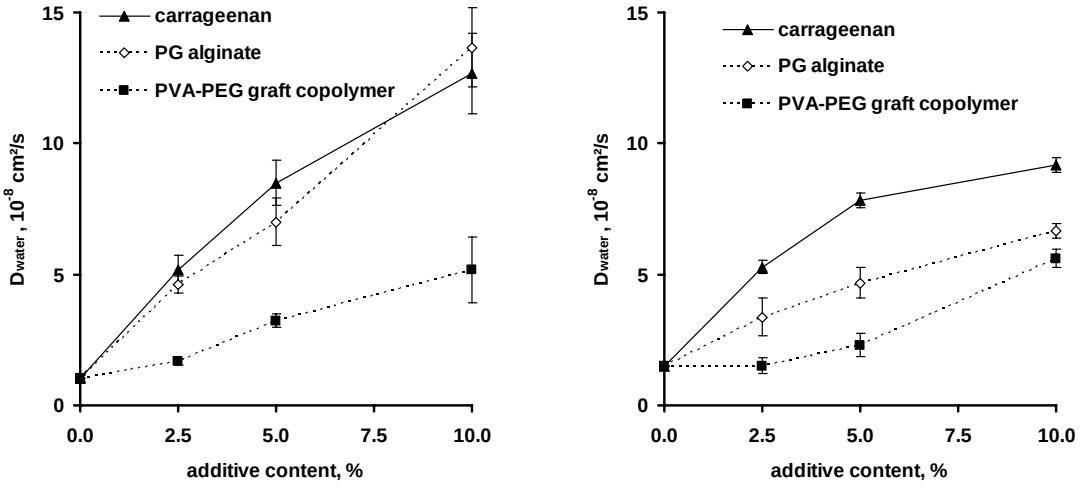


Figure 3.3: Water diffusivity in ethylcellulose-based films upon exposure to: (a) 0.1 N HCl; (b) phosphate buffer pH 7.4: Effects of the type and amount of additive (the results obtained with PG alginate and PVA-PEG graft copolymer are reproduced from [18] for reasons of comparison).

3.3.3. Dry mass loss of thin, free films

In addition to water uptake, the kinetics of dry mass loss of polymeric film coatings are also of fundamental importance to control drug release from pharmaceutical dosage forms. If major parts of the films are water-soluble and leach into the surrounding bulk fluid, the density of the polymeric network decreases, thereby reducing the barrier to drug diffusion. Figure 3.4 illustrates the experimentally determined dry mass loss of pure (plasticized) ethylcellulose films (filled squares) as well as of ethylcellulose:carrageenan films (open diamonds, filled triangles and crosses) upon exposure to simulated gastric and intestinal fluids. Clearly, the dry mass loss of pure (plasticized) ethylcellulose films is limited, due to the water-insolubility of this compound. The observed slight mass loss is due to leaching of the water-soluble plasticizer triethyl citrate, which is limited by the water-insoluble polymer [the films contain 25 % (w/w) water-soluble plasticizer referred to the ethylcellulose mass, thus, the dry mass could theoretically decrease down to 80 %, referred to the total film mass]. The significant increase in the dry mass loss upon addition of as little as 2.5 % (w/w) water-soluble carrageenan can be attributed to the facilitated leaching of the water-soluble plasticizer. As shown in Figure 3.2, the carrageenan containing films are composed of at least 50% water upon swelling. This high water content facilitates the diffusion of water-soluble substances within the polymeric networks. Importantly, the increase in dry mass loss upon carrageenan addition is similar to that observed with PG alginate [19] and much more pronounced than that observed with (the synthetic) PVA-PEG graft copolymer [18].

Both phenomena, the significant increase in the rate & extent of water uptake as well as the increase in the dry mass loss of the polymeric films upon addition of only minor amounts of carrageenan to ethylcellulose films indicate that this biomacromolecule is a very promising drug release modifier for pharmaceutical dosage forms.

(a) (b)

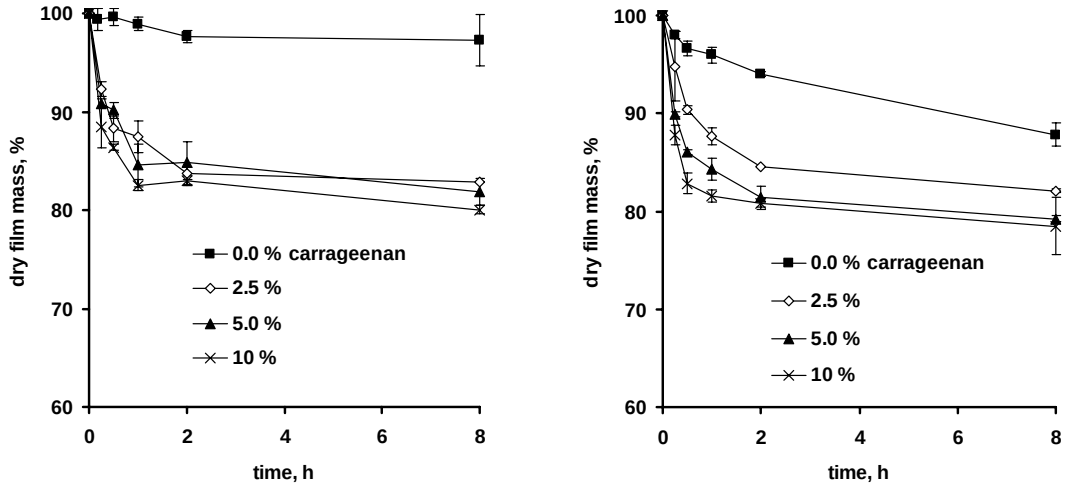


Figure 3.4: Effects of the addition of small amounts of carrageenan (indicated in the figures) on the dry mass loss of ethylcellulose-based films upon exposure to: (a) 0.1 N HCl; (b) phosphate buffer pH 7.4.

3.3.4. Drug release from thin, free films

Figure 3.5 shows the experimentally measured release of the model drug theophylline from thin ethylcellulose films (filled squares). To account for slight differences in the films' thickness (2L) (all films were prepared in triplicate), the time (t) has been normalized with respect to this parameter: t was divided by L^2. This type of normalization is possible, because the release of the drug can quantitatively be described by the same analytical solution of Fick's law of diffusion as used for the description of the water uptake kinetics (Equation 3.6). But in this case the direction of the mass transport is reversed: out of the films into the bulk fluid. Here, M_t and M_∞ represent the absolute cumulative amounts of drug released at time t and $t=\infty$, respectively; D denotes the apparent diffusion coefficient of the drug in the polymeric system. The initial condition takes into account that the drug is homogeneously and molecularly dispersed within the device (clear films). The boundary conditions are based on negligible edge effects (large surface area with respect to the films' thickness) and perfect sink conditions (the drug concentration within the release media remains below 10 % of its

solubility and does, thus, not hinder further drug release by saturation effects). The fittings of this theory to the experimentally measured drug release kinetics are shown in Figure 3.5 (curves). Clearly, good agreement between theory and experiment was obtained, indicating that theophylline diffusion with the ethylcellulose films is the dominant mass transport phenomenon.

Importantly, the addition of only 2.5-10 % (w/w) carrageenan to the ethylcellulose films tremendously accelerates drug release, irrespective of the type of release medium (Figure 3.5). This can be attributed to the increase in the water content and decrease in the dry mass of the films (Figures 3.2 and 3.4), resulting in increased macromolecular mobilities and, thus, increased free volumes available for drug diffusion.

Interestingly, the presence of the hydrophilic biomacromolecule carrageenan does not alter the dominant mass transport mechanism: The good agreement between theory (curves) and experiment (symbols) in all cases indicates that theophylline diffusion remains the rate limiting step, irrespective of the films' composition and type of release medium. Based on these calculations, the apparent diffusivity of the drug within the polymeric systems could quantitatively be determined for all carrageenan contents (Figure 3.6, filled triangles). Clearly, the diffusivity of theophylline in the films significantly increases when adding only small amounts of carrageenan. Importantly, this biomacromolecule is a much more efficient drug release modifier than the synthetic PVA-PEG graft copolymer (filled squares). The ability of carrageenan to alter the drug permeability of ethylcellulose films is similar to that of PG alginate, but pH-independent [19].

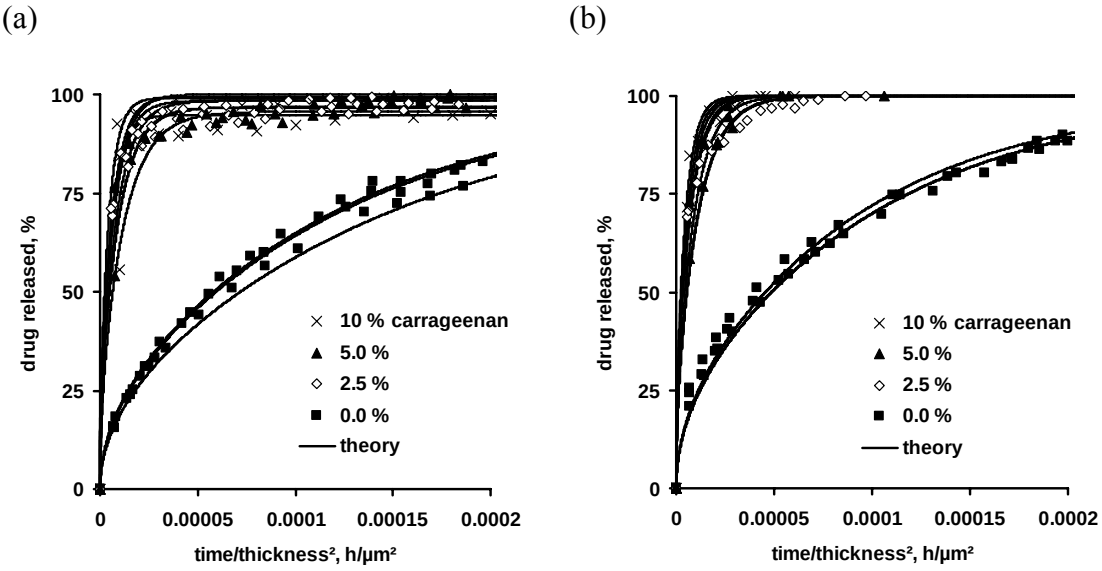


Figure 3.5: Theophylline release from ethylcellulose-based films upon exposure to: (a) 0.1 N HCl; (b) phosphate buffer pH 7.4: Effects of the addition of small amounts of carrageenan (indicated in the figures). The results are normalized to the films' thickness. The symbols represent the experimentally measured values, the curves the fitted theory (Equation 3.6).

Based on these results, it can be expected that carrageenan is a very potent biomacromolecule allowing easy adjustment of drug release kinetics from ethylcellulose-coated pharmaceutical dosage forms.

3.3.5. Drug release from coated pellets

Figure 3.7 illustrates the release of the model drug theophylline from pellets coated with pure (plasticized) ethylcellulose and with ethylcellulose:carrageenan blends in simulated gastric and intestinal fluids at 10 and 20 % (w/w) coating level, respectively. Clearly, the presence of only small amounts of carrageenan effectively increases the resulting drug release rates, irrespective of the type of release medium and coating level. In practice, desired release

profiles (leading to optimal therapeutic effects) can easily be provided by adjusting the carrageenan content.

(a) (b)

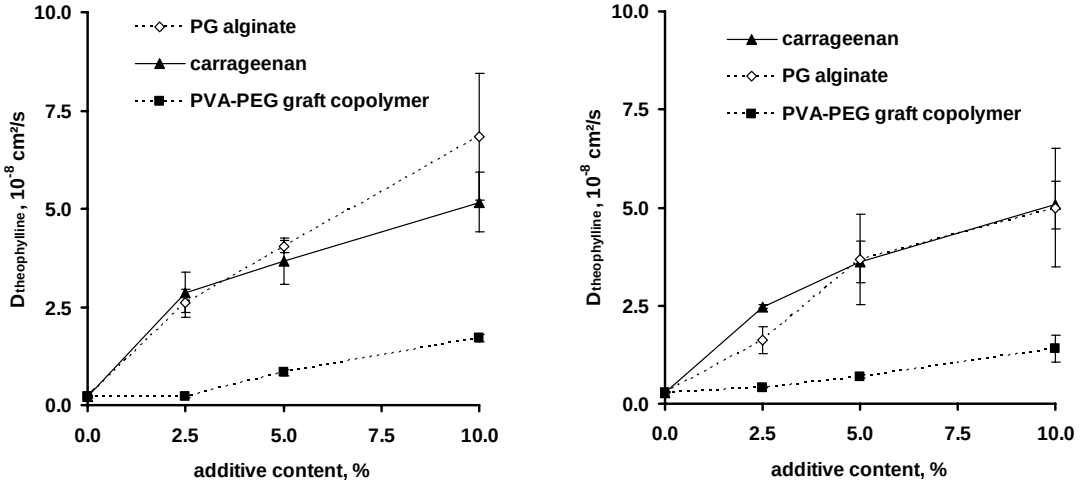


Figure 3.6: Apparent diffusion coefficient of theophylline in ethylcellulose-based films upon exposure to (a) 0.1 N HCl; (b) phosphate buffer pH 7.4: Effects of the type and amount of additive (the results obtained with PVA-PEG graft copolymer are reproduced from [18] for reasons of comparison).

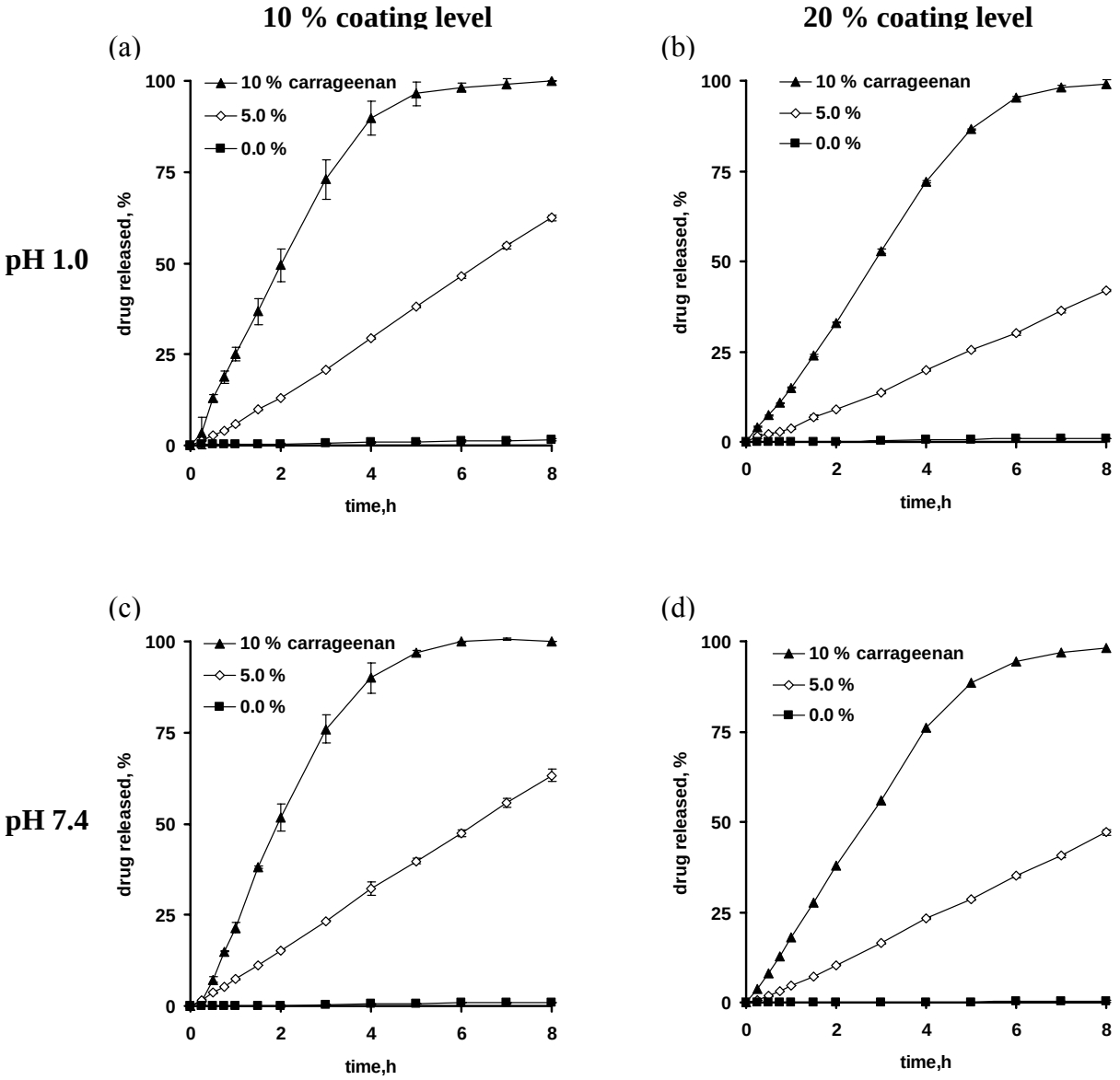


Figure 3.7: Theophylline release from pellets coated with ethylcellulose containing small amounts of carrageenan (indicated in the figures) upon exposure to: (a) 0.1 N HCl, 10 % coating level; (b) 0.1 N HCl, 20 % coating level; (c) phosphate buffer pH 7.4, 10 % coating level; (d) phosphate buffer pH 7.4, 20 % coating level (curing = 1 d at 60° C & ambient RH).

For reasons of comparison, theophylline release from pellets coated with 90 % ethylcellulose and 10 % carrageenan, PVA-PEG graft copolymer or PG alginate in 0.1 N HCl and phosphate buffer pH 7.4 is shown in Figure 3.8 (coating level = 20 %). Clearly, carrageenan is the most efficient drug release modifier. This can be attributed to the more

pronounced increase in the water uptake rate & extent and in the dry mass loss of the film coatings. Thus, to provide similar drug release rates lower amounts of this additive are required.

(a) (b)

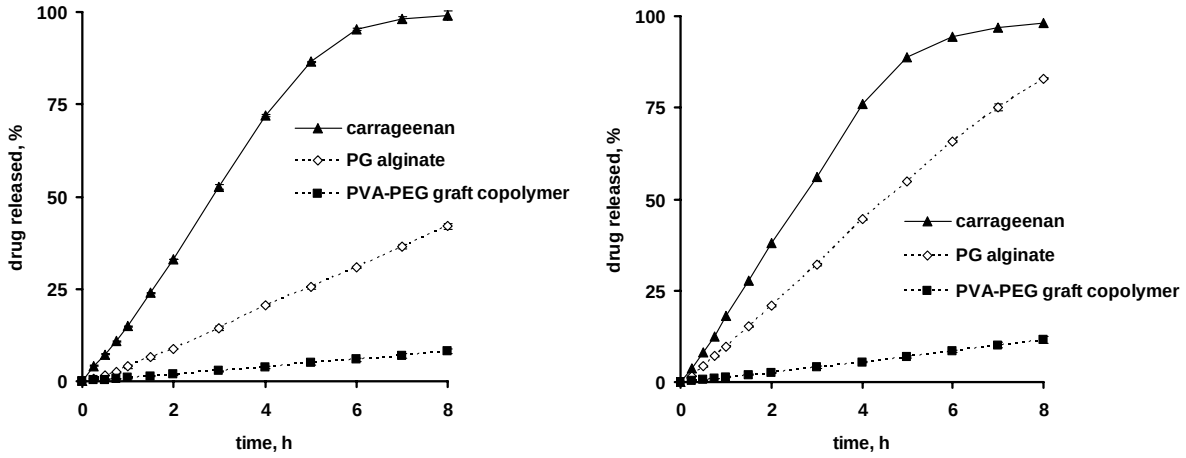


Figure 3.8: Importance of the type of additive (indicated in the figures) on theophylline release from pellets coated with ethylcellulose containing 10 % carrageenan, PG alginate or PVA-PEG graft copolymer upon exposure to: (a) 0.1 N HCl; (b) phosphate buffer pH 7.4 [20 % coating level; curing = 1 d at 60° C & ambient RH] (the results obtained with PVA-PEG graft copolymer and PG alginate are reproduced from [18] for reasons of comparison).

For long term stability during storage, it is decisive that there are no major structural changes within the polymeric film coatings. For example, if the film formation is not complete after coating, further polymer particle coalescence during storage can lead to decreased drug permeabilities and, thus, decreased drug release rates [23]. To avoid/minimize this phenomenon, a thermal treatment (called curing) is generally performed after coating. The idea is that at elevated temperature the mobility of the macromolecules is increased and, thus, particle coalescence facilitated. In some cases, curing is also conducted at elevated relative humidity (RH) to facilitate film formation: Coalescence depends on the capillary

pressure of the interstitial water [24], and water also acts as a plasticizer for many coating polymers and, thus, decreases the glass transition temperature of the polymeric particles. This leads to an increased macromolecular mobility and, consequently, facilitated polymer particle coalescence. Figure 3.9 shows the release of the model drug theophylline from pellets coated with ethylcellulose containing 5 % carrageenan, at 10 and 20 % coating level, in simulated gastric and intestinal fluids, as a function of the curing conditions: 1 or 2 days at 60 °C & ambient RH, or 1 or 2 days at 60 °C & 75 % RH (followed by 1 day at 60 °C & ambient RH for drying). Drug release from uncured pellets (filled squares) is illustrated for comparison. Clearly, a curing step is required in all cases to allow appropriate film formation (polymer particle coalescence). Interestingly, two types of release profiles were observed, dependent on whether curing was conducted at ambient or elevated RH. The lower drug release rates observed after curing at elevated RH suggest a higher degree of polymer particle coalescence. This may reflect potential overdrying of the pseudolatex during coating (which hinders coalescence by removing the driving force of capillary pressure of the interstitial water [24]). The absence of any change between samples cured at 60ºC & ambient RH for 1 day and 2 days is a false stability endpoint if this release profile can be affected by elevated humidity storage. Based on these results it can be concluded that curing must be validated with respect to the effects of both elevated temperature and humidity, not just elevated temperature alone.

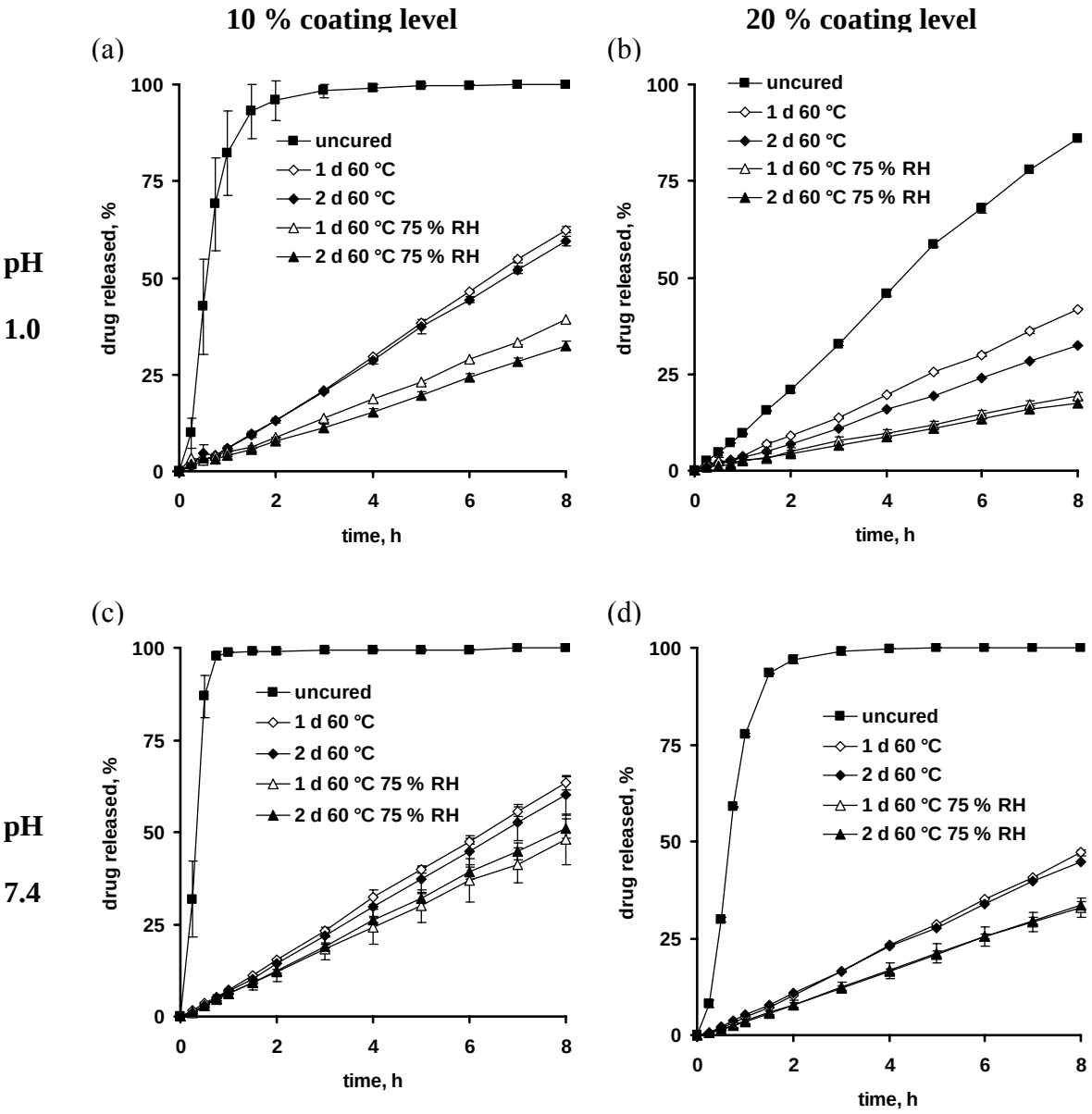


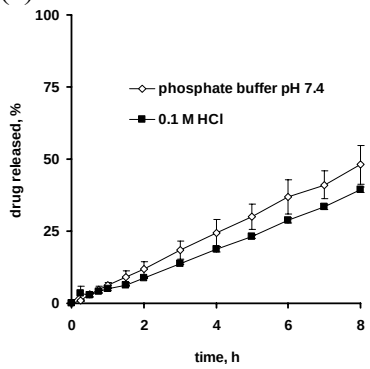
Figure 3.9: Effects of the curing conditions (indicated in the figures) on theophylline release from pellets coated with ethylcellulose containing 5 % carrageenan upon exposure to: (a) 0.1 N HCl, 10 % coating level; (b) 0.1 N HCl, 20 % coating level; (c) phosphate buffer pH 7.4, 10 % coating level; (d) phosphate buffer pH 7.4, 20 % coating level.

3.3.6. Effects of pH on drug release.

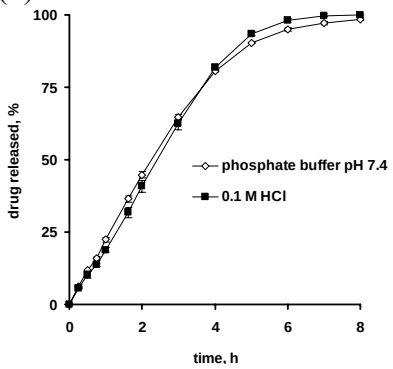
It is well known that the pH - time profile experienced by a pharmaceutical dosage form within the different segments of the human gastro-intestinal tract (e.g., stomach, small and large intestine) can significantly vary from patient to patient and even within the same patient (e.g., due to food effects or diseases which alter the motility of the gastro-intestinal tract). The effects of the pH of the release medium on theophylline release from ethylcellulose:carrageenan coated pellets in simulated gastric and intestinal fluids (0.1 N HCl and phosphate buffer pH 7.4) are shown in Figure 3.10. As it can be seen, the release rates were higher in phosphate buffer for film coatings containing 5 % (w/w) carrageenan, whereas there was no significant difference in the release rates at 10 % carrageenan content, irrespective of the coating level and curing time. Wesseling & Bodmeier [25] reported a similar pH dependency for uncured Aquacoat ECD coatings, which they attributed to the pH-dependent charge of sodium dodecyl sulfate affecting the water penetration rate into a partially coalesced polymeric system. At the higher 10% carrageenan level the film coating is sufficiently hydrophilic (Figure 3.2) to avoid this pH dependency.

5 % carrageenan **10 % carrageenan**

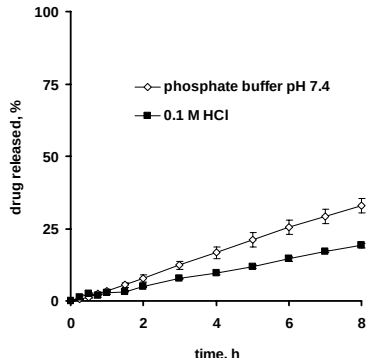
(a)



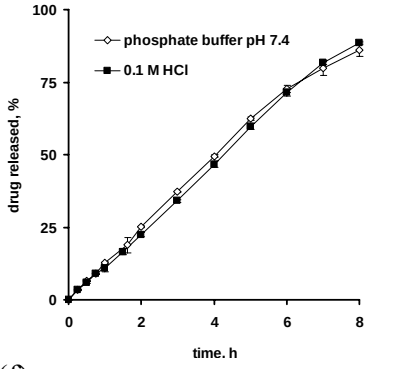
(b)



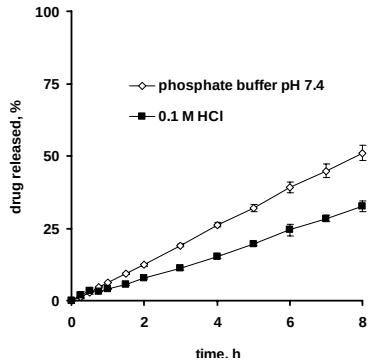
(c)



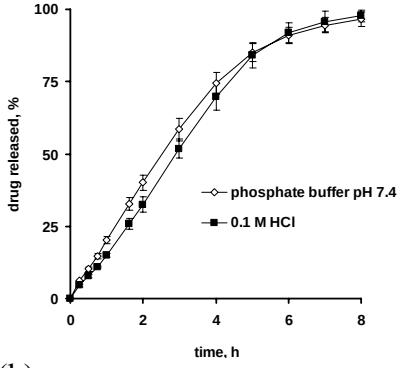
(d)



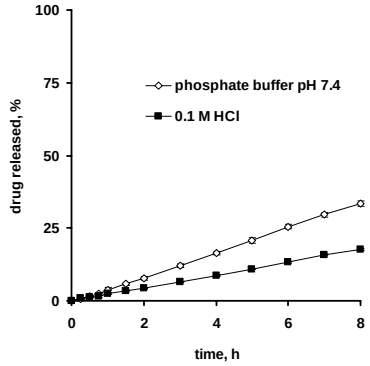
(e)



(f)



(g)



(h)

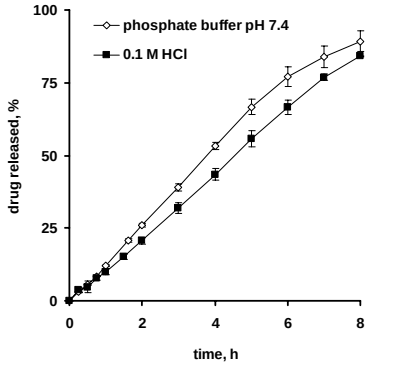


Figure 3.10: Effects of the type of the release medium on theophylline release from pellets coated with ethylcellulose containing 5 or 10 % carrageenan (as indicated): (a+b) 10 % coating level, curing = 1 d 60 °C & 75 % RH; (c+d) 20 % coating level, curing = 1 d 60 °C & 75 % RH; (e+f) 10 % coating level, curing = 2 d 60 °C & 75 % RH; (g+h) 20 % coating level, curing = 2 d 60 °C & 75 % RH.

3.4. Conclusions

The biomacromolecule carrageenan is a highly efficient release modifier for ethylcellulose-coated pharmaceutical dosage forms. The addition of only small amounts allows effective adjustment of drug release kinetics for optimal therapeutic effects. Importantly, carrageenan does not cause flocculation of the coating dispersions, and long term stability during storage seems to be achievable upon appropriate curing.

3.5. References

1. Stenekes, R.J.H., et al., *Pore Sizes in Hydrated Dextran Microspheres.* Biomacromolecules, 2000. **1**(4): p. 696-703.
2. Francis, M.F., et al., *In Vitro Evaluation of pH-Sensitive Polymer/Niosome Complexes.* Biomacromolecules, 2001. **2**(3): p. 741-749.
3. Yilmaz, G., et al., *Modulated Release of a Volatile Compound from Starch Matrixes via Enzymatically Controlled Degradation.* Biomacromolecules, 2002. **3**(2): p. 305-311.
4. Roux, E., et al., *On the Characterization of pH-sensitive Liposome/Polymer Complexes.* Biomacromolecules, 2003. **4**(2): p. 240-248.
5. Stubbe, B.G., et al., *Tailoring the Swelling Pressure of Degrading Dextran Hydroxyethyl Methacrylate Hydrogels.* Biomacromolecules 2003. **4**(3): p. 691-695.
6. Csaba, N., et al., *PLGA:Poloxamer and PLGA:Poloxamine Blend Nanoparticles: New Carriers for Gene Delivery.* Biomacromolecules 2005. **6**(1): p. 271-278.
7. Siepmann, J., et al., *How Autocatalysis Accelerates Drug Release from PLGA-Based Microparticles: A Quantitative Treatment.* Biomacromolecules 2005. **6**(4): p. 2312-2319.
8. Venkatraman, S., et al., *An overview of controlled release systems.*, in *In Handbook of pharmaceutical controlled release technology*, D.L. Wise, Editor. 2000, Marcel Dekker: New York. p. 431-463.
9. McGinity, J.W., *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. 2 ed. 1997, New York: Marcel Dekker.
10. Siepmann, J. and N. Peppas, *Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC).* Adv. Drug Deliver. Rev., 2001. **48**(2-3): p. 139-157.

11. Siepmann, J. and A. Göpferich, *Mathematical modeling of bioerodible, polymeric drug delivery systems.* Adv. Drug Deliver. Rev., 2001. **48**(2-3): p. 229-247.

12. Wade, A. and P.J. Weller, *Handbook of pharmaceutical excipients*. 2 ed. 1994, Washington: American Pharmaceutical Association.

13. Lecomte, F., et al., *pH-Sensitive Polymer Blends used as Coating Materials to Control Drug Release from Spherical Beads: Importance of the Type of Core.* Biomacromolecules, 2005. **6**(4): p. 2074-2083.

14. Frohoff-Hülsmann., M.A., A. Schmitz, and B.C. Lippold, *Aqueous ethyl cellulose dispersions containing plasticizers of different water solubility and hydroxypropyl methylcellulose as coating material for diffusion pellets I. Drug release rates from coated pellets.* Int. J. Pharm., 1999. **177**(1): p. 69-82.

15. Frohoff-Hülsmann, M.A., B.C. Lippold, and J.W. McGinity, *Aqueous ethyl cellulose dispersion containing plasticizers of different water solubility and hydroxypropyl methyl-cellulose as coating material for diffusion pellets II: properties of sprayed films.* Eur. J. Pharm. Biopharm., 1999. **48**(1): p. 67-75.

16. Wong, D. and R. Bodmeier, *The impact of the use of flocculated colloidal dispersions on the drug release from drug-containing films and coated tablets.* Pharm. Res., 1994. **11**: p. S-185.

17. Wong, D. and R. Bodmeier, *Flocculation of an aqueous colloidal ethyl cellulose dispersion (Aquacoat) with a water-soluble polymer, hydroxypropyl methyl cellulose.* Eur. J. Pharm. Biopharm., 1996. **42**(1): p. 12-15.

18. Siepmann, F., et al., *How to adjust desired drug release patterns from ethylcellulose-coated dosage forms.* Journal of Controlled Release, 2007. **119**(2): p. 182-189.

19. Siepmann, F., et al., *pH-sensitive film coatings: Towards a better understanding and facilitated optimization.* European Journal of Pharmaceutics and Biopharmaceutics, 2008. **68**(1): p. 2-10.

20. Crank, J., *The Mathematics of Diffusion*. 2 ed. 1975, Oxford: Clarendon Press.

21. Carslaw, H.S. and J.C. Jaeger, *Conduction of Heat in Solids*. 1959, Oxford: Clarendon Press.

22. Vergnaud, J.M., *Controlled Drug Release of Oral Dosage Forms*. 1993, Chichester: Ellis Horwood.

23. Petereit, H.U. and W. Weisbrod, *Formulation and process considerations affecting the stability of solid dosage forms formulated with methacrylate copolymers.* Eur. J. Pharm. Biopharm., 1999. **47**(1): p. 15-25.

24. Brown, G., *Formation of films from polymer dispersions.* J. Polymer Sci., 1956. **22**(102): p. 423-434.

25. Wesseling, M. and R. Bodmeier, *Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat(R), or an organic ethylcellulose solution.* European Journal of Pharmaceutics and Biopharmaceutics, 1999. **47**(1): p. 33-38.

4. IMPROVED STORAGE STABILITY

Abstract: The major aim of this study was to identify an easy tool to improve the long term stability of polymeric film coatings applied from aqueous dispersions. Drug release profiles from ethylcellulose-coated theophylline pellets were monitored during 6 months *open* storage under ambient and stress conditions ["room temperature/ambient relative humidity (RH)" and "40°C/75 %RH"]. The pellets were cured for 1 or 2 d at 60 °C or for 1 or 2 d at 60°C/75 %RH (followed by 1 d at 60 °C for drying). Drug release was measured in 0.1 N HCl and in phosphate buffer pH 7.4. Interestingly, the addition of only small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer provided stable drug release profiles under all the investigated conditions, irrespective of the type of release medium, coating level, polymer blend ratio and curing conditions. The addition of small amounts of propylene glycol alginate resulted in unaltered drug release kinetics during *open* storage under ambient conditions, but decreasing theophylline release rates during *open* storage under stress conditions, due to further gradual polymer particle coalescence. When adding small amounts of carrageenan to the ethylcellulose coatings, essentially stable theophylline release patterns (with slight variations) were obtained. As coating conditions were not optimized for each system, further work is necessary to distinguish polymer from process effects. The observed stabilizing effects of the investigated added polymers might be attributable to their hydrophilic nature, trapping water within the coatings during film formation and, thus, facilitating polymer particle coalescence. This new concept can be used to overcome one of the major practical obstacles associated with aqueous polymeric film coatings today: storage instability.

4. Improved storage stability

4.1. Introduction

The use of aqueous polymer dispersions instead of organic polymer solutions for film coating offers several advantages, including avoidance of the environmental toxicity and explosion hazards associated with organic solvents, and reduced processing times due to higher polymer contents in the coating formulations (the latter being limited by the spraying viscosities) [1, 2].

However, the mechanism of film formation is fundamentally different when using aqueous polymer dispersions instead of organic polymer solutions: Once the latter are sprayed onto a surface, the organic solvent evaporates, the polymer chains approach each other and finally form a continuous homogeneous film. In contrast, upon spraying aqueous polymer dispersions onto the dosage form's surface, water evaporates, the polymer particles approach each other and - under appropriate conditions (in particular temperature, presence of sufficient amounts of water and/or other plasticizers) - coalesce to form a homogeneous polymeric film. In practice, it is often difficult to assure complete film formation during coating. That is why generally a thermal after-treatment (curing) is performed, in order to complete polymer particle coalescence [3]. However, it is often difficult to ascertain the completeness of film formation even after curing. In these cases, there is a risk of further gradual coalescence on storage, resulting in denser film structures and reduced permeabilites for water and drug. Consequently, the release rates significantly decrease, especially under storage at elevated humidity [4-6].

Ethylcellulose is a very suitable coating polymer, because it is a good film former and generally regarded as nontoxic, non allergenic and nonirritant [7]. It is widely used in oral pharmaceutical formulations for various purposes, including moisture protection and controlled drug delivery. However, if the dosage forms are surrounded by a continuous, completely formed ethylcellulose film, drug release may be too slow, because this polymer is poorly permeable for water and most drugs. To overcome this restriction the addition of

hydroxypropyl methylcellulose (HPMC) as a pore former has been proposed [8, 9]. Unfortunately, HPMC causes flocculation of aqueous ethylcellulose dispersions [10, 11] and the formation of inhomogeneous films. It has also been reported that drug release from pellets coated with ethylcellulose:HPMC blends significantly decreases during storage [8, 12, 13], indicating further polymer particle coalescence. Recently, poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer [PVA-PEG graft copolymer], propylene glycol alginate (PG alginate) and carrageenan have been shown to act as efficient release modifiers for ethylcellulose-coated pellets [14-16]: Broad ranges of drug release profiles can easily be provided by varying the additive's content. Importantly, and in contrast to HPMC, these release modifiers do not cause flocculation of colloidal ethylcellulose dispersions. However, it is not yet clear whether these hybrid coatings are stable on long term storage.

The aim of this study was to monitor drug release profiles from pellets coated with ethylcellulose blended with PVA-PEG graft copolymer, PG alginate or carrageenan, in simulated gastric and intestinal fluids during 6 months *open* storage under ambient and stress conditions (40 °C/75 % relative humidity).

4.2. Experimental section

4.2.1. Materials

Theophylline pellets (70 % w/w drug content; FMC, Philadelphia, PA), Ethylcellulose Aqueous Dispersion NF (Aquacoat ECD; FMC), λ-carrageenan (Viscarin GP 209; FMC), poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer, Kollicoat IR; BASF, Ludwigshafen, Germany), propylene glycol alginate (PG alginate, Protanal ester SD-LB; FMC), triethyl citrate (TEC; Morflex, Greensboro, NC).

4.2.2. Preparation of coated pellets

Theophylline pellets (70 % w/w drug content) were coated with aqueous ethylcellulose dispersion (Aquacoat ECD) containing small amounts of PVA-PEG graft copolymer, PG alginate or carrageenan in a fluidized bed coater equipped with a Wurster insert (Strea 1; Niro Inc., Aeromatic-Fielder AG, Bubendorf, Switzerland). All dispersions were plasticized overnight with triethyl citrate (25 % w/w, based on the ethylcellulose mass). The following ethylcellulose:PVA-PEG graft copolymer/PG alginate/carrageenan blend ratios were investigated: 85:15, 90:10, 95:5 (w/w). The coating dispersions were sprayed onto theophylline pellets until a weight gain of 15 and 20 % (w/w) was achieved. The process parameters were as follows: inlet temperature = 40 °C, product temperature = 38 ± 2 °C, spray rate = 3-5 g/min, atomization pressure = 1.2 bar, air volume = 100 m³/h, nozzle diameter = 1.2 mm. After coating the pellets were further fluidized for 10 min and subsequently cured for 24/48 h at 60°C/ambient relative humidity (RH) or for 24/48 h at 40°C/75 %RH (followed by an additional drying step of 24 h at 60 °C/ambient RH).

4.2.3. Drug release from coated pellets

Theophylline release from the pellets was measured in 0.1 N HCl and phosphate buffer pH 7.4 (USP XXIX) using the paddle apparatus (USP XXIX; Sotax, Basel,

Switzerland) (900 mL; 37 °C, 100 rpm; n = 3). At pre-determined time intervals, 3 mL samples were withdrawn and analyzed UV-spectrophotometrically (λ = 271 nm; Anthelie Advanced; Secomam, Domont, France).

4.2.4. Storage stability

Coated pellets were stored in *open* glass vials at room temperature (23 +/- 2 °C)/ambient RH (55 +/- 5 %) as well as under stress conditions: 40°C/75 %RH. Theophylline release from the pellets was measured before and after 3 and 6 months storage as described in *section 4.2.3*.

4.3. Results and discussion

4.3.1. Storage stability of pellets coated with ethylcellulose:PVA-PEG graft copolymer

Figure 4.1 shows the theophylline release kinetics from pellets coated with 85:15 ethylcellulose:PVA-PEG graft copolymer in 0.1 N HCl before (dotted lines) and after 3 and 6 months *open* storage (full lines). The curing conditions (indicated on the left) were as follows:

(i) 1 d at 60°C/ambient relative humidity (RH);

(ii) 2 d at 60°C/ambient RH;

(iii) 1 d at 60°C/75 %RH (followed by an additional drying step of 1 d at 60 °C/ambient RH); and

(iv) 2 d at 60°C/75 %RH (followed by an additional drying step of 1 d at 60 °C/ambient RH).

The storage conditions were either: “room temperature (RT)/ambient RH” (ambient conditions), or “40°C/75 %RH” (stress conditions) (as indicated at the top). The coating level was 20 % (w/w) in all cases. After 3 and 6 months there were no significant time, temperature or humidity dependent changes in the drug release profiles. This is of great practical importance, because it indicates that:

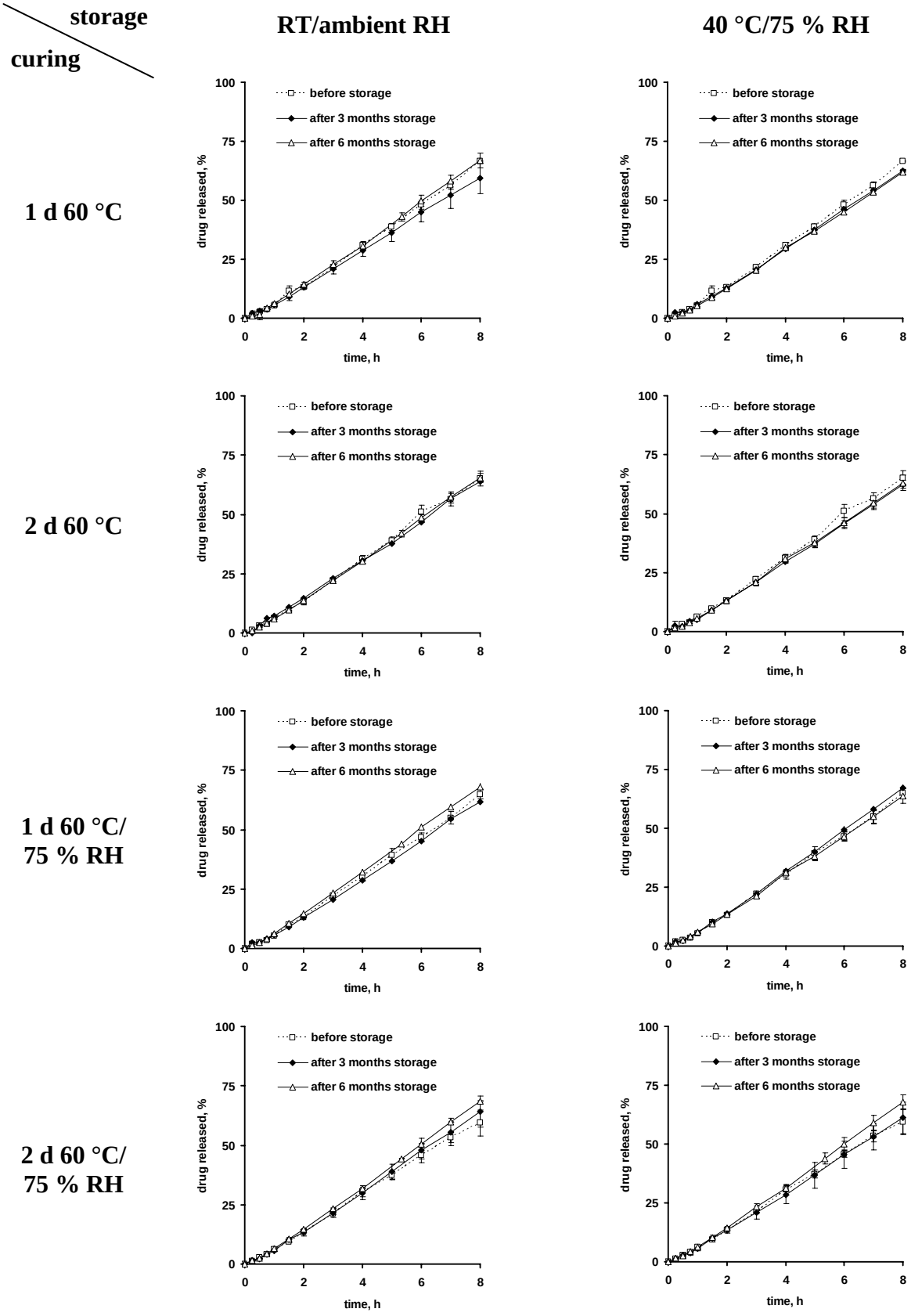


Figure 4.1: Storage stability of pellets coated with 85:15 ethylcellulose:PVA-PEG graft copolymer: Theophylline release in 0.1 N HCl before (dotted lines) and after 3 and 6 months

storage (full lines, as indicated). The curing conditions are shown on the left, the storage conditions at the top (coating level = 20 %).

- The presence of small amounts of PVA-PEG graft copolymer in aqueous ethylcellulose dispersions used for controlled release coatings effectively improves film formation during coating/curing and/or hinders further polymer particle coalescence during long term storage. Importantly, significant structural changes within the polymeric systems during *open* storage under ambient as well as stress conditions are effectively avoided. Improved film formation during coating/curing might be attributable to the hydrophilic nature of PVA-PEG graft copolymer, trapping water within the polymeric systems during film formation. At this stage, the water content is of crucial importance, because: (i) water is mandatory for the capillary effects driving the individual polymer particles together, and (ii) water acts as a plasticizer for ethylcellulose and, thus, increases the mobility of the macromolecules and facilitates polymer particle fusion. Alternatively, the presence of PVA-PEG graft copolymer chains between incompletely fused ethylcellulose particles might sterically hinder further film formation during long term storage.
- In this case curing for 1 d at 60°C was sufficient to provide a release profile insensitive to further temperature and humidity challenge. Shorter curing times may be used in production (it was beyond the scope of this study to identify the minimum curing time), but longer periods of thermal and humidity challenge are useful during development to confirm that maximum retardation of release has been achieved: e.g. no further changes occur on long term storage.

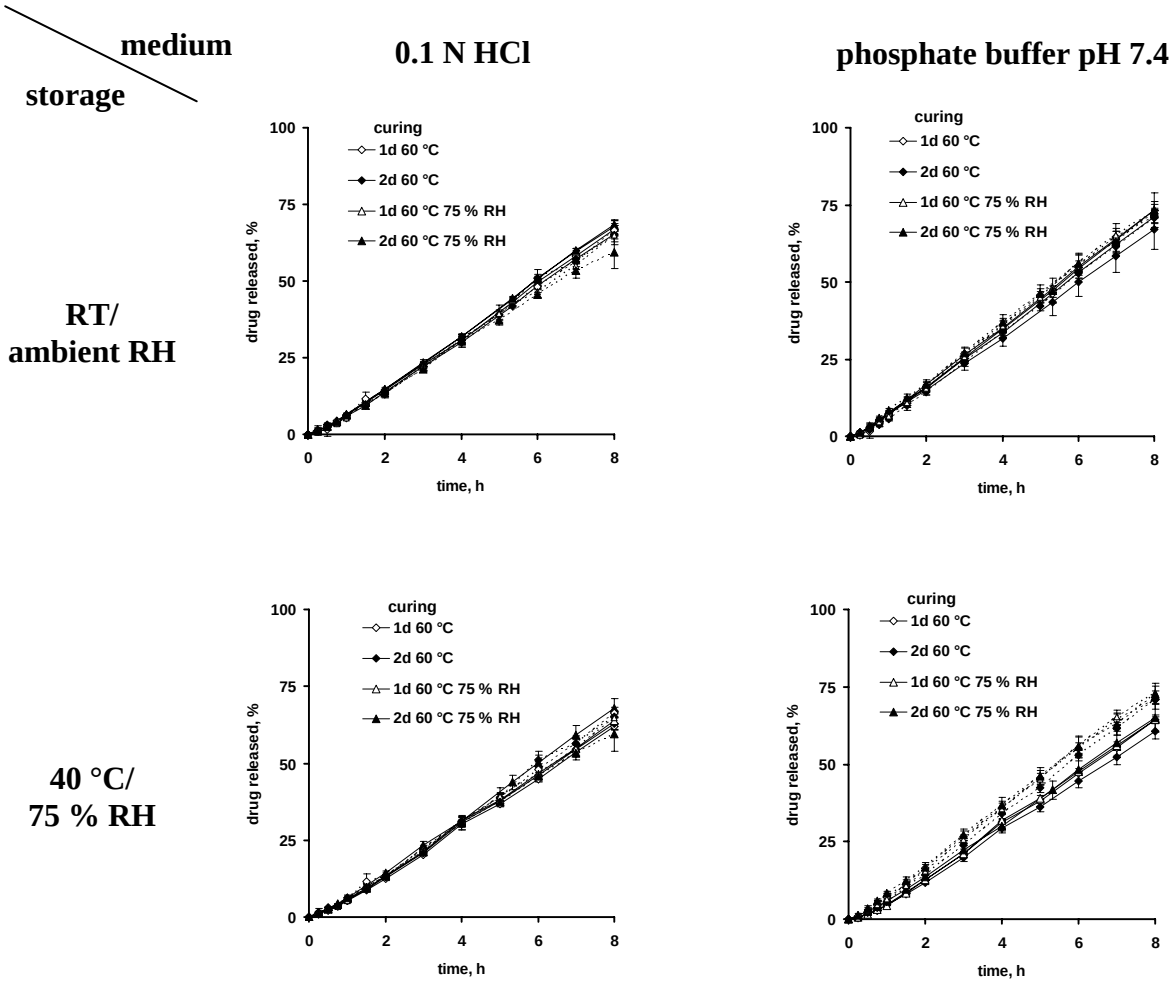


Figure 4.2: Effects of the curing conditions (indicated in the diagrams) on theophylline release from pellets coated with 85:15 ethylcellulose:PVA-PEG graft copolymer before (dotted lines) and after 6 months open storage (full lines) at different temperatures and relative humidities (as indicated on the left) in 0.1 N HCl or phosphate buffer pH 7.4 (as indicated at the top) (coating level = 20 %).

Figure 4.2 shows that the curing conditions did not influence the long term stability of theophylline pellets coated with ethylcellulose:PVA-PEG graft copolymer. On the left/right hand side drug release in 0.1 N HCl/phosphate buffer pH 7.4 is plotted. The effects of the curing conditions on theophylline release before and after 6 months storage (dotted and full lines) at either ambient conditions or stress conditions are illustrated. Clearly, there are no significant changes in the drug release kinetics and no significant effects of the type of curing

conditions. Figures 4.1 and 4.2 are representative of the other ethylcellulose:PVA-PEG graft copolymer formulations, which also showed stable drug release profiles, irrespective of the type of release medium (data not shown).

The fact that in all cases constant drug release rates (zero order kinetics) were observed can be explained as follows: Drug release is predominantly controlled by diffusion through the intact polymer coating. At the inner surface of the ethylcellulose:PVA-PEG graft copolymer membrane a saturated theophylline solution is provided during most of the release period (due to the relatively low solubility of theophylline at 37 °C in 0.1 N HCl and phosphate buffer pH 7.4: 15.4 mg/mL and 12.0 mg/mL [17] and comparatively high initial drug loading). At the same time, perfect sink conditions are provided at the outer surface of the pellets' coatings. Thus, the resulting drug concentration gradients (the driving forces for diffusion) remain constant. Consequently, the drug release rates are constant. The presence of PVA-PEG graft copolymer within the coatings leads to increased water uptake rates and extents, increased dry mass loss upon exposure to the release medium (due to PVA-PEG graft copolymer leaching) and, hence, to increased drug permeability and drug release rates as compared to pure (plasticized) ethylcellulose films [14].

4.3.2. Storage stability of pellets coated with ethylcellulose:PG alginate

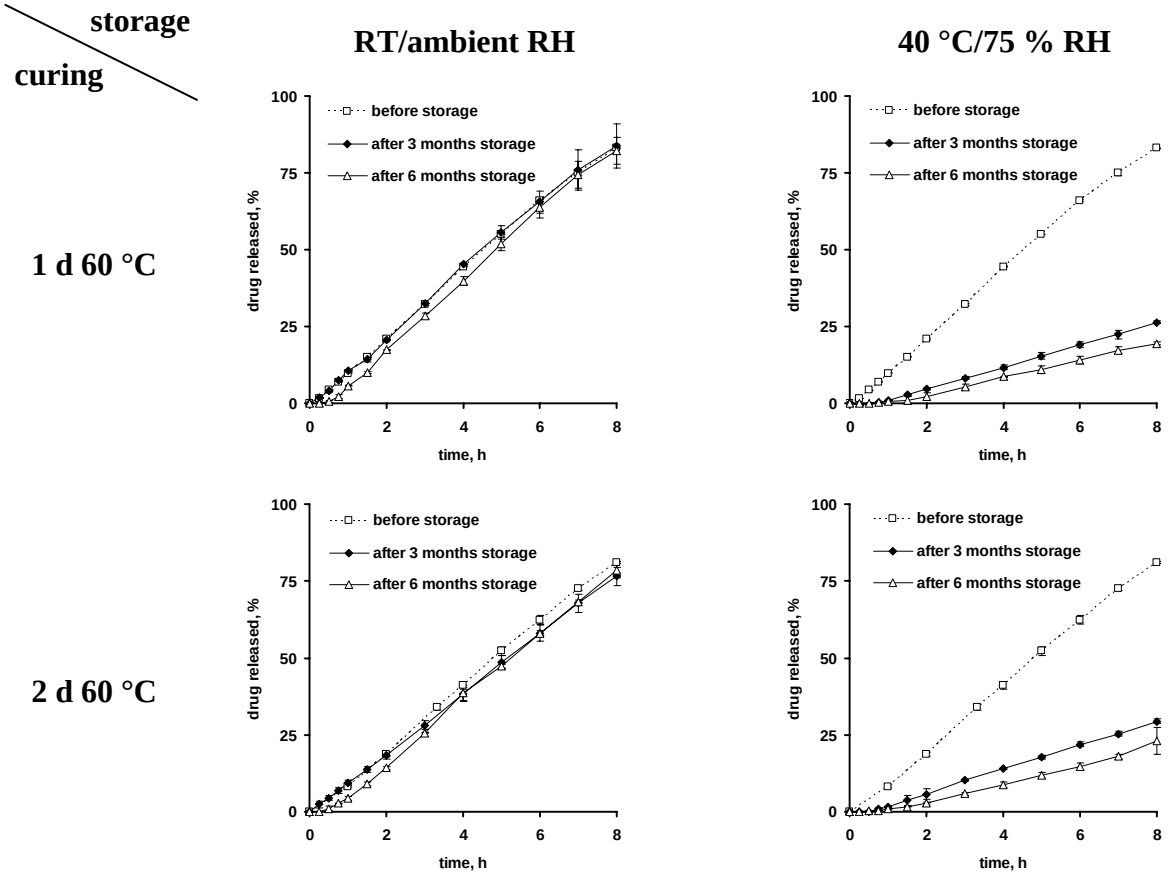


Figure 4.3: Storage stability of pellets coated with ethylcellulose:PG alginate 90:10 blends: Theophylline release in phosphate buffer pH 7.4 before (dotted curves) and after 3 and 6 months storage (full curves, as indicated). The curing conditions are shown on the left, the storage conditions at the top (coating level = 20 %).

Figure 4.3 shows the effects of the storage on theophylline release from pellets coated with 90:10 ethylcellulose:PG alginate. The release medium is phosphate buffer pH 7.4 and the coating level 20 % w/w. Curing conditions are indicated on the left hand side and the storage conditions at the top. Similar tendencies were observed for 1 d 60°C/75 % RH and 2 d 60°C/75 % RH curing (data not shown). Figure 4.4 shows the effects of the curing conditions on the long term stability of theophylline release from these pellets at low and high

pH under ambient and stress conditions. All other investigated ethylcellulose:PG alginate-coated pellets differing in the coating level (10 %) showed similar tendencies (data not shown).

As it can be seen, all the ethylcellulose:PG alginate formulations were stable during 6 months *open* storage under ambient conditions, irrespective of the curing conditions, coating level and type of release medium. Thus, the presence of small amounts of PG alginate allows the formation of polymeric films the structure of which does not significantly alter during *open* storage under ambient conditions.

However, significant time dependent decreases in release rate were observed after 6 months *open* storage at 40°C/75 % RH, the effect being more pronounced in pH 7.4 phosphate buffer. The significantly increased mobility of the ethylcellulose chains at this elevated temperature and elevated relative humidity (water acts as a plasticizer for this polymer) results in further polymer particle coalescence during storage and, thus, denser film structures with lower water and drug permeabilites.

In contrast to the ethylcellulose:PVA-PEG-graft copolymer coatings the ethylcellulose:PG alginate films did not yield equivalent profiles when initially cured at 60°C dry versus 60°C/75% RH. The short and long term humidity dependence of the release profiles suggests overdrying during coating (insufficient water contents to allow for complete film formation, water being mandatory for the capillary effects and acting as a plasticizer for ethylcellulose). The failure to achieve initial humidity-independent performance is reflected in further gradual coalescence on long term high humidity storage. It can be hypothesized that optimization of the ethylcellulose:PG alginate coating conditions can provide similar long term stability of the release profiles as observed in the case of ethylcellulose:PVA-PEG-graft copolymer blends. However, such optimization was not the scope of this study.

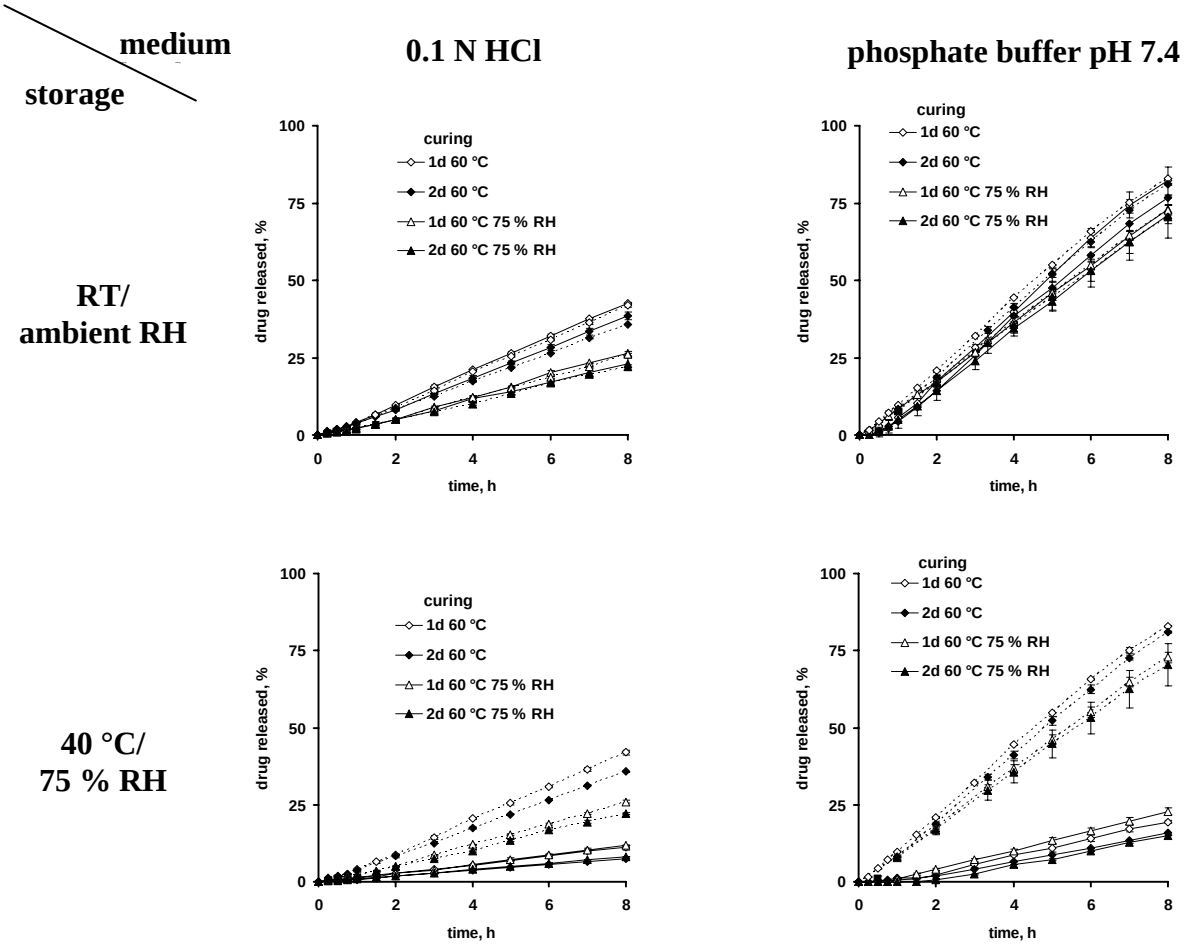


Figure 4.4: Importance of the curing conditions (indicated in the diagrams) for theophylline release from pellets coated with ethylcellulose:PG alginate 90:10 blends before (dotted curves) and after 6 months storage (full curves) at different temperatures and relative humidities (as indicated on the left) in 0.1 N HCl or phosphate buffer pH 7.4 (as indicated at the top) (coating level = 20 %).

The greater release rates at high pH can be attributed to the pH-dependent charge of: (i) sodium dodecyl sulfate (which is present as a stabilizer in the aqueous ethylcellulose dispersion) [2], and (ii) free alginate groups in the partially esterified PG-alginate.

4.3.3. Storage stability of pellets coated with ethylcellulose:carrageenan

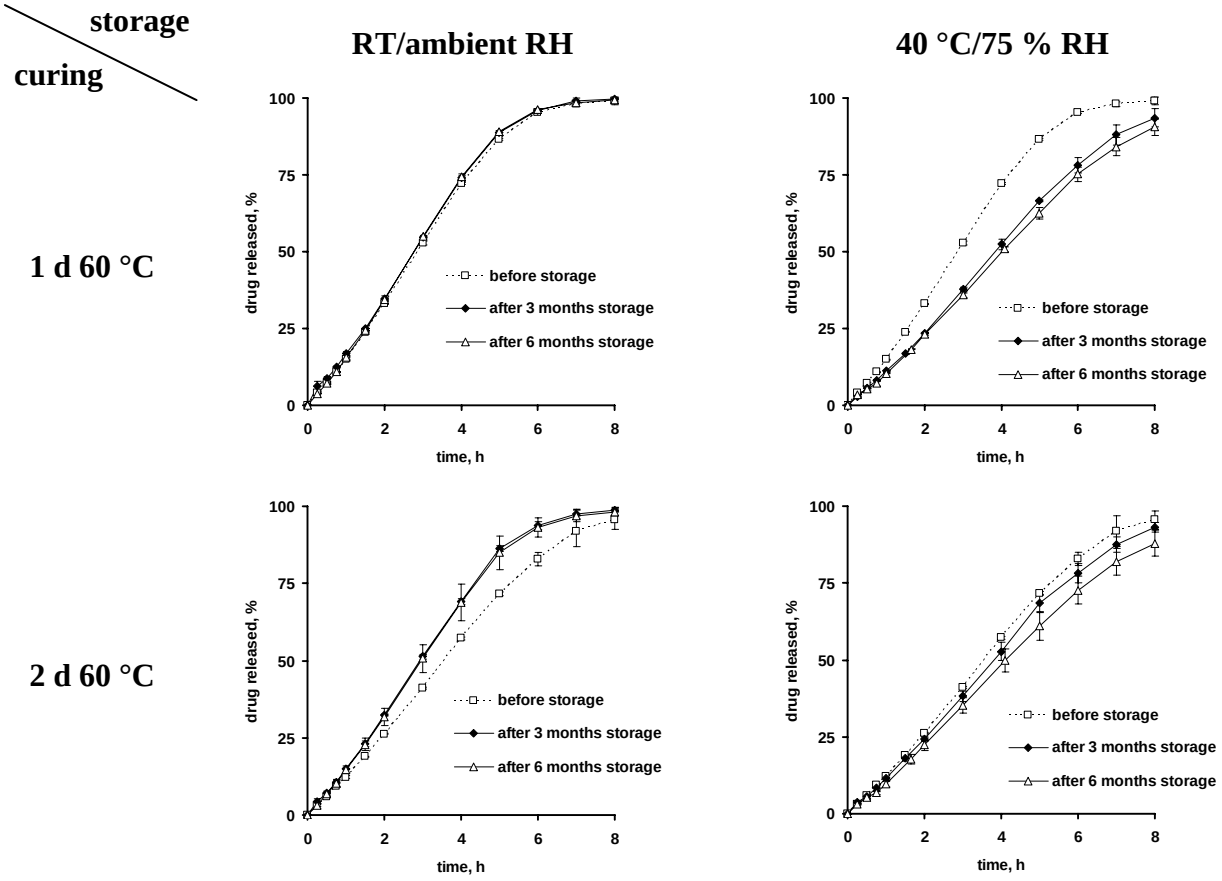


Figure 4.5: Storage stability of pellets coated with ethylcellulose:carrageenan 90:10 blends: Theophylline release in 0.1 N HCl before (dotted curves) and after 3 and 6 months storage (full curves, as indicated). The curing conditions are shown on the left, the storage conditions at the top (coating level = 20 %).

Figure 4.5 shows the effects of long term storage under ambient and stress conditions on theophylline release from pellets coated with ethylcellulose:carrageenan 90:10 in 0.1 N HCl (coating level = 20 % w/w). The curing conditions are indicated on the left hand side, the storage conditions at the top. Similar tendencies were observed for 1 d 60°C/75 % RH and 2 d 60°C/75 % RH curing (data not shown).

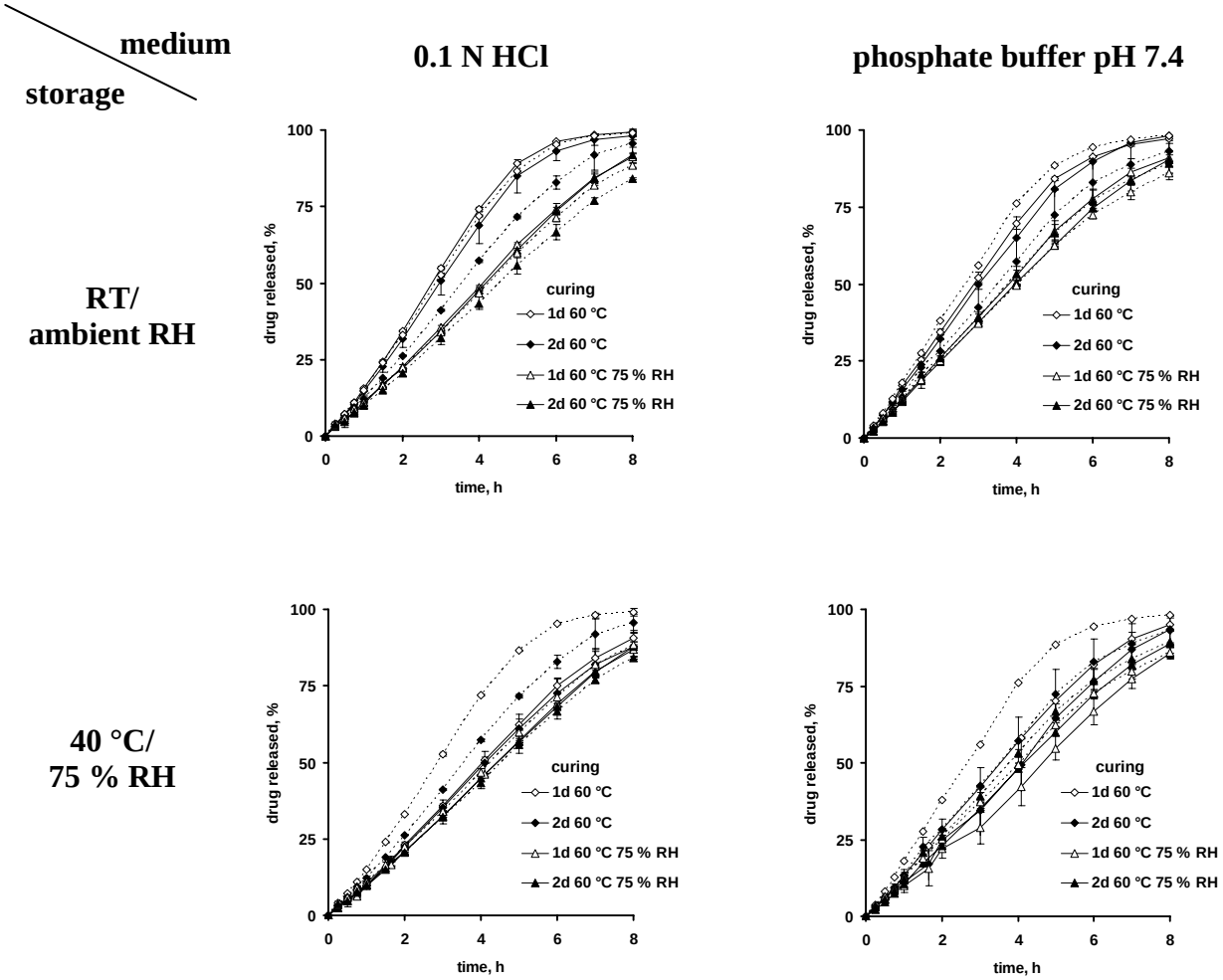


Figure 4.6: Importance of the curing conditions (indicated in the diagrams) for theophylline release from pellets coated with ethylcellulose:carrageenan 90:10 blends before (dotted curves) and after 6 months storage (full curves) at different temperatures and relative humidities (as indicated on the left) in 0.1 N HCl and phosphate buffer pH 7.4 (as indicated at the top) (coating level = 20 %).

Figure 4.6 shows the effects of the curing conditions (indicated in the diagrams) on the storage stability with respect to drug release at low and high pH from pellets coated with ethylcellulose:carrageenan 90:10 blends. The illustrated tendencies were similar for all the investigated formulations, including results obtained with pellets coated with 10 % w/w ethylcellulose:carrageenan as well as with pellets coated with ethylcellulose:carrageenan 95:5 blends (data not shown).

Clearly, in all cases there were only slight variations in the resulting drug release patterns, irrespective of the carrageenan content, curing conditions, coating level, type of release medium and storage conditions. Interestingly, there was no evident relationship between any of the investigated parameters and the direction of the slight changes in the drug release rate: The latter decreased in some cases, increased in others, or remained unaltered. The reason for the slightly increasing/decreasing drug release rates is not fully understood. Further partial polymer particle coalescence (leading to denser and less permeable films and, thus, decreased drug release rates) as well as potential drug migration into the film coatings (leading to increased concentration gradients and, thus, increased drug release rates) might be involved. It was beyond the scope of this study to fully elucidate this aspect. Importantly, the extent of the changes in the drug release rates is limited in all cases, even during 6 months *open* storage under stress conditions. As in *section 4.3.2* optimisation of the coating conditions to give initial humidity independence was not included in this study.

4.3.4. Reproducibility and robustness of the coating process

From a practical point of view, it is of fundamental importance to have an idea of the reproducibility and robustness of a film coating process. To assess the effects of day-to-day reproducibility, batch-to-batch variability of Aquacoat ECD, and variations in the coating level, the 85:15 ethylcellulose:PVA-PEG graft copolymer system was the subject of further reproducibility/robustness studies.

Figure 4.7 shows the release of theophylline from pellets coated with 85:15 ethylcellulose:PVA-PEG-graft copolymer on three different days (coating trials #1-3) in 0.1 N HCl (results in phosphate buffer pH 7.4 were similar, data not shown). The coating level was 15 % w/w, the pellets were cured for 1 d at 60 °C. Clearly, the observed variations in the drug release kinetics were only minor in all cases (irrespective of the type of release

medium), indicating the good reproducibility of the coating process with this type of polymer blend.

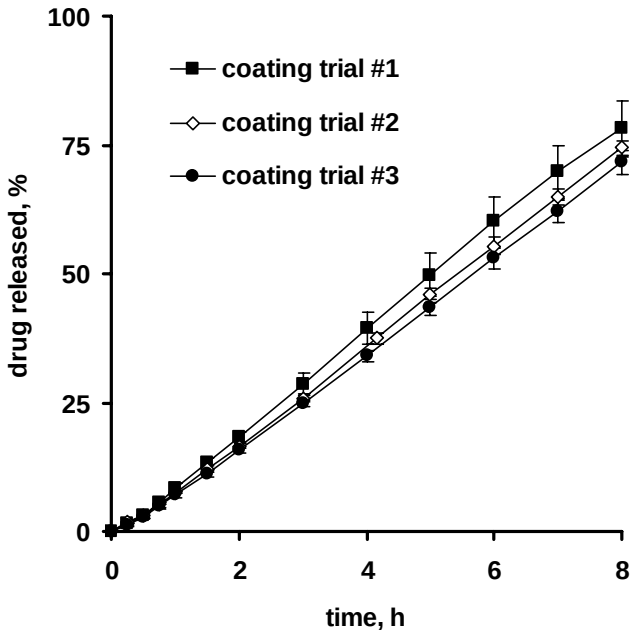


Figure 4.7: Reproducibility of the coating process with ethylcellulose:PVA-PEG graft copolymer 85:15 blends: Theophylline release in 0.1 N HCl from pellets coated in three different trials (the number is indicated in the diagrams) (coating level = 15 %; curing = 1 d 60 °C).

Importantly there was no effect to use of different batches of Aquacoat ECD on drug release from theophylline pellets coated with 15% 85:15 ethylcellulose:PVA-PEG-graft copolymer and cured for 1 d at 60 °C, irrespective to the type of release medium (data not shown).

Actual film coating levels can vary slightly from batch-to-batch or when using different types of coating equipment, or operating at different scales. By allowing the use of higher Aquacoat coating levels the effects of film coating thickness variations should be minimized. The ± 0.5% coating level range in Figure 4.8 represents a ± 3.3% error range. As

it can be seen, there was no significant difference in release rates in 0.1 N HCl which demonstrates the utility and reproducibility of these types of hybrid ethylcellulose pseudolatex coatings. In phosphate buffer pH 7.4, similar results were obtained (data not shown).

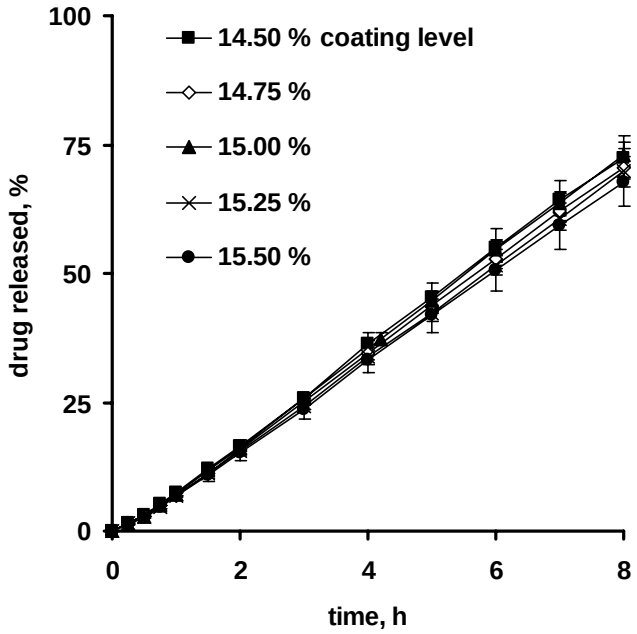


Figure 4.8: Robustness of the coating process with ethylcellulose:PVA-PEG graft copolymer blends: Effects of slight variations in the coating level (indicated in the diagrams) on theophylline release in 0.1 N HCl (polymer blend ratio = 85:15; curing = 1 d 60 °C).

4.4. Conclusions

The presented new concept of adding small amounts of a physically compatible polymer to aqueous ethylcellulose dispersions tracking water within the system during film formation can be used to overcome one of the major practical obstacles associated with polymeric film coatings today: storage instability.

4.5. References

1. McGinity, J.W., *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. 2 ed. 1997, New York: Marcel Dekker.
2. Wesseling, M. and R. Bodmeier, *Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat(R), or an organic ethylcellulose solution.* European Journal of Pharmaceutics and Biopharmaceutics, 1999. **47**(1): p. 33-38.
3. Lippold, B.C. and R. Monells Pages, *Film formation, reproducibility of production and curing with respect to release stability of functional coatings from aqueous polymer dispersions.* Pharmazie, 2001, Pages 5-17. **56**(1): p. 5-17.
4. Siepmann, F., et al., *Aqueous HPMCAS coatings: Effects of formulation and processing parameters on drug release and mass transport mechanisms.* European Journal of Pharmaceutics and Biopharmaceutics, 2006. **63**(3): p. 262-269.
5. Wu, C. and J.W. McGinity, *Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer.* European Journal of Pharmaceutics and Biopharmaceutics, 2000. **50**(2): p. 277-284.
6. Amighi, K. and A.J. Moes, *Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit RS 30D film-coated sustained-release theophylline pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42**(1): p. 29-35.
7. Wade, A. and P.J. Weller, *Handbook of Pharmaceutical Excipients*. 2 ed. 1994, Washington: American Pharmaceutical Association.
8. Frohoff-Hülsmann., M.A., A. Schmitz, and B.C. Lippold, *Aqueous ethyl cellulose dispersions containing plasticizers of different water solubility and hydroxypropyl*

methylcellulose as coating material for diffusion pellets I. Drug release rates from coated pellets. Int. J. Pharm., 1999. **177**(1): p. 69-82.

9. Frohoff-Hülsmann, M.A., B.C. Lippold, and J.W. McGinity, *Aqueous ethyl cellulose dispersion containing plasticizers of different water solubility and hydroxypropyl methyl-cellulose as coating material for diffusion pellets II: properties of sprayed films.* Eur. J. Pharm. Biopharm., 1999. **48**(1): p. 67-75.
10. Wong, D. and R. Bodmeier, *The impact of the use of flocculated colloidal dispersions on the drug release from drug-containing films and coated tablets.* Pharm. Res., 1994. **11**: p. S-185.
11. Wong, D. and R. Bodmeier, *Flocculation of an aqueous colloidal ethyl cellulose dispersion (Aquacoat) with a water-soluble polymer, hydroxypropyl methyl cellulose.* Eur. J. Pharm. Biopharm., 1996. **42**(1): p. 12-15.
12. Hoffart, V., et al., *Storage stability of pellets coated with the aqueous ethylcellulose dispersion-Aquacoat ECD at elevated temperature and humidity,* in *2005 AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists*. 2005: Nashville, USA.
13. Hoffart, V., et al., *Effect of unconventional curing conditions on storage stability of pellets coated with Aquacoat ECD,* in *2005 AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists*. 2005: Nashville, USA.
14. Siepmann, F., et al., *How to adjust desired drug release patterns from ethylcellulose-coated dosage forms.* Journal of Controlled Release, 2007. **119**(2): p. 182-189.
15. Siepmann, F., et al., *pH-sensitive film coatings: Towards a better understanding and facilitated optimization.* European Journal of Pharmaceutics and Biopharmaceutics, 2008. **68**(1): p. 2-10.

16. Siepmann, F., et al., *Carrageenan as an Efficient Drug Release Modifier for Ethylcellulose-Coated Pharmaceutical Dosage Forms.* Biomacromolecules, 2007. **8**(12): p. 3984-3991.

17. Bodmeier, R. and H. Chen, *Evaluation of biodegradable poly(lactide) pellets prepared by direct compression.* Journal of Pharmaceutical Sciences, 1989. **78**(10): p. 819 - 822.

5. LONG TERM STABILITY: IMPORTANCE OF THE TYPE OF DRUG AND STARTER CORE

Abstract: Instability during long term storage due to further gradual coalescence of the film remains one of the major challenges when using aqueous polymer dispersions for controlled release coatings. It has recently been shown that the addition of small amounts of poly(vinyl acetate)-poly(ethylene glycol)-graft-copolymer (PVA-PEG-graft-copolymer) to aqueous ethylcellulose dispersion provides long term stable drug release patterns even upon open storage under stress conditions in the case of theophylline matrix cores. However, the transferability of this approach to other types of drugs and starter cores exhibiting different osmotic activity is yet unknown. The aim of this study was to evaluate whether this novel approach is also applicable to freely water-soluble drugs and osmotically active sugar starter cores. Importantly, long term stable drug release profiles from coated diltiazem HCl layered sugar cores could be achieved even upon open storage for 1 year under stress conditions (40 °C and 75 % relative humidity). However, to provide desired drug release profiles the amount of added PVA-PEG-graft-copolymer must be adjusted. A minimal critical content of 10 % w/w of this hydrophilic additive was identified, under which further polymer particle coalescence upon long term storage under stress conditions cannot be excluded. Potentially too rapid drug release can effectively be slowed down by increasing the coating level. Thus, adapting the polymer blend ratio and coating thickness desired and long term stable drug release profiles (even under stress conditions and open storage) can be provided for very different types of drugs and starter cores by the addition of small amounts of PVA-PEG-graft-copolymer to aqueous ethylcellulose dispersion.

5. Long term stability: Importance of the type of drug and starter core

5.1. Introduction

Ethylcellulose is a highly suitable polymer for film coating [1-3]. It is nontoxic, non allergenic, nonirritant and a good film former [4, 5]. For many years this polymer has been widely used in oral pharmaceutical formulations for various purposes, including moisture protection, taste masking [6] and controlled release.

Ethylcellulose-based film coatings can either be applied from organic solutions or from aqueous dispersions [7]. The use of *aqueous* polymer dispersions instead of *organic* polymer solutions offers various major advantages, including reduced processing times (due to the higher solids' contents that can be used in the coating formulations, as a result of the comparatively low viscosity of aqueous polymer dispersions versus that of organic polymer solutions), avoidance of potential product toxicity due to residual organic solvents and reduced environmental concerns [7, 8]. But care needs to be taken, because the underlying film formation mechanisms are fundamentally different: In organic polymer solutions the individual macromolecules are highly mobile. Upon solvent evaporation the polymer chains approach each other and finally form a continuous homogenous network with a high degree of polymer chain entanglement [9]. In contrast, in the case of aqueous polymer dispersions the polymer is initially deposited as polymer spheres, which must fuse or coalesce to form a continuous homogenous network. Failure to achieve full coalescence will give film coatings with significantly different microstructure [10]. Upon water evaporation the polymer particles approach each other and form densely packed arrays [11, 12]. Under appropriate conditions (in particular at an appropriate temperature and water content) the individual particles fuse together. The presence of water during this process has two major impacts: (i) It acts as a plasticizer for many polymers (including ethylcellulose), increasing the macromolecular mobility and, thus facilitating polymer particle coalescence, and (ii) it provides the capillary forces driving the polymer particles together. Often, complete polymer particle coalescence is difficult to be assured during the *coating* process. This is why generally a thermal after-

treatment (curing step) is required [7, 13]. The idea is to increase the temperature and, thus, the mobility of the polymer chains, facilitating further polymer particle coalescence. If the curing is performed at elevated relative humidity, significant amounts of water act as plasticizer and at the same time increase the capillary forces. However, in practice/in production curing is generally conducted only at ambient relative humidity and the acceptable curing times and temperatures are limited. Thus, even an additional curing step (feasible during production) cannot assure fully coalesced films in various cases, resulting in further polymer particle coalescence during long term storage. This often leads to decreasing drug permeability of the film coatings and, thus, to decreasing drug release rates [14, 15].

To overcome these restrictions the addition of small amounts of poly(vinyl acetate)-poly(ethylene glycol)-graft-copolymer (PVA-PEG-graft-copolymer) to aqueous ethylcellulose dispersion was recently proposed [16, 17]. The presence of this hydrophilic compound can be expected to trap water within the film coatings during *coating* and *curing*, thus, facilitating polymer particle coalescence. For theophylline matrix cores an ethylcellulose film coating containing 15 % PVA-PEG-graft-copolymer was shown to provide long term stable drug release profiles even upon open storage under stress conditions (40 °C, 75 % relative humidity). However, yet it is not clear whether this approach can also be applied to other types of drugs and other types of pellet starter cores, exhibiting different osmolarity.

The aim of this study was to evaluate the transferability of this novel approach allowing for significantly improved long term stability of aqueous polymeric coatings, which remains one of the major challenges to be addressed when coating solid dosage forms with aqueous polymer dispersions, to other types of pellets.

5.2. Experimental section

5.2.1. Materials

Sugar starter cores (sugar spheres NF, 710–850 µm; NP Pharm, Bazainville, France), diltiazem hydrochloride (diltiazem HCl; VWR, Fontenay-sous-Bois, France), Ethylcellulose Aqueous Dispersion NF (Aquacoat ECD; FMC, Philadelphia, PA), poly(vinyl alcohol)-poly(ethylene glycol)-graft-copolymer (PVA-PEG-graft-copolymer, Kollicoat IR; BASF, Ludwigshafen, Germany), triethyl citrate (TEC; Morflex, Greensboro, NC, USA), dibutyl sebacate (DBS; Morflex).

5.2.2. Preparation of drug layered starter cores

Sugar starter cores were coated with an aqueous solution of diltiazem HCl (18.2 % w/w) and hydroxypropyl methylcellulose (HPMC, Methocel E 5; Colorcon, Dartford, UK) (0.9 % w/w) in a fluidized bed coater (Strea 1, Wurster insert; Niro, Bubendorf, Switzerland). The process parameters were as follows: inlet temperature = 40 °C, product temperature = 40±2 °C, spray rate = 1-3 g/min, atomization pressure = 1.2 bar, air volume = 100 m³/h, nozzle diameter = 1.2 mm. The final drug loading of the diltiazem HCl layered sugar cores was 10 and 20 % w/w, respectively.

5.2.3. Preparation of polymer coated pellets

The drug layered sugar cores were coated with aqueous ethylcellulose dispersion (Aquacoat ECD) containing small amounts of PVA-PEG-graft-copolymer in a fluidized bed coater (Strea 1, Wurster insert). All dispersions were plasticized overnight with TEC or DBS (25 % w/w, based on the ethylcellulose content), respectively. The following ethylcellulose:PVA-PEG-graft-copolymer blend ratios were investigated: 85:15, 90:10, 95:5 (w:w). The coating dispersions were sprayed onto the diltiazem HCl layered sugar cores until a weight gain of 5-30 % (w/w) was achieved (as indicated). The process parameters were as

follows: inlet temperature = 38 °C, product temperature = 38 ± 2 °C, spray rate = 2-3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. After coating the pellets were further fluidized for 10 min and subsequently cured for 24 h at 60°C at ambient relative humidity.

5.2.4. Drug release studies

Diltiazem HCl release from the pellets was measured in 0.1 N HCl and phosphate buffer pH 7.4 (USP 30) using the paddle apparatus (USP 30; Sotax, Basel, Switzerland) (900 mL, 37 °C, 100 rpm; n = 3). At pre-determined time intervals, 3 mL samples were withdrawn and analyzed UV-spectrophotometrically (λ = 236.9 nm in 0.1 N HCl and λ = 237.4 nm in phosphate buffer pH 7.4; UV-1650PC, Shimadzu, Champs-sur-Marne, France).

5.2.5. Long term storage stability

Coated pellets were stored in open glass vials at room temperature and ambient relative humidity (RH) as well as under stress conditions (40 °C and 75 % RH). Diltiazem HCl release from the pellets was measured before and after 3, 6 or 12 months storage as described in section 5.2.4.

5.2.6. Determination of the drug solubility

Excess diltiazem HCl was placed in contact with 0.1 N HCl and phosphate buffer pH 7.4 (USP 30) at 37 °C in a horizontal shaker (80 rpm, GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany) for at least 48 h. Every 12 h, samples were withdrawn, filtered and analyzed for their drug content as described in section 5.2.4 until equilibrium was reached.

5.3. Results and discussion

5.3.1. Ethylcellulose:PVA-PEG-graft-copolymer 85:15 blends

Recently, long term stable and constant drug release rates during 8-12 h were reported for theophylline matrix cores coated with ethylcellulose:PVA-PEG-graft-copolymer 85:15 blends at a coating level of 15 % [17]. In contrast to those pellets containing poorly water-soluble theophylline, in the present case very rapid drug release was observed when using this type of film coating at the same coating level and similarly sized diltiazem HCl layered sugar cores, irrespective of the type of release medium (Figure 5.1, dotted curves). This significant difference can at least partially be attributed to the much higher aqueous solubility of diltiazem HCl compared to theophylline: 662 mg/ml versus 15.4 mg/ml in 0.1 N HCl at 37 °C, and 581 mg/ml versus 12.0 mg/ml in phosphate buffer pH 7.4 at 37 °C, respectively (values in phosphate buffer are reproduced from Bodmeier and Chen, 1989 [18]). Furthermore, the presence of the sugar core can be expected to result in more pronounced water penetration into the pellet (driven by osmosis) upon contact with the release media, resulting in an increased hydrostatic pressure acting against the film coating [19]. Importantly, as in the case of theophylline matrix cores, diltiazem HCl release from the pellets coated with ethylcellulose:PVA-PEG-graft-copolymer 85:15 blends was stable during open storage for 3 and 6 months under ambient as well as under stress conditions (40 °C and 75 % RH), irrespective of the type of release medium (Figure 5.1, solid curves).

Thus, the overall approach to add small amounts of PVA-PEG-graft-copolymer to aqueous ethylcellulose dispersion to provide long term stability even under stress conditions is applicable also to other types of drugs than theophylline and to osmotically active starter cores. However, the exact thickness and composition of the film coatings suitable to achieve controlled drug release during 8-12 h need to be adjusted. In order to slow down diltiazem HCl release from the investigated pellets, two strategies were followed: the

percentage of the water-soluble PVA-PEG-graft-copolymer was decreased and the coating level was increased.

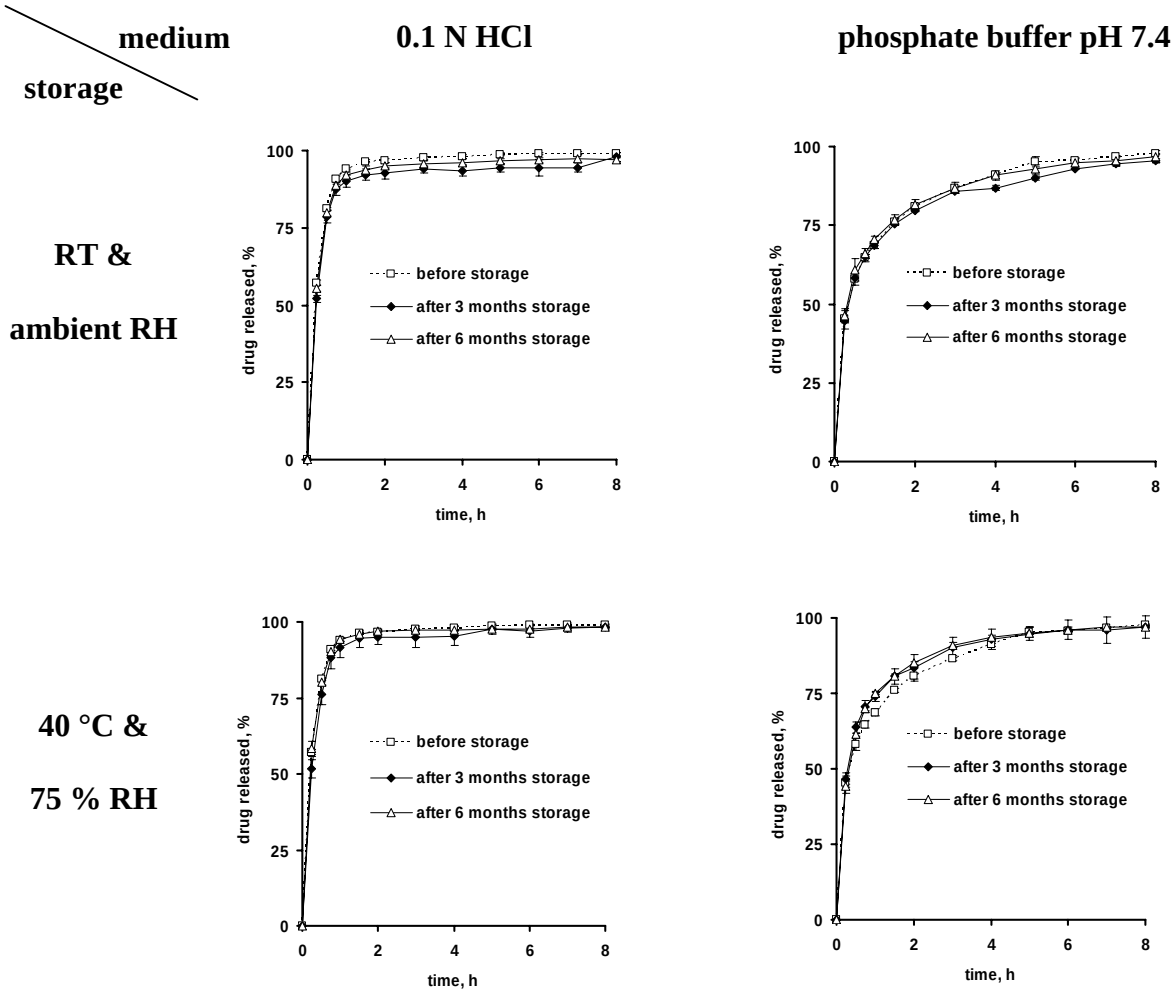


Figure 5.1: Drug release from diltiazem HCl layered sugar cores coated with ethylcellulose:PVA-PEG-graft-copolymer 85:15 before (dotted lines) and after 3 and 6 months storage (full lines, as indicated). The release media are shown at the top and the storage conditions on the left (coating level: 15 %, plasticizer: TEC, drug loading of the diltiazem HCl layered sugar cores: 10 %).

5.3.2. Effects of the PVA-PEG-graft-copolymer content on drug release

As it can be seen in Figure 5.2, the lowering of the PVA-PEG-graft-copolymer content in the film coating from 15 to 0 % was very efficient to slow down drug release from the coated diltiazem HCl layered sugar cores, irrespective of the type of release medium. This can

be explained by the water-*in*solubility and lower permeability of ethylcellulose compared to PVA-PEG-graft-copolymer [16]. In contrast to theophylline matrix cores coated with this type of polymer blend, no zero order release kinetics were observed. This can be attributed to the significantly higher water-solubility of diltiazem HCl compared to theophylline: The entire drug dose is rapidly dissolved upon water penetration into the pellets, and drug molecules that leave the system are not replaced by dissolving drug excess. Thus, the drug concentration gradients (inside – outside the polymeric membranes) decrease with time, resulting in decreasing absolute and relative drug release rates, irrespective of the type of release medium and PVA-PEG-graft-copolymer content (Figure 5.2).

Based on these findings, ethylcellulose:PVA-PEG-graft-copolymer 95:5 blends were selected for further studies, allowing for intermediate drug release rates.

(a) (b)

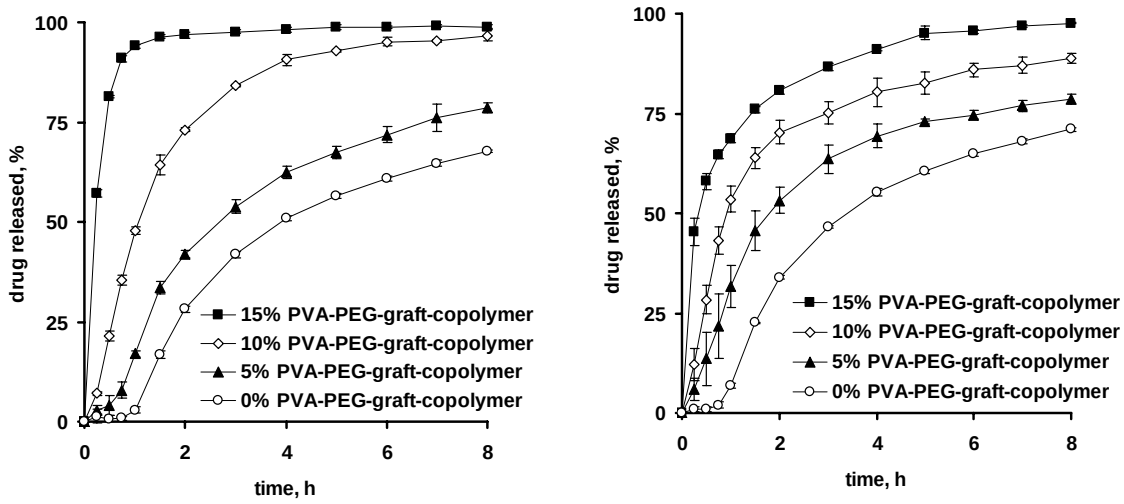


Figure 5.2: Effects of the PVA-PEG graft-copolymer content (indicated in the diagrams) in the ethylcellulose-based film coatings on drug release in: (a) 0.1 N HCl and (b) phosphate buffer pH 7.4 (coating level: 15 %, plasticizer: TEC, drug loading of the diltiazem HCl layered sugar cores: 10 %).

5.3.3. Ethylcellulose:PVA-PEG-graft-copolymer 95:5 blends

In addition to the variation of the PVA-PEG-graft-copolymer content also the variation of the coating level is an efficient tool to adjust desired release patterns from the investigated systems (Figure 5.3).

(a) (b)

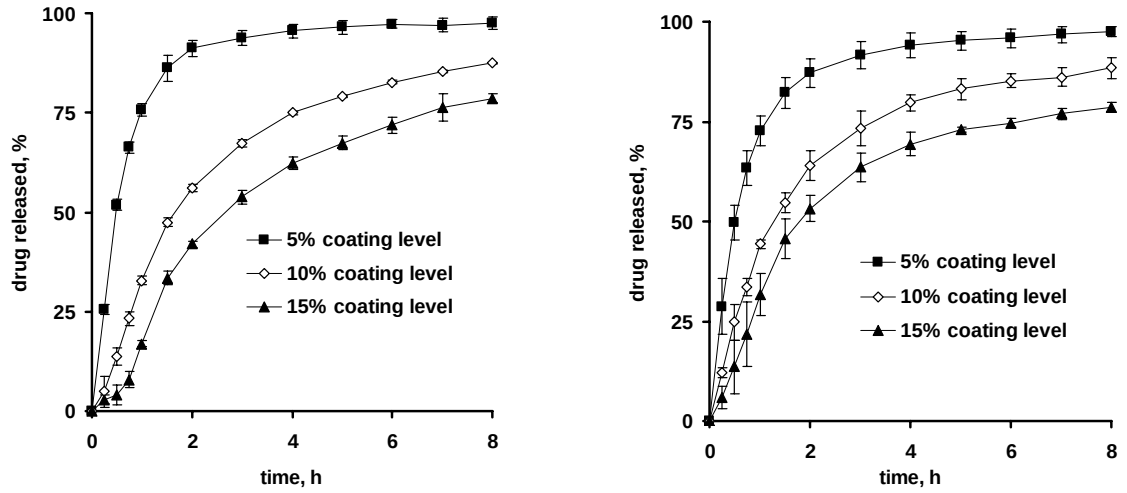


Figure 5.3: Effects of the coating level (indicated in the diagrams) on drug release from ethylcellulose:PVA-PEG-graft-copolymer 95:05 coated diltiazem HCl layered sugar cores in: (a) 0.1 N HCl and (b) phosphate buffer pH 7.4 (plasticizer: TEC, drug loading of the diltiazem HCl layered sugar cores: 10 %).

An increase in the coating level from 5 to 15 % w/w resulted in a significant decrease in the absolute and relative release rates, irrespective of the type of release medium. Importantly, the drug release patterns from these pellets did not significantly change upon open storage for 3 and 6 months under *ambient* conditions (irrespective of the type of release medium) and under *stress* conditions in 0.1 N HCl (Figure 5.4). However, the release rate decreased upon open long term storage under *stress* conditions in *phosphate buffer pH 7.4*. This phenomenon can probably be attributed to further polymer particle coalescence. The

effect is more pronounced under stress conditions than under ambient conditions, because the mobility of the ethylcellulose chains significantly increases with increasing temperature and because water acts as a plasticizer for ethylcellulose and is mandatory for the capillary forces driving the particles together. The effect is also more pronounced at pH 7.4 than at pH 1.0, because Aquacoat ECD contains the anionic surfactant sodium dodecyl sulphate (SDS): In only partially coalesced films, the wettability of the film coatings and their permeability

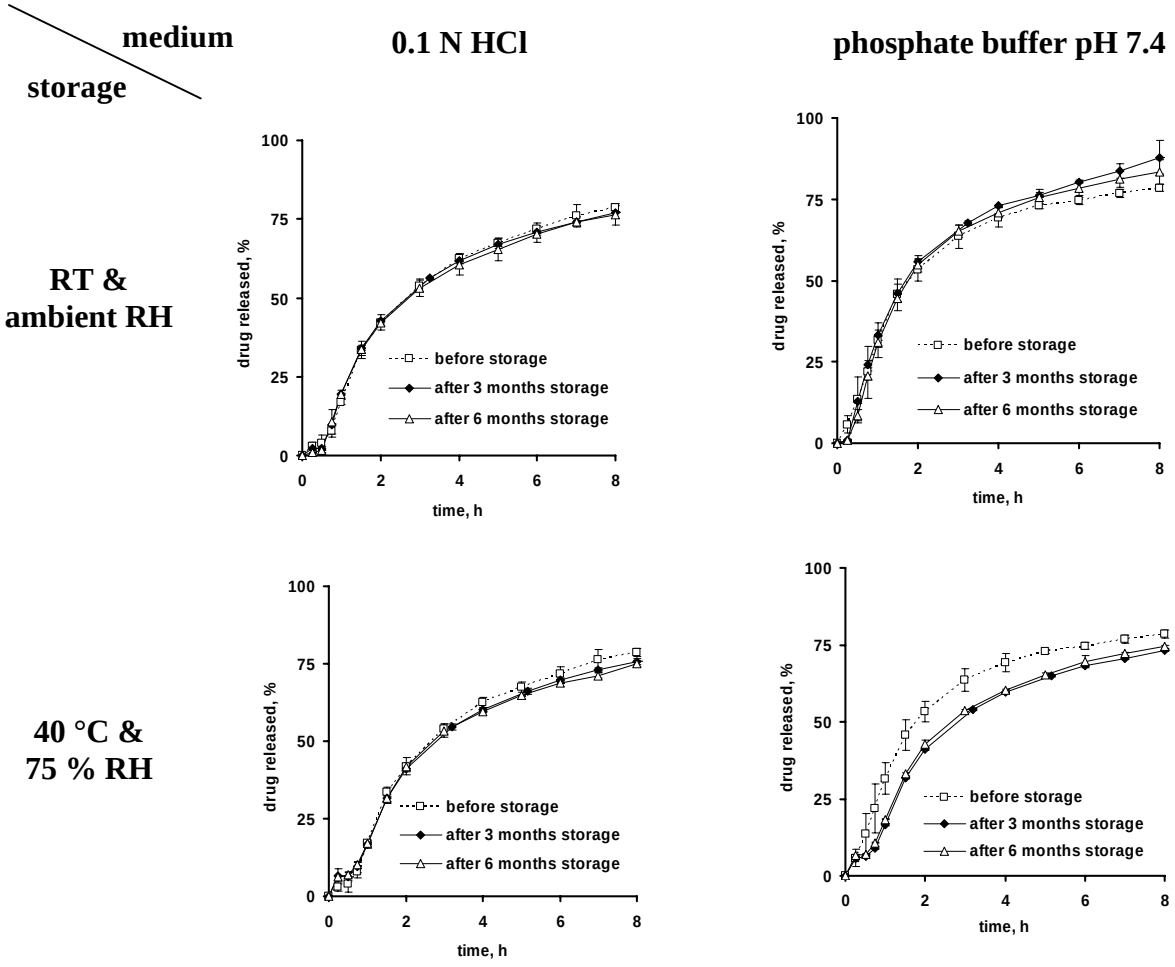


Figure 5.4: Drug release from diltiazem HCl layered sugar cores coated with ethylcellulose:PVA-PEG-graft-copolymer 95:5 before (dotted lines) and after 3 and 6 months storage (full lines, as indicated). The release media are shown at the top, the storage conditions on the left (coating level: 15 %, plasticizer: TEC, drug loading of the diltiazem HCl layered sugar cores: 10 %).

depend on the charge of this surfactant. At low pH, SDS is protonated and, thus, neutral, whereas at pH 7.4 it is deprotonated and, thus, negatively charged. The negatively charged SDS more effectively lowers the surface tension and facilitates water penetration into the partially coalesced film.

Please note that the *relative* and not the *absolute* drug release rates are plotted in Figure 5.4. To minimize the importance of the decrease in the *relative* drug release rate observed upon open long term storage under stress conditions from the investigated pellets in phosphate buffer pH 7.4, the *total* drug loading was increased from 10 to 20 % w/w (referred to the drug layered sugar core). The idea was that the absolute drug release rate might be unaffected from this change, and that due to the increase in the 100 % reference value the decrease in the *relative* drug release should be reduced.

However, this strategy failed as it can be seen in Figure 5.5: The decrease in the relative release rate in phosphate buffer pH 7.4 remained approximately the same, whereas now also in 0.1 N HCl a (slight) instability upon 3 and 6 months open storage under *stress* conditions (40 °C and 75 % RH) was observed. As in the case of diltiazem HCl layered sugar cores with 10 % drug loading, storage under *ambient* conditions did not alter the release profiles, irrespective of the type of release medium.

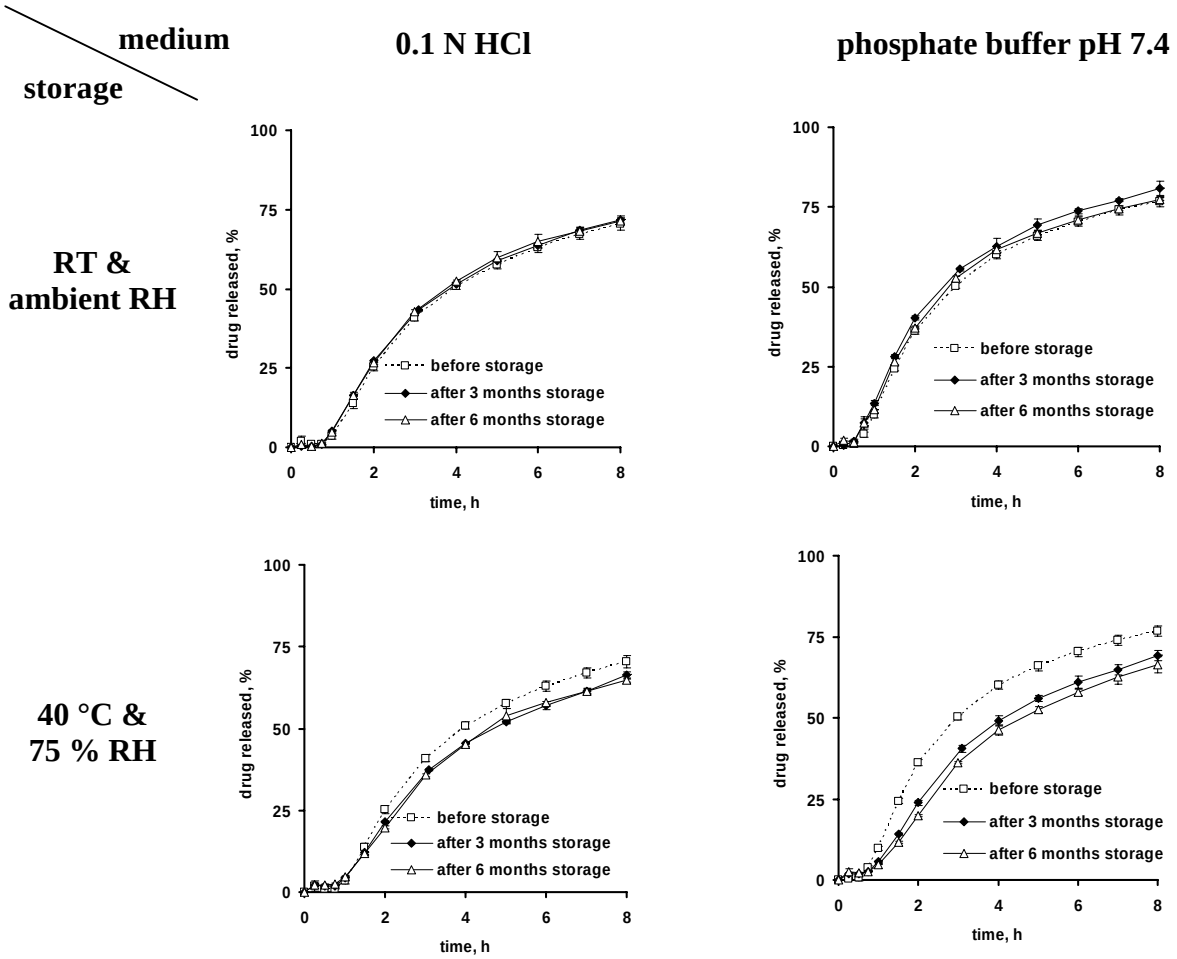


Figure 5.5: Drug release from diltiazem HCl layered sugar cores coated with ethylcellulose:PVA-PEG-graft-copolymer 95:5 before (dotted lines) and after 3 and 6 months storage (full lines, as indicated). The release media are shown at the top, the storage conditions on the left (coating level: 15 %, plasticizer: TEC, drug loading of the diltiazem HCl layered sugar cores: 20 %).

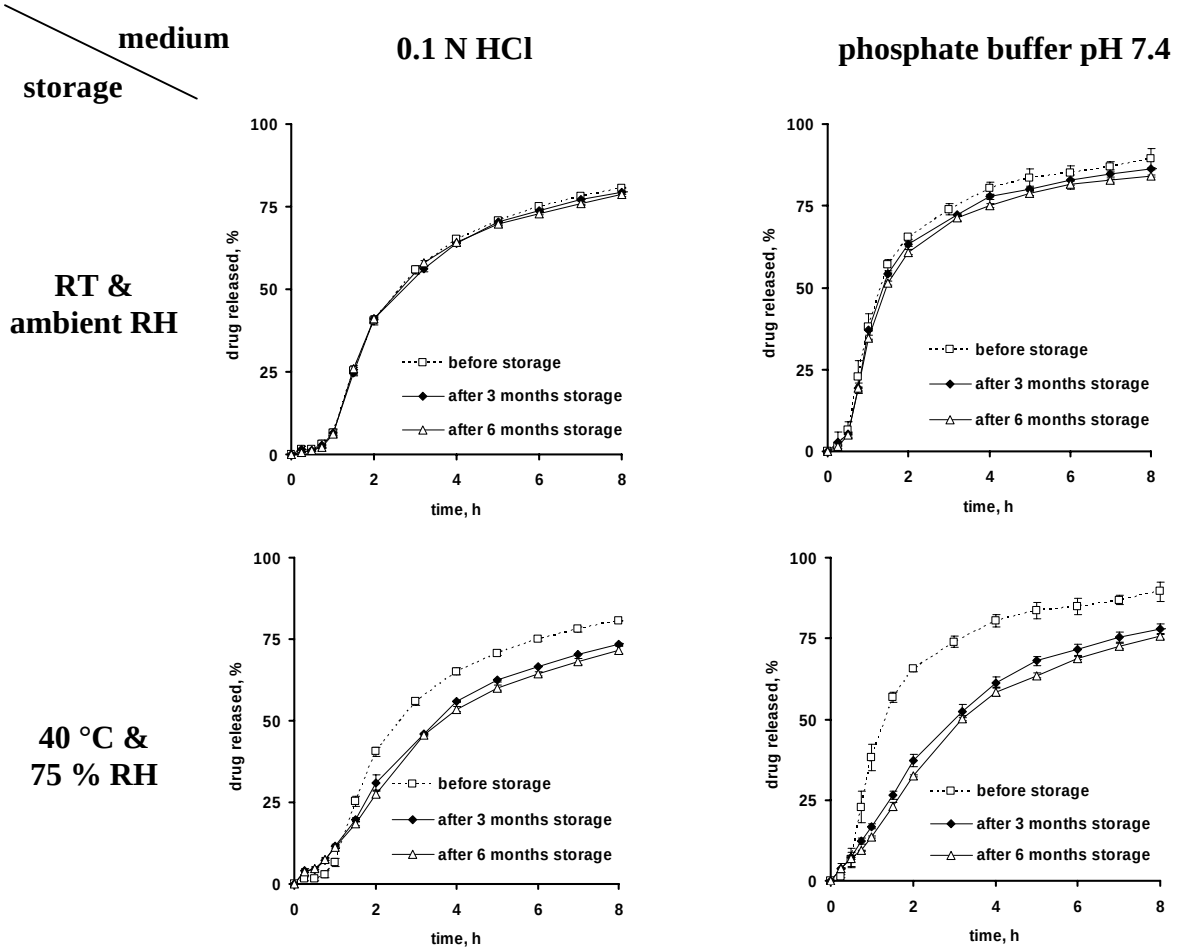


Figure 5.6: Drug release from diltiazem HCl layered sugar cores coated with ethylcellulose:PVA-PEG-graft-copolymer 95:5, plasticized with DBS, before (dotted lines) and after 3 and 6 months storage (full lines, as indicated). The release media are shown at the top, the storage conditions on the left (coating level: 15 %, drug loading of the diltiazem HCl layered sugar cores: 10 %).

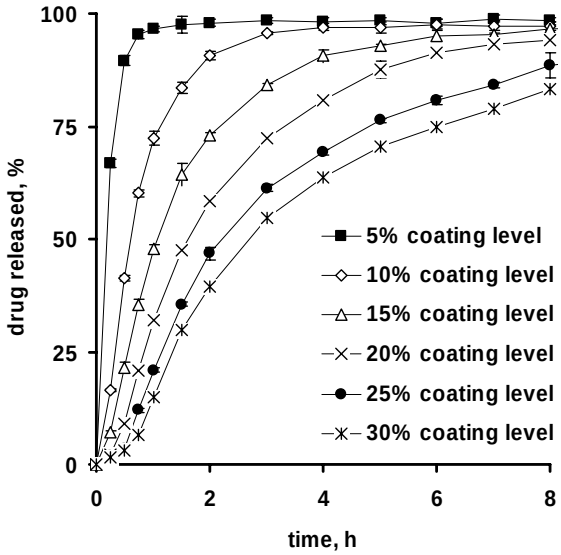


Figure 5.7: Importance of the coating level (indicated in the diagram) on drug release from diltiazem HCl layered sugar cores coated with ethylcellulose:PVA-PEG-graft-copolymer 90:10 in 0.1 N HCl (plasticizer: TEC, drug loading of the diltiazem HCl layered sugar cores: 10 %).

Since plasticizer is essential for mobility of the macromolecules, the type of plasticizer might affect the degree of polymer particle coalescence in the film coatings and/or the release profile. In an attempt to alter the film formation, the water-*in*soluble plasticizer dibutyl sebacate (DBS) was used instead of the water-soluble plasticizer triethyl citrate (TEC). However, as it can be seen in Figure 5.6, both, the storage *stability* under *ambient* conditions as well as the storage *instability* under *stress* conditions remained. Please note that the drug loading of the diltiazem HCl layered sugar cores was again 10 % for reasons of comparison. The decrease in the *relative* drug release rate upon 3 and 6 months storage under stress conditions was even more pronounced than in the case of the water-soluble plasticizer TEC (Figure 5.6 versus Figure 5.4).

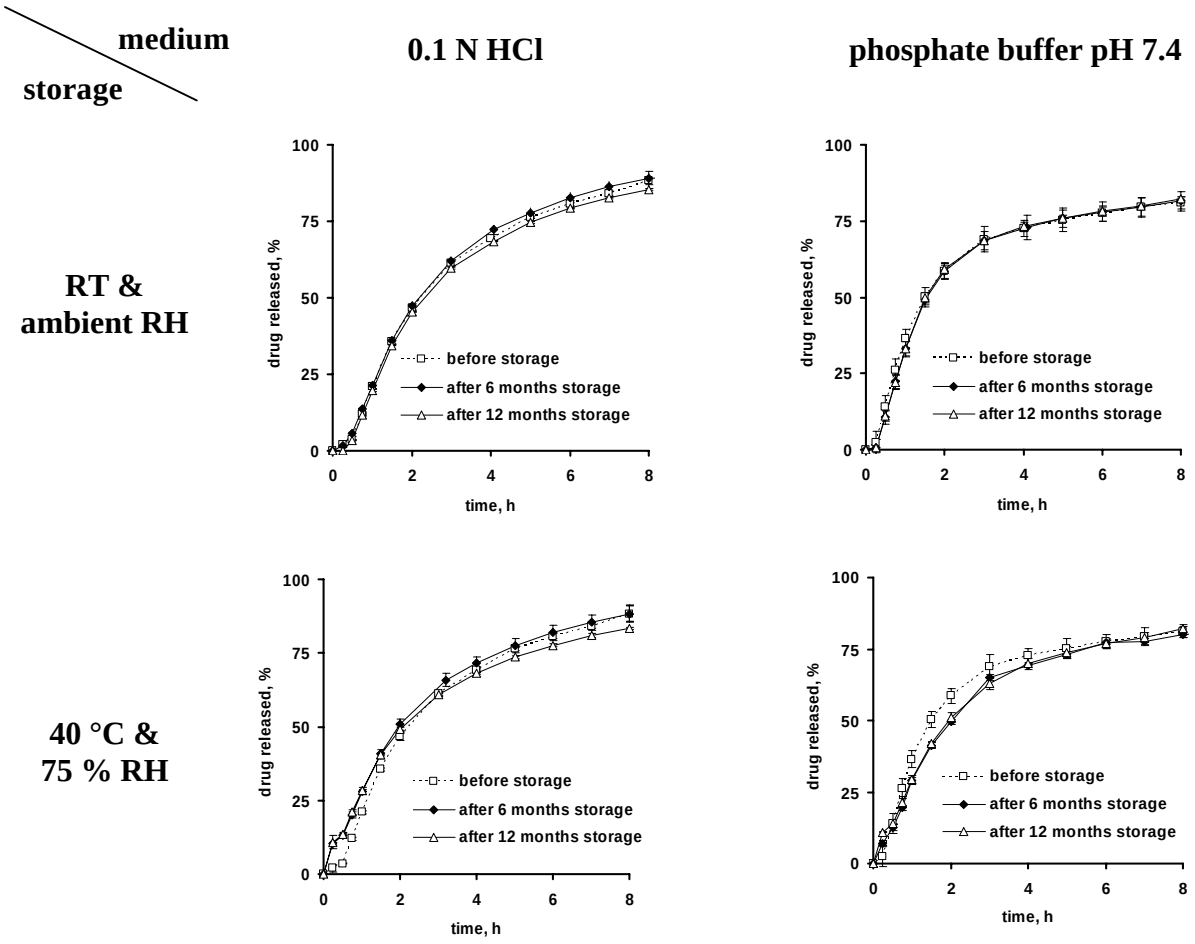


Figure 5.8: Drug release from diltiazem HCl layered sugar cores coated with ethylcellulose:PVA-PEG-graft-copolymer 90:10 before (dotted lines) and after 6 and 12 months storage (full lines, as indicated). The release media are shown at the top, the storage conditions on the left (plasticizer: TEC, coating level: 30 %, drug loading of the diltiazem HCl layered sugar cores: 10 %).

Thus, it can be concluded that the presence of only 5 % PVA-PEG-graft-copolymer is not sufficient to provide appropriate film formation during coating/curing and/or to avoid structural changes within the film coatings during storage, irrespective of the initial drug loading and type of plasticizer.

5.3.4. Ethylcellulose:PVA-PEG-graft-copolymer 90:10 blends

In order to sufficiently improve film formation during coating/curing and/or stabilize the film coatings during storage, the PVA-PEG-graft-copolymer content was increased to 10 % w/w. As the resulting drug release rates were rather rapid at a coating level of 15 % (Figure 5.2), the sensitivity of the relative drug release rate to the coating level was determined under these conditions. As it can be seen in Figure 5.7, a coating level of 30 % was appropriate to allow for around 80 % drug release within the first 8 h.

Importantly, the presence of 10 % PVA-PEG-graft-copolymer proofed to be sufficient to allow for appropriate film formation during coating/curing and/or film stabilisation even upon open long term storage under stress conditions. Figure 5.8 shows the observed diltiazem HCl release profiles before and after 6 and 12 months storage under ambient and stress conditions upon exposure to 0.1 N HCl and phosphate buffer pH 7.4, respectively (the release patterns observed upon 2 h exposure to 0.1 N HCl and subsequent exposure for 6 h to phosphate buffer pH 7.4 were also stable, data not shown).

5.4. Conclusions

Adding small amounts of PVA-PEG-graft-copolymer to aqueous ethylcellulose dispersion, to provide long term stability of drug release profiles from coated pellets, is applicable to drugs of varying solubility, whether using drug matrix pellets (spheronised) or drug layered sugar cores. To achieve desired drug release profiles the PVA-PEG-graft-copolymer content as well as the coating level can be adjusted. In the case of matrix cores consisting of poorly water-soluble drugs 15 % PVA-PEG-graft-copolymer and a coating level of 15 % are a good starting point, whereas in the case of freely water-soluble drugs layered onto osmotically active starter cores, 10 % PVA-PEG-graft-copolymer and a coating level of 30 % can be expected to result in controlled drug release during 8-12 h.

5.5. References

1. Wallace, J.W., *Cellulose derivatives and natural products utilized in pharmaceutics*, in *Encyclopedia of Pharmaceutical Technology*, J.S.a.J.C. Boylan, Editor. 1990, Marcel Dekker: New York. p. 319-339.
2. Iyer, R.M., L.L. Augsburger, and D.M. Parikh, *Evaluation of drug layering and coating: effect of process mode and binder level.* Drug Dev. Ind. Pharm., 1993. **19**: p. 981-998.
3. Ye, Z.-w., et al., *Correlation between the permeability of metoprolol tartrate through plasticized isolated ethylcellulose/hydroxypropyl methylcellulose films and drug release from reservoir pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 2007. **67**(2): p. 485-490.
4. Wade, A. and P.J. Weller, *Handbook of Pharmaceutical Excipients*. 2nd ed. 1994, Washington: American Pharmaceutical Association.
5. Naelapää, K., et al., *Coating of potassium chloride with ethylcellulose aqueous dispersion--Effects of processing parameters on film formation and film properties.* European Journal of Pharmaceutical Sciences, 2007. **32**(1, Supplement 1): p. S20-S20.
6. DeMerlis, C.C., D.R. Schoneker, and J.F. Borzelleca, *A subchronic toxicity study in rats and genotoxicity tests with an aqueous ethylcellulose dispersion.* . Food and Chemical Toxicology, 2005. **43**: p. 1355-1364.
7. McGinity, J.W., *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. 2 ed. 1997, New York: Marcel Dekker.
8. Fukumori, Y., *Coating of Multiparticulates Using Polymeric dispersions*, in *Multiparticulate Oral Drug Delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 79-111.

9. Banker, G.S., *Film coating theory and practice.* Journal of Pharmaceutical Sciences, 1966. **55**: p. 81-89.

10. Lecomte, F., et al., *Polymer blends used for the coating of multiparticulates: comparison of aqueous and organic coating techniques.* Pharm. Res., 2004. **21**: p. 882-890.

11. Chevalier, Y., et al., *Film formation with latex particles.* Colloid Polym. Sci., 1992. **270**: p. 806-821.

12. Wheatley, T.A. and C.R. Steuernagel, *Latex emulsion for controlled drug delivery*, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York. p. 1-54.

13. Bodmeier, R. and O. Paeratakul, *Process and formulation variables affecting the drug release from chlorpheniramine maleate-loaded beads coated with commercial and self-prepared aqueous ethyl cellulose pseudolatexes.* International Journal of Pharmaceutics, 1991. **70**(1-2): p. 59-68.

14. Amighi, K. and A.J. Moes, *Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit RS 30D film-coated sustained-release theophylline pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42**: p. 29-35.

15. Hamdani, J., A.J. Moës, and K. Amighi, *Development and in vitro evaluation of a novel floating multiple unit dosage form obtained by melt pelletization.* International Journal of Pharmaceutics, 2006. **322**(1-2): p. 96-103.

16. Siepmann, F., et al., *How to adjust desired drug release patterns from ethylcellulose-coated dosage forms.* J. Control. Release, 2007. **119**: p. 182-189.

17. Siepmann, F., et al., *How to improve the storage stability of aqueous polymeric film coatings.* Journal of Controlled Release, 2008. **126**(1): p. 26-33.

18. Bodmeier, R. and H. Chen, *Evaluation of biodegradable poly(lactide) pellets prepared by direct compression.* International Journal Pharmaceutics, 1989. **78**: p. 819-822.

19. Lecomte, F., et al., *pH-sensitive film blends used as coating materials to control drug release from spherical beads: elucidation of the underlying mass transport mechanisms.* Pharmaceutical Research, 2005. **22**: p. 1129-1141.

6. PREDICTABILITY OF DRUG RELEASE

Abstract. The aim of this study was to elucidate the underlying drug release mechanisms in pellets coated with aqueous ethylcellulose dispersion, providing long term stable drug release profiles and containing different types of starter cores. The systems were thoroughly characterized using mechanical analysis; the sensitivity of drug release to the osmolality of the release medium was measured; scanning electron microscopy and optical macroscopy were used to monitor the pellets' morphology and dimensions upon exposure to different media, and drug release was measured from *single* and *ensembles* of pellets as well as from thin, free films. All experimental results indicate that diltiazem HCl release from pellets coated with ethylcellulose containing small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer is primarily controlled by drug diffusion through the intact polymeric membranes, irrespective of the type of starter core (consisting of microcrystalline cellulose or sugar, optionally coated with ethylcellulose). Importantly, the apparent diffusion coefficient of the drug in the macromolecular networks could easily be determined with thin free films and successfully be used to quantitatively predict the release rate from coated pellets. Thus, based on this knowledge and using the presented mathematical theories the development of new/ optimization of existing controlled drug delivery systems of this type can be significantly facilitated.

6. Predictability of drug release

6.1. Introduction

Coated pellets are frequently used for oral controlled drug delivery [1-5]. Compared to coated *tablets* and *capsules* they avoid the all-or-nothing effect of single unit dosage forms and provide less variable transit times within the gastro intestinal tract (GIT), together with a facilitated spreading of the administered drug dose within the contents of the GIT. Compared to controlled release *matrix* pellets and *mini-tablets*, generally higher drug loadings can be achieved. Ethylcellulose is a highly suitable polymer for controlled release pellet coatings, since it is nontoxic, nonallergenic, nonirritant and a good film former. This polymer can be applied from organic solutions or aqueous dispersions [6-8]. The use of *aqueous* dispersions avoids toxicity and environmental concerns associated with organic solvents and decreasing the viscosity of the coating formulation (at similar polymer contents) compared to organic solutions. Thus, higher polymer contents can be applied, resulting in shorter processing times. However, long term stability might be difficult to achieve, in particular upon storage under stress conditions (elevated temperature and relative humidity): If the polymer particles are not completely coalesced, the release rate might decrease with time due to ongoing film formation [9-11]. It has recently been shown that the addition of small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer) to aqueous ethylcellulose dispersion can effectively overcome this restriction [12-15]. The presence of this hydrophilic compound is likely to trap water within the film coating during coating and curing, resulting in improved film formation (water acting as a plasticizer for ethylcellulose and being mandatory for the capillary forces driving the polymer particles together).

However, yet it is unclear which mechanisms control drug release from such pellets. In addition, it is unknown how the type of pellet starter core (consisting for example of sugar or microcrystalline cellulose) and the osmolality of the release medium affect the resulting drug release kinetics. Different types of release mechanisms have been reported in the literature for polymer coated solid dosage forms [1, 16-18], including for instance drug

diffusion through intact macromolecular networks, crack formation and subsequent drug release through water-filled pores, drug dissolution, water penetration into the pellets, polymer swelling and/or (partial) dissolution, and osmotic effects generated by the pellet core. The mechanical stability of the film coatings and the hydrostatic pressure generated upon water penetration into the pellet core determine whether or not crack formation in the polymeric membranes occurs. In general, drug release through water-filled cracks is much more rapid than through the intact polymer membrane. Depending on the complexity of the involved mass transport mechanisms, more or less straightforward mathematical theories have been proposed to quantify drug release from coated dosage forms [19-23]. For instance, Axelsson and co-workers proposed interesting theories taking into account internal and external mass transfer resistances in addition to drug diffusion through the film coating, as well as effects of the osmotic pressure of the pellet core on the resulting drug release kinetics from pellets coated with *organic* ethylcellulose solutions. However, the film formation mechanism from *aqueous* polymer dispersions is fundamentally different and the properties of the resulting polymeric membranes can substantially differ, despite of identical coating compositions [8]. Yet, it is unclear which are the dominant mass transport mechanisms from pellets coated with aqueous ethylcellulose dispersion and how drug release can be easily predicted based on a few, straightforward experiments. Ideally, thin free films might serve as surrogates for real film coatings surrounding the pellets, because they are much easier to prepare.

The aim of this study was to better understand the underlying drug release mechanisms from pellets coated with aqueous ethylcellulose dispersion providing long term stable drug release profiles and to present a mathematical theory that allows for quantitative predictions of the resulting drug release kinetics based on only a few, simple experimental trials with thin, free films. The practical benefit of this model is to facilitate the development

of new/ optimization of existing controlled drug delivery systems of this type, minimizing the number of required labor-intensive coating trials.

6.2. Experimental section

6.2.1. Materials

Diltiazem hydrochloride (diltiazem HCl; VWR, Fontenay-sous-Bois, France), sugar cores (sugar spheres NF, 710–850 µm; NP Pharm, Bazainville, France), microcrystalline cellulose cores (MCC cores, Celpheres CP-708, 710–850 µm; Asahi Kasei, Tokyo, Japan), Ethylcellulose Aqueous Dispersion NF (Aquacoat ECD; FMC Biopolymer, Philadelphia, USA), poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer, Kollicoat IR; BASF, Ludwigshafen, Germany), triethyl citrate (TEC; Morflex, Greensboro, USA), hydroxypropyl methylcellulose (HPMC, Methocel E 5; Colorcon, Dartford, UK), saccharose (Beghin Say, Thuleries, France), sodium chloride (NaCl; Fisher Bioblock Scientific, Illkirch, France).

6.2.2. Preparation of free films

Thin polymeric films were prepared by casting blends of aqueous ethylcellulose dispersion (plasticized with 25 % w/w TEC, based on the ethylcellulose content; overnight stirring) and aqueous PVA-PEG graft copolymer solution (6.6 % w/w). The mixtures were stirred for 30 min prior to casting into Teflon molds and subsequent controlled drying for 24 h at 60 °C in an oven. Drug loaded films were prepared accordingly, adding 1.3 % w/w drug (referred to the dry film mass) to the aqueous blend. Under these conditions the drug was dissolved in the film.

6.2.3. Characterization of free films

The thickness of the films (around 400 µm) was measured using a thickness gauge (Minitest 600; Erichsen, Hemer, Germany).

The mechanical properties of the films were measured using a texture analyzer (TA.XT Plus, Stable Micro Systems, Surrey, UK) before and after exposure to 0.1 N HCl, optionally saturated with saccharose. Film pieces of 7×7 cm were placed into 250 mL plastic flasks filled with 200 mL pre-heated medium and agitated in a horizontal shaker (80 rpm, 37 °C; GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany). After pre-determined time points, samples were withdrawn and mounted on a film holder (n= 6). The puncture probe (spherical end: 5 mm diameter) was fixed on the load cell (5 kg), and driven downward with a cross-head speed of 0.1 mm/s to the center of the film holder's hole. Load versus displacement curves were recorded until rupture of the film and used to determine the mechanical properties as follows:

$$\text{puncture strength} = \frac{F}{A} \tag{6.1}$$

Where F is the load required to puncture the film and A the cross-sectional area of the edge of the film located in the path.

$$\%\,\text{elongationat break} = \frac{\sqrt{R^2 + D^2} - R}{R} \cdot 100\,\% \tag{6.2}$$

Here, R denotes the radius of the film exposed in the cylindrical hole of the holder and D the displacement.

$$\text{energy at break per unit volume} = \frac{AUC}{V} \tag{6.3}$$

Where AUC is the area under the load versus displacement curve and V the volume of the film located in the die cavity of the film holder.

6. Predictability of drug release

Drug release from thin free films was measured by placing 2×2 cm specimen into 100 mL plastic flasks filled with 80 mL pre-heated 0.1 N HCl or phosphate buffer pH 7.4 (USP 30) followed by horizontal shaking (37 °C, 80 rpm; GFL 3033; n=3). At predetermined time points, 3 mL samples were withdrawn (replaced with fresh medium) and analyzed UV-spectrophotometrically (λ = 236.9 nm in 0.1 N HCl and λ = 237.4 nm in phosphate buffer pH 7.4; UV-1650PC, Shimadzu, Champs-sur-Marne, France).

The partition coefficient of the drug between the polymeric film and the release medium at 37 °C was determined by placing film pieces of 2.5×2.5 cm in preheated 0.1 N HCl and phosphate buffer pH 7.4 (USP 30), with an excess of diltiazem HCl, and subsequent agitation in a horizontal shaker (80 rpm; GFL 3033; n = 3) until equilibrium was reached. The saturation concentration of the drug in the *bulk fluids* was determined UV-spectrophotometrically as described above. The drug concentration in the saturated *polymeric film*s was determined as follows: The film specimen were withdrawn from the release medium, excess water removed, weighed, and the diltiazem HCl content determined UV-spectrophotometrically upon dissolution in ethanol (λ = 242 nm, UV-1650PC).

6.2.4. Preparation of coated pellets

Sealed sugar cores: Sugar starter cores were coated with aqueous ethylcellulose dispersion (plasticized with 25 % w/w TEC, overnight stirring) in a fluidized bed coater equipped with a Wurster insert (Strea 1, Niro Inc.; Aeromatic-Fielder, Bubendorf, Switzerland) until a coating level of 15 % w/w was achieved. The process parameters were as follows: inlet temperature = 38 °C, product temperature = 38±1 °C, spray rate = 2-3 g/min, atomization pressure=1.2 bar, nozzle diameter = 1.2 mm.

Drug layered starter cores: Sugar cores, MCC cores and sealed sugar cores were coated with an aqueous solution of diltiazem HCl (18.2 % w/w) and HPMC (0.9 % w/w) in a fluidized bed coater (Strea 1, Wurster insert). The process parameters were as follows: inlet

temperature = 40 °C, product temperature = 40±2 °C, spray rate = 1-3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. The final drug loading was 10 % w/w.

Controlled release pellets: The drug layered sugar, MCC and sealed sugar cores were coated with aqueous ethylcellulose dispersion containing 10 % (w/w) PVA-PEG graft copolymer in a fluidized bed coater (Strea 1, Wurster insert) until a weight gain of 5 to 30 % (w/w) was achieved. The aqueous ethylcellulose dispersion was plasticized with 25 % w/w TEC (based on the ethylcellulose content; overnight stirring) and blended with aqueous PVA-PEG graft copolymer solution (6.6 % w/w) 30 min prior to coating (under gentle stirring). The process parameters were as follows: inlet temperature = 38 °C, product temperature = 38 ± 2 °C, spray rate = 2-3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. After coating the pellets were further fluidized for 10 min and subsequently cured for 24 h at 60°C.

6.2.5. Characterization of coated pellets

Diltiazem HCl release from *ensembles* of pellets was measured in 0.1 N HCl and phosphate buffer pH 7.4 (USP 30) using the USP 30 paddle apparatus (Sotax, Basel, Switzerland) (900 mL, 37 °C, 100 rpm; n = 3). Optionally, the osmotic pressure of the release medium was adjusted with NaCl (as indicated). Drug release from *single* pellets was measured in 6 mL 0.1 N HCl in agitated glass vials (80 rpm, horizontal shaker, GFL 3033) at 37 °C. At pre-determined time intervals, 3 mL (ensemble of pellets) or 2 mL (single pellets) samples were withdrawn and analyzed UV-spectrophotometrically as described above (UV-1650PC, Shimadzu).

To monitor pellet swelling, the same setup as for the single pellet release studies was used. At pre-determined time points, samples were withdrawn and their diameter measured with an optical image analysis system (Nikon SMZ-U; Nikon, Tokyo, Japan) equipped with a Sony camera (Hyper HAD model SSC-DC38DP; Elvetec, Templemars, France).

The morphology of the surfaces of the pellets upon 2 h exposure to 0.1 N HCl (same setup as for the single pellet release studies) was monitored using a scanning electron microscopy (S-4000; Hitachi High-Technologies Europe, Krefeld, Germany) upon covering the samples under an argon atmosphere with a fine gold layer (10 nm; SCD 040; BAL-TEC, Witten, Germany).

6.3. Results and discussion

6.3.1. Impact of the type of starter core

Importantly, the type of starter core had only a minor/moderate effect on the resulting diltiazem HCl release kinetics, irrespective of the type of release medium. Figure 6.1 shows the results obtained in 0.1 N HCl, the tendencies were similar in phosphate buffer pH 7.4 (data not shown).

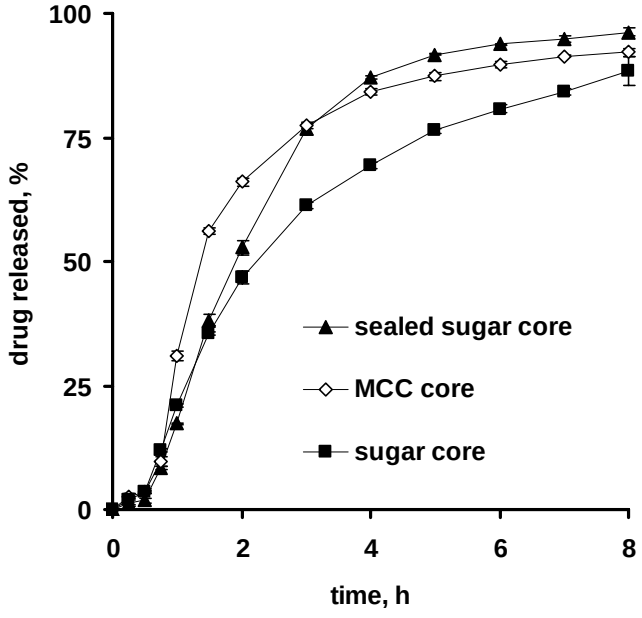


Figure 6.1: Importance of the type of starter core (indicated in the figure) on diltiazem HCl release from pellets coated with ethylcellulose:PVA-PEG graft copolymer 90:10 in 0.1 N HCl (coating level: 25 %).

This indicates that fundamental changes in the underlying drug release mechanisms (e.g., diffusion through the intact polymeric film coatings vs. diffusion through water-filled cracks) are unlikely. Drug release seems to be pre-dominantly controlled by the polymeric membrane barrier, and not by the starter core. Interestingly, the relative release rate slightly decreased in the following rank order: MCC core > sealed sugar core > sugar core. This might be explained by the different osmotic activity of the starter cores: Sugar spheres can be expected to attract more water, resulting in a more pronounced influx of liquid that counteracts drug transport out of the dosage form. The fact that pellets containing *ethylcellulose sealed* sugar cores show intermediate drug release kinetics (in-between those from MCC cores and sugar cores) indicates that the seal coating is efficient and minimizes the osmotically driven water influx into the pellets.

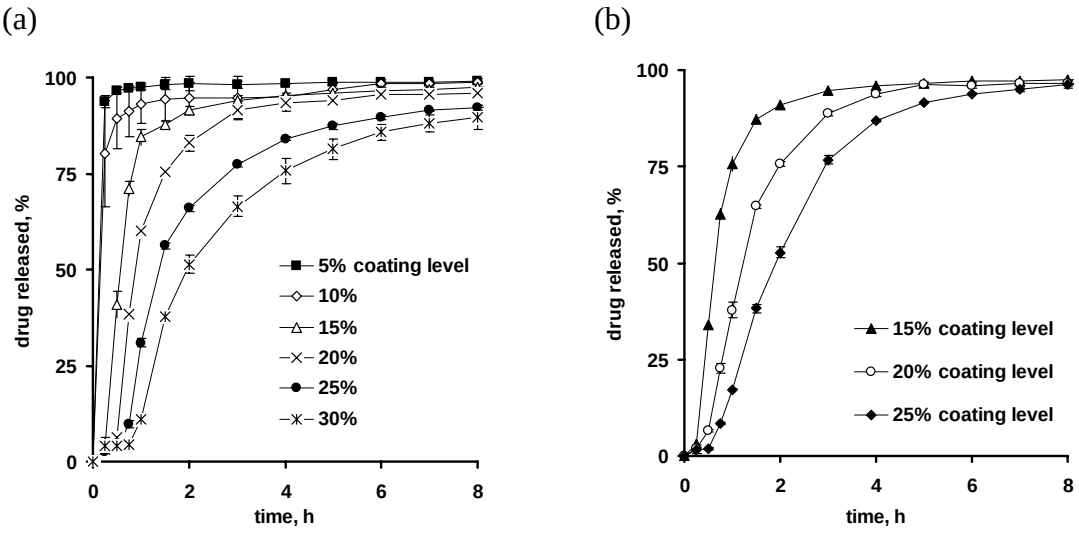


Figure 6.2: Effects of the coating level (indicated in the figures) on drug release from ethylcellulose:PVA-PEG graft copolymer 90:10 coated diltiazem HCl layered: (a) MCC cores and (b) sealed sugar cores in 0.1 N HCl.

It has recently been shown that the variation of the coating level of diltiazem HCl layered *sugar cores* coated with PVA-PEG graft copolymer can be used to fine tune the resulting drug release kinetics [24]. As it can be seen in Figure 6.2, this type of release rate

adjustment is also possible in the case of drug layered *MCC cores* and *sealed sugar cores*. Similar tendencies were obtained in phosphate buffer pH 7.4 (data not shown).

6.3.2. Sensitivity to the osmolality of the release medium

In order to better understand the underlying drug release mechanisms, the sensitivity of the resulting drug release patterns to changes in the osmolality of the release medium was determined for the different types of starter cores. As shown in Figure 6.3, the relative drug release rate significantly decreased when increasing the osmolality from 0.28 to 3.58 osmol/kg, irrespective of the type of starter core and pH of the release medium. This can be explained by a decrease in the water penetration rate into the system: With decreasing difference in the osmotic pressure "inside the pellets – outside the pellets" the water penetration rate decreases. This leads to delayed drug dissolution and subsequent diffusion through the polymeric coatings (only dissolved drug being able to diffuse). Importantly, these effects become only significant under non-physiological conditions [25, 26], irrespective of the type of starter core and pH of the release medium. Under *physiological* conditions the variation in the drug release rates are only minor. Thus, potential food effects based on this mechanism can be expected to be negligible in all cases.

Interestingly, pellets containing drug layered *sugar cores* showed much smaller changes in the release rate when increasing the osmolality of the release medium from 0.28 to 3.58 osmol/kg than pellets containing *MCC or sealed sugar cores*, irrespective of the type of release medium (Figure 6.3). This can be explained by the fact that the osmotically active sugar core provides a minimum water influx, even upon exposure to a release medium with an osmolality of 3.58 osmol/kg. It should be noted that the different behavior of the sugar cores is probably also not of practical relevance for the above mentioned reasons.

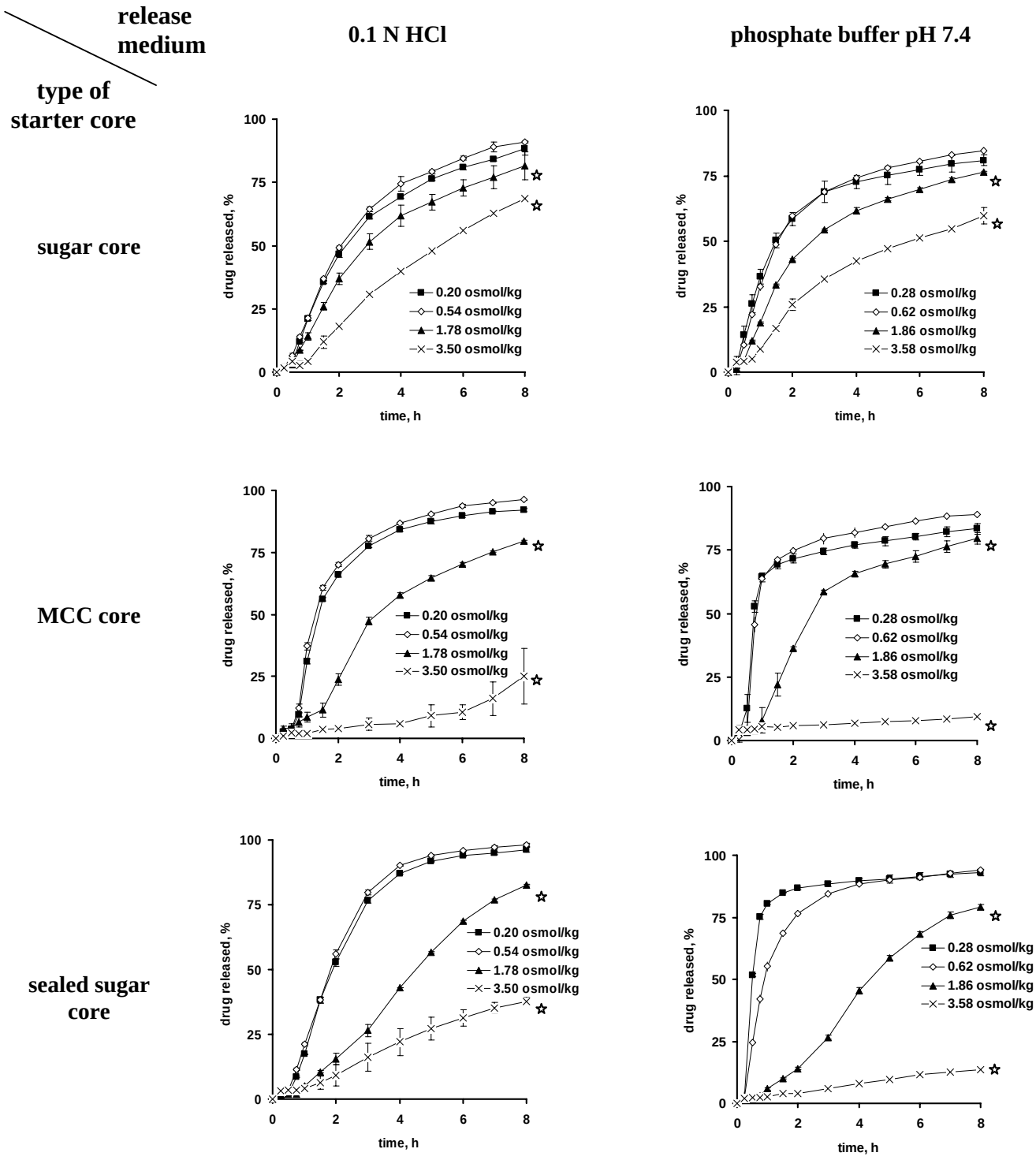
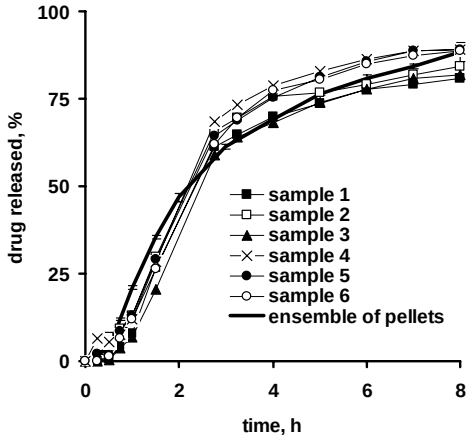


Figure 6.3: Impact of the osmolality of the release medium (indicated in the figures) on drug release from different types of diltiazem HCl layered starter cores coated with ethylcellulose:PVA-PEG graft copolymer 90:10. The release media are shown at the top, the type of cores is indicated on the left (coating level: 25 %, the stars indicate non-physiological conditions).

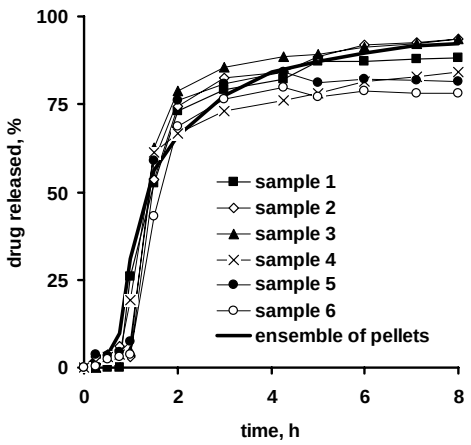
6.3.3. Drug release mechanisms

When elucidating the underlying drug release mechanisms from coated pellets, one of the fundamental aspects to be clarified is whether the drug release kinetics from different *single* pellets substantially varies, or whether all pellets behave similarly. It has for instance been reported in the literature that the overall drug release profile from an *ensemble* of pellets can be the sum of very different release patterns from individual pellets [21]. If drug release occurs very rapidly upon crack formation within the polymeric film coating through water-filled pores (pulsatile drug release) and if the lag times are homogeneously distributed within the observation period, apparent zero order drug release kinetics result. Importantly, drug release from single pellets is very similar to drug release from ensembles of pellets in the present case, irrespective of the type of starter core and type of release medium. Figure 6.4 shows the results obtained in 0.1 N HCl, the tendencies were similar in phosphate buffer pH 7.4 (data not shown). Thus, there seems to be one uniform drug release mechanism and time-dependent crack formation is unlikely (otherwise the onset and extent of this crack formation would be highly reproducible).

(a)



(b)



(c)

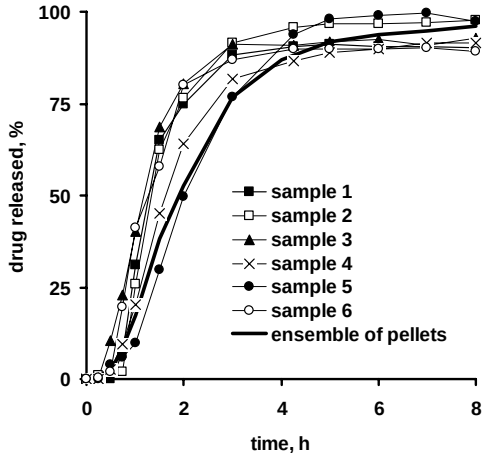


Figure 6.4: Drug release from single pellets coated with ethylcellulose:PVA-PEG graft copolymer 90:10 in 0.1 N HCl, containing: (a) sugar cores, (b) MCC cores and (c) sealed sugar cores (coating level: 25 %). For reasons of comparison also drug release from ensembles of pellets is shown.

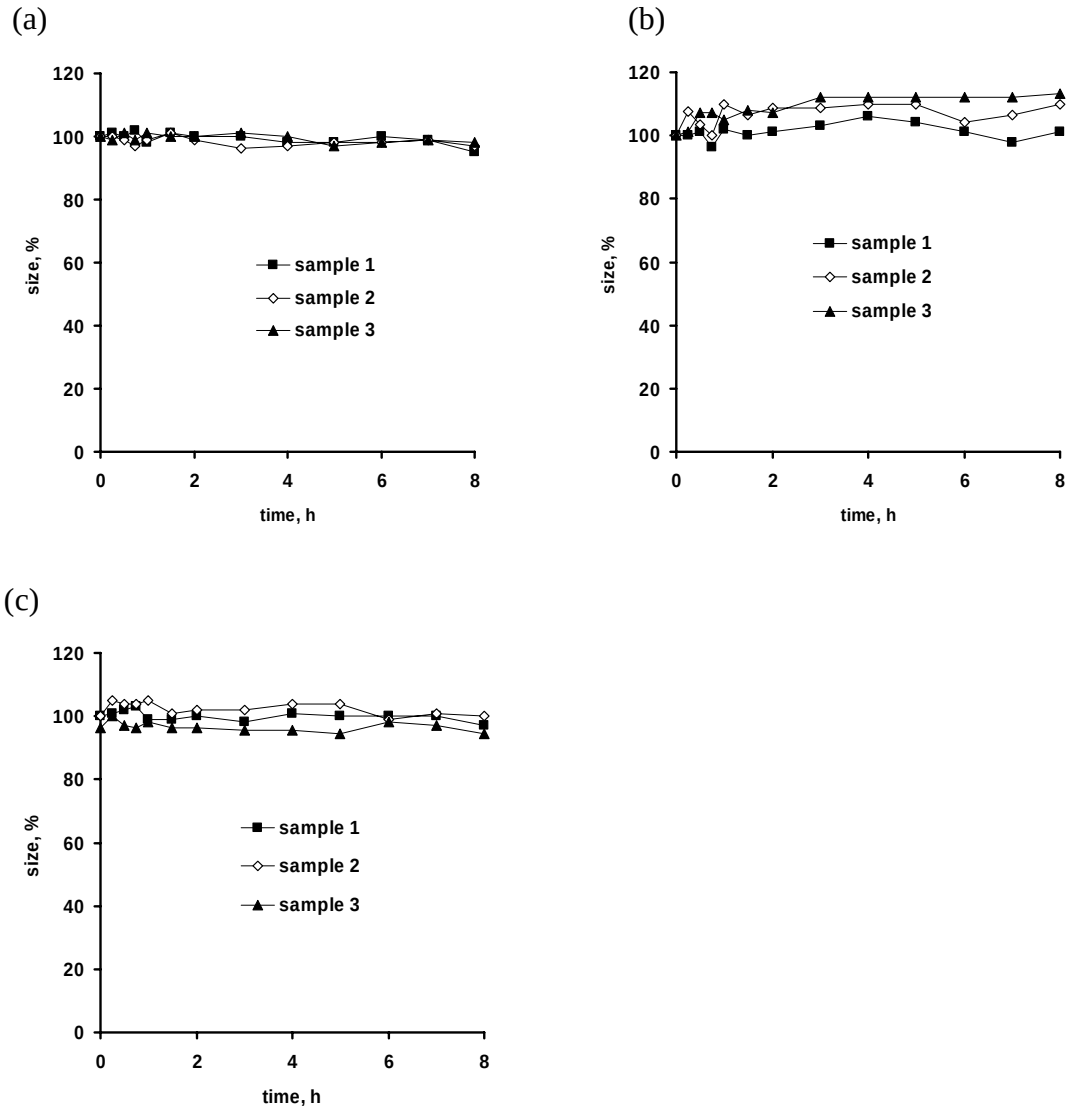
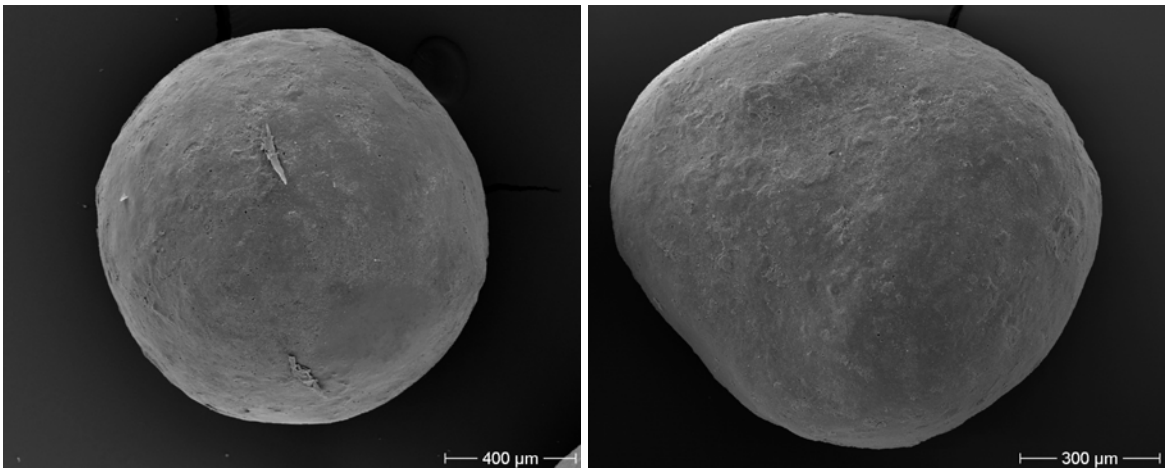


Figure 6.5: Swelling behavior of diltiazem HCl layered (a) sugar cores, (b) MCC cores and (c) sealed sugar cores coated with ethylcellulose:PVA-PEG graft copolymer 90:10 upon exposure to 0.1 N HCl (single pellets, coating level: 25 %).

In order to further distinguish between drug release through intact polymeric film coatings and drug release through water-filled cracks, the swelling behavior of the coated pellets was monitored upon exposure to 0.1 N HCl and phosphate buffer pH 7.4. Figure 6.5 shows the results obtained in 0.1 N HCl, the tendencies were similar in phosphate buffer pH 7.4 (data not shown).

(a) (b)



(c)

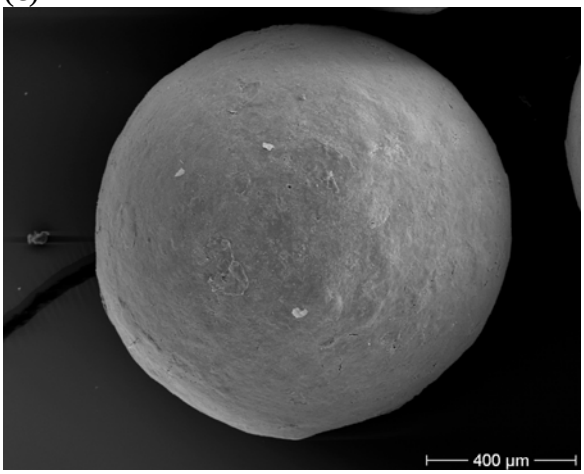


Figure 6.6: Scanning electron microscopy pictures of pellets coated with ethylcellulose:PVA-PEG graft copolymer 90:10, containing: (a) sugar cores, (b) MCC cores and (c) sealed sugar cores after 2 h exposure to 0.1 N HCl (coating level: 30 % in the case of sugar and MCC cores, 25 % in the case of sealed sugar cores).

Clearly, the pellet diameter remains about constant during the 8 h observation period, irrespective of the type of starter core. This is a further indication for the fact that crack formation within the film coatings does not play a major role [27]. The continuous water penetration into the pellets is likely to generate a monotonically increasing hydrostatic pressure within the system. This can lead to steadily increasing pellet dimensions until a

critical threshold value is reached at which crack formation is induced. At this time point the inner liquid is pulled out of the system and the pellet diameter suddenly decreases [27]. In none of the investigated systems any sign of such crack formation is visible (Figure 6.5). Furthermore, scanning electron microscopy showed no evidence for crack formation in pellets which were exposed to 0.1 N HCl for 2 h, irrespective of the type of starter core (Figure 6.6).

Table 6.1: Mechanical properties of ethylcellulose:PVA-PEG graft copolymer 90:10 films in the dry state and upon exposure to 0.1 N HCl (optionally saturated with saccharose).

	dry state	1 h 0.1 N HCl	1 h 0.1 N HCl, saturated with saccharose	24 h 0.1 N HCl	24 h 0.1 N HCl, saturated with saccharose
elongation at break (%)	5.01 +/- 3.00	13.9 +/- 2.4	12.3 +/- 1.5	7.06 +/- 2.88	7.21 +/- 2.10
puncture strength (MPa)	0.81 +/- 0.07	0.42 +/- 0.17	0.51 +/- 0.09	0.81 +/- 0.09	0.44 +/- 0.13
energy at break (kJ/m^3)	94.7 +/- 53.8	69.6 +/- 26.5	80.8 +/- 11.6	116 +/- 29	57.4 +/- 18.0

To further confirm the hypothesis that drug release from the investigated pellets is controlled by diffusion through the intact polymeric film coatings, the mechanical properties of thin polymeric films of identical composition as the film coatings were determined before and after 1 and 24 h exposure to 0. 1 N HCl, optionally saturated with saccharose. Table 6.1 lists the determined % elongation, puncture strength and energy at break of the films. Importantly, the obtained values indicate mechanically stable film coatings, irrespective of the exposure period and the absence or presence of saccharose. Please note that the values for the

dry state were determined at room temperature, whereas those for the wet state were measured at 37 °C. The differences *dry vs. wet* state can, thus, at least partially be explained by the difference in temperature, the fact that water acts as a plasticizer for these polymers, and/or by (partial) PVA-PEG graft copolymer and plasticizer leaching into the bulk fluids. Hence, also these mechanical stability measurements are in good agreement with the hypothesis that crack formation does not occur in the investigated film coatings and that drug release is primarily controlled by diffusion through the intact polymeric membranes, irrespective of the type of starter core and release medium.

6.3.4. Mathematical modeling

Based on the experimental results and hypothesized drug release mechanism, an appropriate mathematical model was identified and used to quantitatively predict the resulting drug release kinetics from the investigated pellets. To be able to provide such quantitative predictions, first the apparent diffusion coefficient of the drug within the film coating must be known. A reliable and easily applicable method allowing for the determination of drug diffusivities in polymeric networks upon exposure to a release medium is to experimentally measure drug release from thin films into this (well stirred) bulk fluid and to fit an appropriate solution of Fick's law of diffusion to the experimental results. Thus, diltiazem HCl release was measured from thin, drug containing films of identical composition as the film coatings upon exposure to 0.1 N HCl and phosphate buffer pH 7.4 at 37 °C. It has to be pointed out that the initial drug loading of these films was very low (1.3 % w/w), limiting the importance of time-dependent changes in the permeability of the polymeric networks due to drug release (resulting in increased film porosity) and assuring that the drug is molecularly dispersed within the system (monolithic solution). The symbols in Figure 6.7 show the experimentally determined release of diltiazem HCl from thin ethylcellulose:PVA-PEG graft copolymer 90:10 films in the respective, well agitated (80 rpm) media. Clearly, the relative drug release

rate monotonically decreased with time, which is due to the increasing length of the diffusion pathways, irrespective of the type of release medium. In the following, the key features of the mathematical model that was fitted to these sets of experimental results (being an appropriate analytical solution of Fick's second law of diffusion considering the given initial and boundary conditions) are briefly presented. The theory takes into account that the drug is molecularly dispersed within the polymeric networks and that the surface of the films is very large compared to their thickness (approximately 4 cm^2 versus 400 µm). Thus, edge effects are negligible and the mathematical analysis can be restricted to one dimension. Under these conditions, the release kinetics can be described by Fick's second law of diffusion in a *plane sheet* [28]:

$$\frac{\partial c}{\partial t} = D \cdot \frac{\partial^2 c}{\partial x^2} \tag{6.4}$$

where c denotes the concentration of the drug within the polymeric system, being a function of the time t and position x. The initial condition for this partial differential equation is as follows, expressing the fact that the drug is uniformly distributed throughout the film at the beginning of the experiment:

$$t=0 \qquad c=c_{initial} \qquad -L \leq x \leq +L \tag{6.5}$$

Here, $c_{initial}$ represents the initial drug concentration in the system and L the half-thickness of the film. The drug concentration far away from the surface of the film is assumed to be constant and equal to zero because the release medium is well stirred and perfect sink conditions are maintained during the experiments. Near to the surface of the film an unstirred liquid layer is considered (even in well-agitated systems thin unstirred layers exist, leading to an additional mass transfer resistance). As there is no accumulation of the drug on the surface of the film, the rate at which the drug is transported to the surface by diffusion through the

polymeric network is always equal to the rate at which it leaves the film. This rate, per unit area, is proportional to the difference of the actual concentration on the surface ($c_{surface}$) and the concentration required to maintain equilibrium with the surrounding environment (c_∞). The constant of proportionality is called the mass transfer coefficient in the boundary layer, h. As the thickness of the boundary layer essentially depends on the rate of stirring, h is a function of the stirring rate. This boundary condition is mathematically expressed as:

$$t > 0 \qquad -D \cdot \left| \frac{\partial c}{\partial x} \right|_{x=\pm L} = h \cdot (c_{surface} - c_\infty) \tag{6.6}$$

This initial value problem (Equations 6.4-6.6) can be solved using the method of Laplace transform, leading to [29, 30]:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{2 \cdot G^2}{\beta_n^2 \cdot (\beta_n^2 + G^2 + G)} \cdot \exp\left(-\frac{\beta_n^2}{L^2} \cdot D \cdot t \right) \tag{6.7}$$

where the ßns are the positive roots of:

$$\beta \cdot \tan \beta = G \tag{6.8}$$

with

$$G = \frac{L \cdot h}{D} \tag{6.9}$$

Here, M_t and M_∞ are the cumulative amounts of drug released at time t and t=∞, respectively; G denotes a dimensionless constant. When fitting this set of equations (Equations 6.7-6.9) to the experimentally measured in vitro drug release kinetics from the thin films, good agreement between theory and experiment was obtained (curves and symbols in Figure 6.7). Thus, drug release out of these films is predominantly controlled by diffusion of the drug through the polymeric network. Based on these calculations the apparent diffusion coefficient of the drug in the polymeric films, D, and the mass transfer coefficient in the

boundary layer, h, could be determined. The diffusion coefficients of the drug within the ethylcellulose:PVA-PEG graft copolymer 90:10 films upon exposure to 0.1 N HCl and phosphate buffer pH 7.4 were equal to 2.40 (+/-0.39) $x10^{-8}$ cm²/s and 2.90 (+/-0.52) $x10^{-8}$ cm²/s. Importantly, the mass transfer resistance within the boundary layer was found to be negligible compared to the mass transfer resistance within the polymeric films: The dimensionless number G=Lh/D was > 100 in all cases. Consequently, also the following, simplified mathematical equation can be used to describe drug release from the investigated films under the given experimental conditions (and can be used to determine the apparent drug diffusivities):

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2 \cdot n + 1)^2 \cdot \pi^2} \cdot \exp\left(- \frac{(2 \cdot n + 1)^2 \cdot \pi^2}{4 \cdot L^2} \cdot D \cdot t \right) \qquad (6.10)$$

6.3.5. Predictability of drug release

Knowing the apparent drug diffusivity in the films and assuming that drug release from the investigated coated pellets is primarily controlled by diffusion through the intact polymeric membranes, and considering: (i) perfect sink conditions, which are maintained throughout the experiments, (ii) the initial amount of drug in the pellets, M_0, (iii) drug partitioning from the pellet core into the polymeric film coatings, and (iv) the dimensions of the system, the following equation can be used to quantitatively predict the amount of drug released at time t, M_t:

$$M_t = M_0 \left[1 - \exp\left(- \frac{ADKt}{Vl} \right) \right] \qquad (6.11)$$

where A is the total surface area of a coated pellet; D denotes the apparent diffusion coefficient of the drug in the polymeric membrane; K represents the partition coefficient of the drug between the film coating and the pellet core (which was experimentally determined

in this study, being equal to 0.10 upon exposure to 0.1 N HCl and equal to 0.16 upon exposure to phosphate buffer pH 7.4); V is the volume of the pellet core and l the thickness of the film coating.

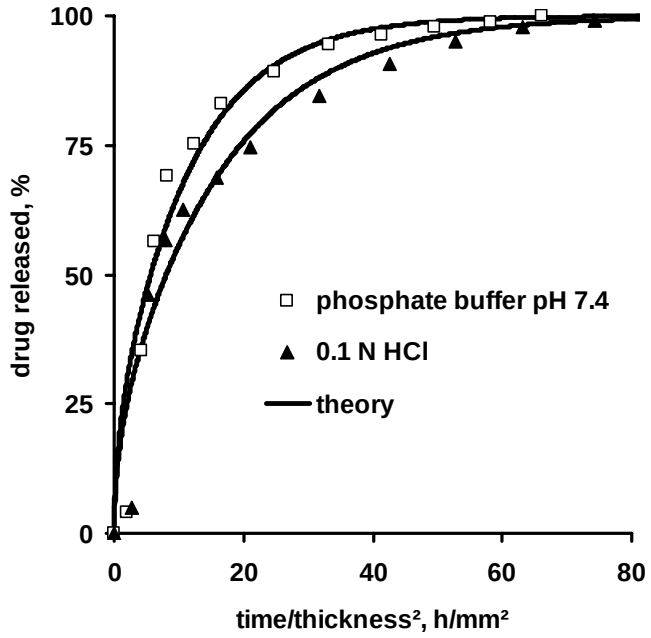


Figure 6.7: Diltiazem HCl release from thin polymeric films based on ethylcellulose:PVA-PEG graft copolymer 90:10 in 0.1 N HCl and phosphate buffer pH 7.4: Experiments (symbols) and theory (curves, Equations 6.7-6.9). Please note that the time plotted on the x-axis is normalized to the thickness of the films in order to account for slight, arbitrary variations of the latter. Each experiment was conducted in triplicate, but only one representative example is shown for each release medium.

The curves in Figures 6.8a and 6.8b show the theoretically predicted drug release kinetics from diltiazem HCl layered sugar cores, MCC cores and sealed sugar cores in 0.1 N HCl and phosphate buffer pH 7.4, respectively. To evaluate the validity of the mathematical calculations, drug release from these pellets in these media was also determined experimentally (symbols in Figure 6.8). Please note that because the applied theory does not take into account the effects of the osmotically driven water influx, there is only one

prediction versus three sets of experimental data from the three types of starter cores. Clearly, the theoretical prediction serves as a reasonable estimate for the resulting drug release patterns. Please note that Figure 6.8 shows theoretical predictions and *independent* experimental results, and *not fittings* of a mathematical model to sets of given experimental data. This good agreement between theory and experiment further confirms the hypothesis that diltiazem HCl release from the investigated coated pellets is primarily controlled by drug diffusion through the intact polymeric films, irrespective of the type of starter core and type of release medium. In addition, this type of theoretical predictions can be very helpful to facilitate the development of new/optimization of existing controlled drug delivery systems of this type: The effects of the formulation and processing parameters considered in Equation 6.7 on the resulting drug release kinetics can be predicted in a quantitative way.

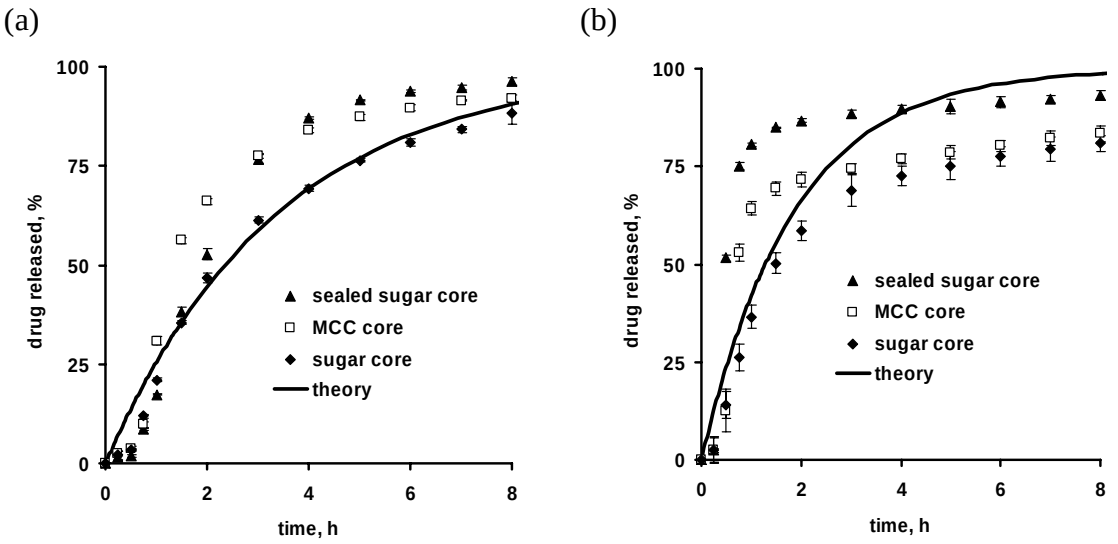


Figure 6.8: Theoretically predicted and experimentally confirmed diltiazem HCl release from pellets coated with ethylcellulose:PVA-PEG graft copolymer 90:10 (the type of starter core is indicated in the figures) in: (a) 0.1 N HCl and (b) phosphate buffer pH 7.4 (coating level: 25 %). The curves show the theoretically predicted release profiles (Equation 6.11), the symbols the independent experimental results.

6.4. Conclusions

Drug release from ethylcellulose:PVA-PEG graft copolymer coated pellets is primarily controlled by diffusion through the intact polymeric membranes, irrespective of the type of starter core and type of release medium. Appropriate analytical solutions of Fick's law can be used to quantitatively predict the resulting drug release kinetics as a function of the major formulation parameters. Importantly, the apparent diffusion coefficients determined with thin free films can be used to predict drug release from coated pellets. Thus, the optimization of this type of controlled drug delivery systems can be significantly facilitated.

6.5. References

1. Ozturk, A.G., et al., *Mechanism of release from pellets coated with an ethylcellulose-based film.* Journal of Controlled Release, 1990. **14**(3): p. 203-213.
2. Fukumori, Y., *Coating of Multiparticulates Using Polymeric dispersions*, in *Multiparticulate Oral Drug Delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 79-111.
3. Ghebre-Sellassie, I., *Multiparticulate oral drug delivery*. 1997, New York: Marcel Dekker.
4. McGinity, J.W., *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. 2 ed. 1997, New York: Marcel Dekker.
5. Sadeghi, F., et al., *Comparative Study of Drug Release from Pellets Coated with HPMC or Surelease.* Drug Development and Industrial Pharmacy, 2000. **26**(6): p. 651-660.
6. Banker, G.S., *Film coating theory and practice.* Journal of Pharmaceutical Sciences, 1966. **55**(1): p. 81-89.
7. Eckersley, S.T. and A. Rudin, *Mechanism of film formation from polymer latexes* Journal of Coatings Technology, 1990. **62**(780): p. 89-100.
8. Lecomte, F., et al., *Polymer blends used for the coating of multiparticulates: comparison of aqueous and organic coating techniques.* Pharmaceutical Research, 2004. **21**(1): p. 882-890.
9. Amighi, K. and A.J. Moes, *Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit RS 30D film-coated sustained-release theophylline pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42**(1): p. 29-35.

10. Wu, C. and J.W. McGinity, *Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer.* European Journal of Pharmaceutics and Biopharmaceutics, 2000. **50**(2): p. 277-284.

11. Siepmann, F., et al., *Aqueous HPMCAS coatings: Effects of formulation and processing parameters on drug release and mass transport mechanisms.* European Journal of Pharmaceutics and Biopharmaceutics, 2006. **63**(3): p. 262-269.

12. Siepmann, F., et al., *How to adjust desired drug release patterns from ethylcellulose-coated dosage forms.* Journal of Controlled Release, 2007. **119**(2): p. 182-189.

13. Siepmann, F., et al., *Carrageenan as an Efficient Drug Release Modifier for Ethylcellulose-Coated Pharmaceutical Dosage Forms.* Biomacromolecules, 2007. **8**(12): p. 3984-3991.

14. Siepmann, F., et al., *pH-sensitive film coatings: Towards a better understanding and facilitated optimization.* European Journal of Pharmaceutics and Biopharmaceutics, 2008. **68**(1): p. 2-10.

15. Siepmann, F., et al., *How to improve the storage stability of aqueous polymeric film coatings.* Journal of Controlled Release, 2008. **126**(1): p. 26-33.

16. Theeuwes, F., *Elementary osmotic pump.* Journal of Pharmaceutical Sciences 1975. **64**(12): p. 1987-1991.

17. Zentner, G.M., G.S. Rork, and K.J. Himmelstein, *Osmotic flow through controlled porosity films: An approach to delivery of water soluble compounds.* Journal of Controlled Release, 1985. **2**(3): p. 217-229.

18. Schultz, P. and P. Kleinebudde, *A new multiparticulate delayed release system.Part I: Dissolution properties and release mechanism.* Journal of Controlled Release, 1997. **47**(2): p. 181-189.

19. Fan, L.T. and S.K. Singh, *Controlled Release: A Quantitative Treatment*. 1989, Berlin: Springer-Verlag.

20. Borgquist, P., et al., *Simulation and parametric study of a film-coated controlled-release pharmaceutical.* Journal of Controlled Release, 2002. **80**(1-3): p. 229-245.

21. Borgquist, P., et al., *Simulation of the release from a multiparticulate system validated by single pellet and dose release experiments.* Journal of Controlled Release, 2004. **97**(3): p. 453-465.

22. Marucci, M., G. Ragnarsson, and A. Axelsson, *Evaluation of osmotic effects on coated pellets using a mechanistic model.* International Journal of Pharmaceutics, 2007. **336**(1): p. 67-74.

23. Marucci, M., et al., *Mechanistic model for drug release during the lag phase from pellets coated with a semi-permeable membrane.* Journal of Controlled Release, 2008. **127**(1): p. 31-40.

24. Muschert, S., et al., *Improved long term stability of ethyl cellulose film coatings: Importance of the type of drug and starter core.* accepted, 2008.

25. Lindahl, A., et al., *Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women.* Pharmaceutical Research, 1997. **14**(4): p. 497-502.

26. Ladas, S.D., P.E. Isaacs, and G.E. Sladen, *Post-prandial changes of osmolality and electrolyte concentration in the upper jejunum of normal man.* Digestion, 1983. **26**(4): p. 218-23.

27. Lecomte, F., et al., *pH-Sensitive Polymer Blends used as Coating Materials to Control Drug Release from Spherical Beads: Importance of the Type of Core.* Biomacromolecules, 2005. **6**(4): p. 2074-2083.

28. Crank, J., *The Mathematics of Diffusion*. 2 ed. 1975, Oxford: Clarendon Press.

29. Carslaw, H.S. and J.C. Jaeger, *Conduction of Heat in Solids*. 1959, Oxford: Clarendon Press.

30. Vergnaud, J.M., *Controlled Drug Release of Oral Dosage Forms*. 1993, Chichester: Ellis Horwood.

7. DRUG RELEASE MECHANISMS

Abstract: The aim of this study was to better understand the underlying drug release mechanisms from aqueous ethylcellulose coated pellets containing different types of drugs and starter cores. Diltiazem HCl, paracetamol, metoprolol succinate, metoprolol tartrate and theopylline were used as model drugs exhibiting significantly different aqueous solubilities. The pellet core consisted of a drug matrix, drug layered sugar bead or drug layered microcrystalline cellulose (MCC) bead, generating different osmotic driving forces upon contact with aqueous media. Importantly, the addition of small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer) to the ethylcellulose coatings allowed controlled drug release within 8-12 h, irrespective of the type of drug and composition of the pellet core. Drug release was found to be controlled by diffusion through the *intact* polymeric membranes, irrespective of the drug solubility and type of core formulation. The ethylcellulose coating was dominant for the control of drug release, minimizing potential effects of the type of pellet core and nature of the surrounding bulk fluid, e.g. osmolality. Thus, this type of controlled drug delivery system can be used for very different drugs and is robust.

7. Drug release mechanisms

7.1. Introduction

Polymer coated pellets offer various important advantages as oral controlled drug delivery systems [1-3]. In contrast to single unit dosage forms, they allow to avoid the all-or-nothing effect and provide less variable transit times within the gastro intestinal tract (GIT). In addition, the drug dose is more homogeneously spread throughout the contents of the digestive tract. Compared to controlled release *matrix* pellets and *mini-tablets*, generally higher drug loadings can be achieved, which is mandatory in various applications. Different types of polymers can be used for pellet coating, for example cellulose derivatives, poly(vinyl acetate), poly(vinyl pyrrolidone) and polymethacrylates [3-6]. Ethylcellulose is particularly suitable, because it is a good film former, nontoxic, nonallergenic and nonirritant [7]. It can be applied either from *organic* solutions or from *aqueous* dispersions [8-10]. The use of *aqueous* dispersions offers the advantage to minimize toxicity and environmental concerns and to shorten processing times. However, long term stable drug release patterns might be difficult to achieve if the film is not fully coalesced. Further gradual coalescence during storage results in decreasing drug permeability and, thus, decreasing release rates [11-13].

It has recently been shown that the addition of small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer) to aqueous ethylcellulose dispersion can significantly improve film formation during coating and/or curing allowing for long term stable drug release profiles, even upon *open* storage under stress conditions for 6 months [14, 15]. This can probably be attributed to the fact that PVA-PEG graft copolymer traps water within the system, water acting as a plasticizer for ethylcellulose and being mandatory for the capillary forces, driving the particles together [13, 16, 17]. In contrast to hydroxypropyl methylcellulose (HPMC), PVA-PEG graft copolymer does not cause flocculation of aqueous ethylcellulose dispersion [15].

However, as yet knowledge on the applicability of this approach to different types of drugs and different types of starter cores is very limited. Importantly, the composition of the

inner pellet core can significantly affect the resulting drug release patterns from polymer coated pellets [10, 18]. For instance, osmotically active sugar cores or drug matrix cores consisting of a freely water-soluble drug can lead to significant water influx into the system upon contact with aqueous media. This water influx can have two major consequences: (i) It presents a potential hindrance for drug diffusion out of the pellets (convective water influx versus countercurrent drug diffusion), and (ii) Significant hydrostatic pressure can built up within the pellet core and stress the coating. This phenomenon might lead to crack formation at a given time point (when the mechanical stability of the polymeric membrane is insufficient to withstand the pressure), and rapid drug release through water filled channels might result [19-21] So far, it is unclear whether such osmotic effects (including crack formation in the film coatings) are of importance for the control of drug release from ethylcellulose:PVA-PEG graft copolymer coated pellets. It has to be pointed out that the underlying drug release mechanisms from polymer coated pellets can be very straightforward (e.g., diffusion through the *intact* polymeric film coatings), but also highly complex [22-24]. Surprisingly little is yet known on the mass transport mechanisms governing drug release from polymer coated pellets and the importance of the type of drug and starter core composition, despite the significant practical importance of this type of advanced drug delivery systems. Furthermore, there is a significant need for appropriate experimental measurement techniques allowing for deeper insight into the involved physico-chemical phenomena [25-27].

The major aims of this study were: (i) to better understand the relative importance of the film coating and of the pellet core for the control of drug release from ethylcellulose coated multiparticulates, and (ii) to evaluate the applicability of the approach of adding small amounts of PVA-PEG graft copolymer as film formation/permeability enhancer to very different types of drugs and pellet starter cores.

7.2. Experimental section

7.2.1. Materials

Diltiazem hydrochloride (diltiazem HCl; VWR, Fontenay-sous-Bois, France); paracetamol, metoprolol succinate and metoprolol tartrate (Salutas, Barleben, Germany); theophylline (BASF, Ludwigshafen, Germany); theophylline matrix pellets (70 % drug content, diameter: 0.71-1.25 mm; FMC, Philadelphia, PA, USA); sugar cores (sugar spheres NF, 710–850 µm; NP Pharm, Bazainville, France); microcrystalline cellulose cores (MCC cores, Celpheres CP-708, 710–850 µm; Asahi Kasei, Tokyo, Japan); microcrystalline cellulose (Avicel PH 101; Seppic, Paris, France); hydroxypropyl methylcellulose (HPMC, Methocel E 5; Colorcon, Dartford, UK); Ethylcellulose Aqueous Dispersion NF (Aquacoat ECD; FMC, Philadelphia, PA, USA); poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer, Kollicoat IR; BASF, Ludwigshafen, Germany); triethyl citrate (TEC; Morflex, Greensboro, NC, USA), sodium chloride (NaCl; Fisher Bioblock Scientific, Illkirch, France).

7.2.2. Preparation of coated pellets

Drug loaded matrix cores:

Metoprolol tartrate and diltiazem HCl-loaded matrix pellets were prepared via extrusion-spheronization. The drug powders and microcrystalline cellulose were mixed with demineralized water in a planetary mixer (Kenwood Chef; Kenwood, Croydon, UK). The obtained wet masses (30 % metoprolol tartrate, 49 % MCC, 21 % water; or 40 % diltiazem HCl, 36.5 % MCC, 23.5 % water] were extruded using a cylinder extruder with two counter-rotating rollers (1 mm orifice, extrusion speed = 63 and 96 rpm for metoprolol tartrate and diltiazem HCl; Alexanderwerk GA 65; Alexanderwerk, Remscheid, Germany). The extrudates were subsequently spheronized (Caleva model 15; Caleva, Dorset, UK) for

150/180 s at 600/750 rpm in the case of metoprolol tartrate/diltiazem HCl. The obtained beads were dried for 24 h in an oven at 40 °C and sieved (fraction: 0.71-1.25 mm).

Drug layered starter cores:

Sugar cores and MCC cores were coated with an aqueous solution of diltiazem HCl or metoprolol succinate (18.2 % w/w) and hydroxypropyl methylcellulose (0.9 % w/w) in a fluidized bed coater (Strea 1, Wurster insert; Niro; Aeromatic-Fielder, Bubendorf, Switzerland). The process parameters were as follows: inlet temperature = 40 °C, product temperature = 40±2 °C, spray rate = 1-3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. The final drug loading was 7 % w/w.

Controlled release pellets:

Drug matrix cores as well as drug layered sugar and MCC cores were coated with aqueous ethylcellulose dispersion containing small amounts of PVA-PEG graft copolymer in a fluidized bed coater (Strea 1, Wurster insert). The coating dispersions were prepared as follows: The aqueous ethylcellulose dispersion was plasticized overnight with triethyl citrate (25 % w/w, based on the ethylcellulose content). Aqueous PVA-PEG graft copolymer solution was added and the blends were stirred for 30 min prior to coating. The process parameters were as follows: inlet temperature = 38 °C, product temperature = 38 ± 2 °C, spray rate = 2-3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. After coating the pellets were further fluidized for 10 min and subsequently cured for 24 h at 60°C.

7.2.3. Drug release from coated pellets

Drug release from *ensembles* of pellets was measured in 0.1 N HCl and phosphate buffer pH 7.4 (USP 30) using the USP 30 paddle apparatus (Sotax, Basel, Switzerland) (900 mL, 37 °C, 100 rpm; n = 3). Optionally, NaCl was added to adjust the osmotic pressure of the release media. Drug release from *single* pellets was measured in 6 mL 0.1 N HCl in agitated glass vials (80 rpm, horizontal shaker, GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel,

Germany) at 37 °C. At pre-determined time intervals, 3 mL (*ensembles* of pellets) or 2 mL (*single* pellets) samples were withdrawn and analyzed by UV-spectrophotometry (diltiazem HCl/theophylline/metoprolol succinate: λ = 236.9/270.4/222.8 nm in 0.1 N HCl and λ = 237.4/272.2/222.2 nm in phosphate buffer pH 7.4; metoprolol tartrate/paracetamol: λ = 222.6/243.4 nm in both media; UV-1650PC, Shimadzu, Champs-sur-Marne, France).

7.2.4. Swelling behavior of single pellets

Single pellets were treated as described in section 7.2.3., single pellet release studies. At pre-determined time intervals, pellet samples were withdrawn and their diameter measured with an optical image analysis system (Nikon SMZ-U; Nikon, Tokyo, Japan) equipped with a Sony camera (Hyper HAD model SSC-DC38DP; Elvetec, Templemars, France).

7.2.5. Scanning Electron Microscopy

The morphology of coated pellets before and after 2 h exposure to 0.1 N HCl (conditions as described for the in vitro drug release studies for single pellets in section 7.2.3.) was monitored using a scanning electron microscopy (S-4000; Hitachi High-Technologies Europe, Krefeld, Germany) after covering the samples under an argon atmosphere with a fine gold layer (10 nm; SCD 040; BAL-TEC, Witten, Germany).

7.2.6. Determination of the drug solubility

Excess drug amounts were placed in contact with 0.1 N HCl and phosphate buffer pH 7.4 (USP 30) at 37 °C in a horizontal shaker (80 rpm, GFL 3033) for at least 48 h. Every 12 h, samples were withdrawn, filtered and analyzed for their drug content as described in section 7.2.3. until equilibrium was reached.

7.3. Results and discussion

7.3.1. Importance of the type of drug

It has recently been shown that theophylline release from spherical drug matrix cores coated with aqueous ethylcellulose dispersion containing small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer) can effectively be controlled during periods of 8-12 h [15]. In contrast to the frequently used pore former hydroxypropyl methylcellulose (HPMC), PVA-PEG graft copolymer does not cause flocculation of the coating dispersions. Furthermore, long term stable drug release profiles can be provided, even upon *open* storage under stress conditions. However, it is yet unclear, whether this approach is applicable also to other types of drugs and pellet starter cores.

(a) (b)

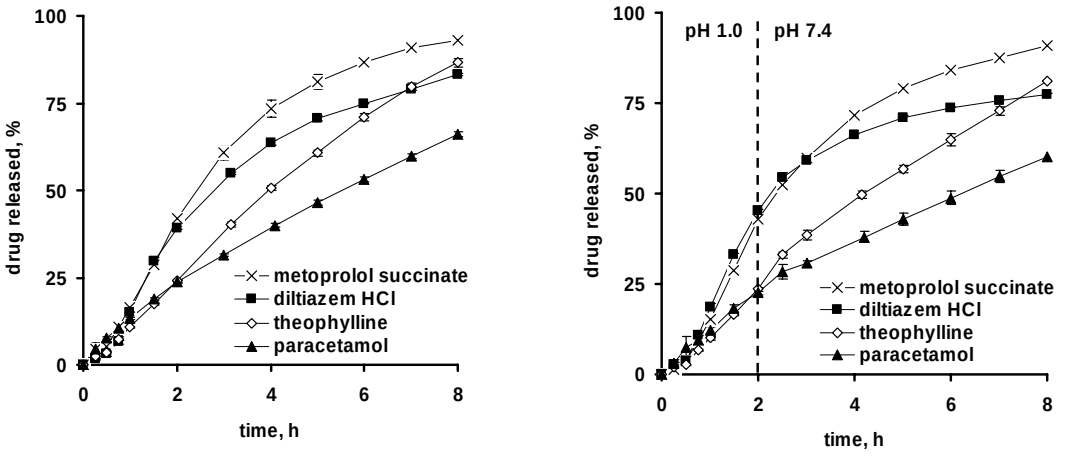


Figure 7.1 Effects of the type of drug (indicated in the figures) on the release patterns from pellets coated with ethylcellulose:PVA-PEG graft copolymer 90:10 in: (a) 0.1 N HCl for 8 h, and (b) 0.1 N HCl for 2 h and subsequent complete medium change to phosphate buffer pH 7.4 (coating level: 30 %, drug layered sugar cores).

Figure 7.1 shows that this strategy can successfully be applied to drugs exhibiting very different solubility, irrespective of the type of release medium. In these cases, the drugs are

layered onto sugar cores. Interestingly, the rank order of drug solubility did not correlate with the rank order of the observed release rates. The experimentally measured drug solubility at 37 °C increased as follows: theophylline < paracetamol < metoprolol succinate < diltiazem HCl (14 < 19 < 284 < 662 mg/mL and 11 < 18 < 251 < 582 mg/mL in 0.1 N HCl and phosphate buffer pH 7.4, respectively). Thus, the permeability of the dissolved drug molecules/ions in the wetted polymeric networks plays a major role for the control of drug release (in addition to drug solubility).

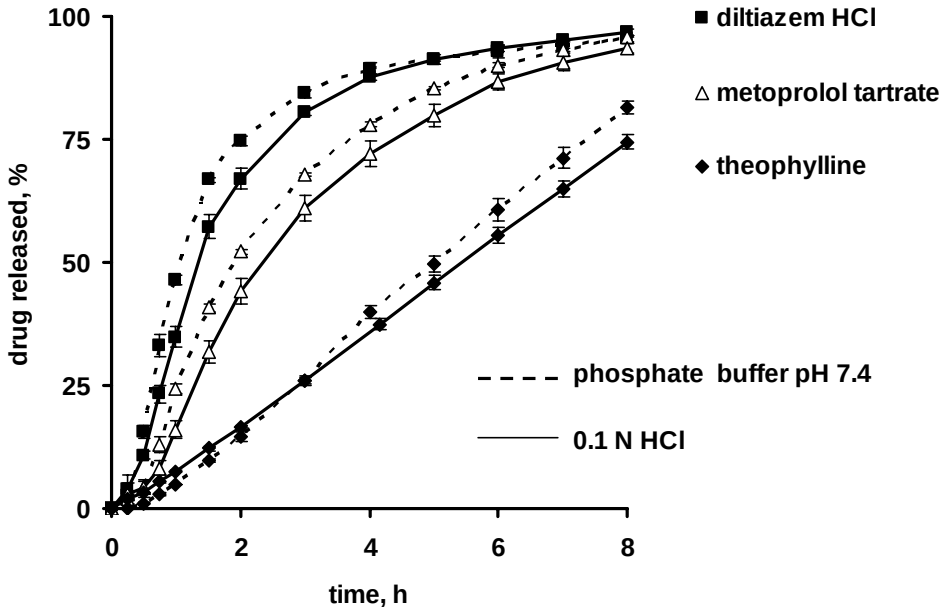


Figure 7.2: Effects of the type of release medium (indicated in the figure) on drug release from ethylcellulose:PVA-PEG graft copolymer coated pellets (matrix cores) (diltiazem HCl/metoprolol tartrate/theophylline: polymer:polymer blend ratio = 90:10/90:10/85:15 and coating level = 25/30/15 %).

Figure 7.2 illustrates that ethylcellulose:PVA-PEG graft copolymer blends can also effectively be used to control drug release from different types of coated *drug matrix cores*. The relative release rate of diltiazem HCl, metoprolol tartrate and theophylline from coated

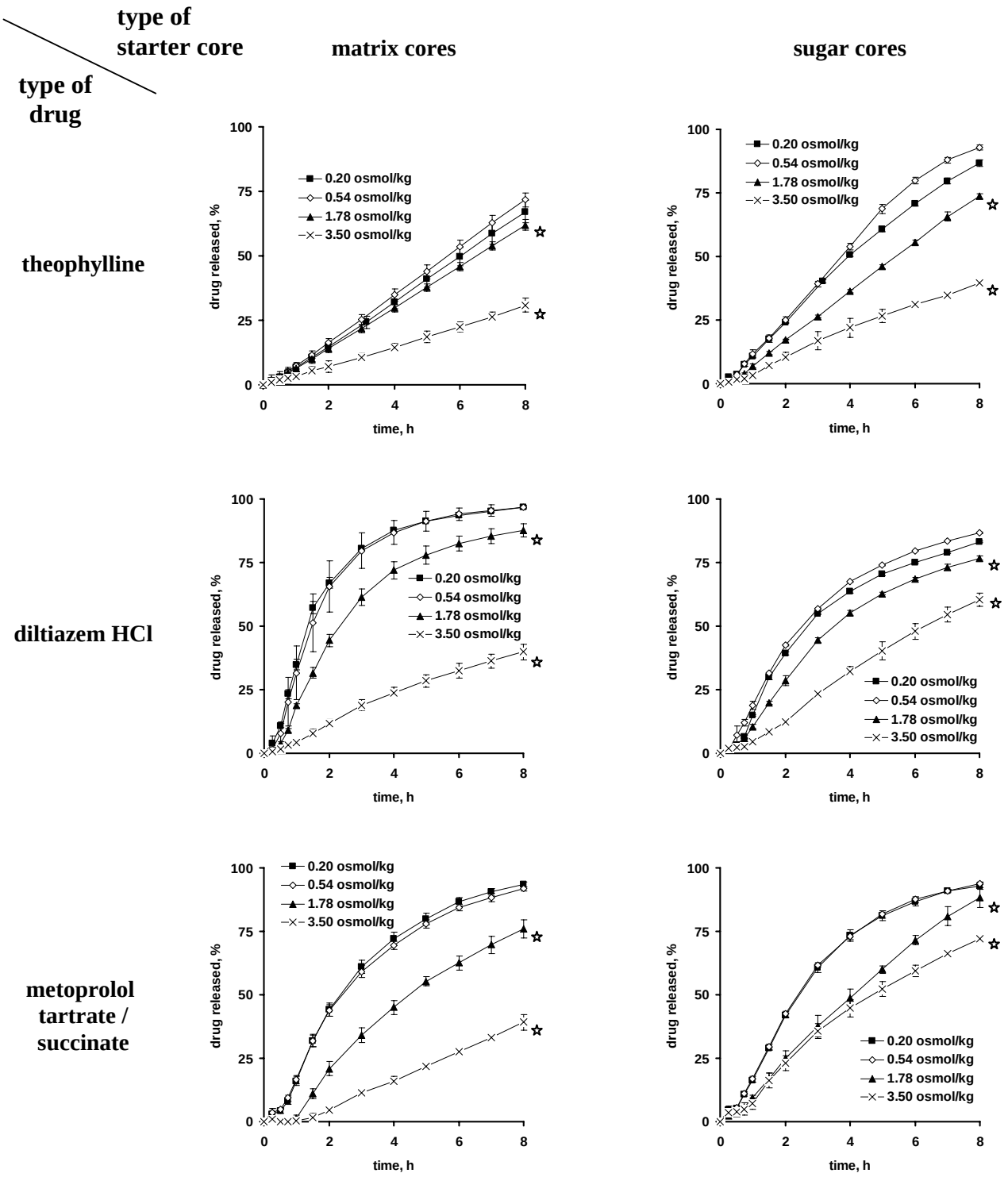


Figure 7.3: Importance of the osmotic pressure of the release medium for drug release from pellets coated with ethylcellulose:PVA-PEG graft copolymer containing different types of cores (as indicated on the top) loaded with different types of drugs (as indicated on the left) in 0.1 N HCl containing different amounts of NaCl (stars indicate non-physiological

conditions). Matrix cores loaded with: theophylline/diltiazem HCl/metoprolol tartrate: polymer:polymer blend ratio = 85:15/90:10/90:10 and coating level = 15/25/30 %; sugar cores layered with: diltiazem HCl/theophylline/metoprolol succinate: polymer:polymer blend ratio = 90:10 and coating level = 30 %.

pellets in 0.1 N HCl and phosphate buffer pH 7.4 are shown. Importantly, the resulting drug release rate is *independent* of the pH of the release medium in all cases (dashed versus solid curves).

To better understand the underlying drug release mechanisms from these various types of coated pellets, the effects of the osmolality of the release medium on the resulting release rate of theophylline, diltiazem HCl and metoprolol succinate from drug layered sugar cores coated with ethylcellulose:PVA-PEG graft copolymer 90:10 (coating level = 30 % w/w) were monitored (Figure 7.3). Please note that osmolalities of 1.78 and 3.50 osmol/kg are higher than physiological [28, 29] and only used to get deeper insight into the underlying drug release mechanisms. Interestingly, the resulting release rate was very similar for the physiologically relevant osmolalities of 0.20 and 0.54 osmol/kg, irrespective of the type of drug. This indicates that significant variations in the drug release rates *in vivo*, due to alterations in the osmotic pressure of the surrounding bulk fluid within the gastro intestinal tract are unlikely. This is very important from a practical point of view, because such changes in the osmolality (for instance caused by the type of ingested food) might fundamentally change the underlying drug release mechanism and release rate from coated solid dosage forms: With decreasing osmolality of the bulk fluid, the water penetration rate into the system increases, resulting in increasing amounts of water available for drug dissolution and a more pronounced/accelerated increase in the hydrostatic pressure acting against the polymeric coatings from inside the system. If the film coatings are not sufficiently (mechanically) stable, crack formation is induced and subsequent drug release primarily controlled via diffusion

through water-filled channels. The resulting release rates can be much higher than through the intact polymeric networks and drug release might be fundamentally faster. The fact that the experimentally measured release rates are very similar, irrespective of the osmolality of the release medium in the physiological range, clearly indicates that a change in the underlying drug release mechanism is highly unlikely *in vivo* due to this phenomenon. The observed decrease in the release rate of theophylline, diltiazem HCl and metoprolol succinate from the coated matrix cores when increasing the osmolality of the bulk fluid up to (non-physiological) 3.50 osmol/kg can be explained by the decrease in the water penetration rate into the systems, water being required for drug dissolution and only dissolved drug being able to diffuse. The fact that the *shape* of the drug release curves does not fundamentally vary even under these very drastic conditions (e.g. pulsatile versus non-pulsatile release profile) indicates that the underlying drug release mechanism remains unaltered. Thus, these formulations are highly robust from a mechanistic point of view, even under non-physiological, extreme conditions. Figure 7.3 also shows the release rates of theophylline, diltiazem HCl and metoprolol tartrate from ethylcellulose:PVA-PEG graft copolymer coated *drug matrix cores* in 0.1 N HCl containing different amounts of NaCl. As in the case of drug layered sugar cores, the resulting release patterns were very similar under physiological conditions, whereas an increase of the osmolality of the bulk fluid up to 3.50 osmol/kg led to a decrease in the release rate. Again, the shape of the respective drug release profiles remained similar, indicating the absence of changes in the underlying drug release mechanism.

(a) (b)

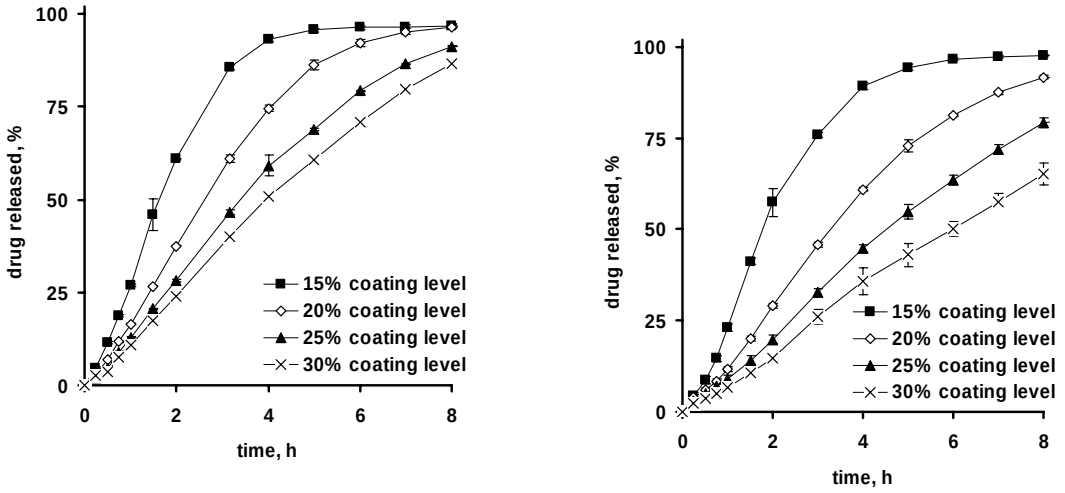


Figure 7.4: Effects of the coating level on theophylline release in 0.1 N HCl from pellets coated with ethylcellulose:PVA-PEG graft copolymer 90:10, containing: (a) drug layered sugar cores, and (b) drug layered MCC cores.

7.3.2. Drug release mechanisms

It has previously been shown that desired drug release patterns from theophylline matrix cores coated with ethylcellulose:PVA-PEG graft copolymer blends can easily be adjusted by varying the coating level. Importantly, this is also true for other types of starter cores as it can be seen in Figures 7.4a and 7.4b for theophylline layered sugar and MCC cores. This indicates that it is the polymeric film coating that controls drug release, and not the type of starter core. The dominance of the film coating has further been confirmed when studying the drug release mechanisms of theophylline from drug matrix cores as well as from drug layered sugar and MCC cores in more detail. In order to distinguish between drug release occurring via diffusion through an intact polymeric coating versus diffusion through water-filled cracks, changes in the size of *single* pellets were monitored upon exposure to 0.1 N HCl (at 37 °C). As soon as the pellets come into contact with aqueous media, water diffuses into the systems, generating a monotonically increasing hydrostatic pressure inside

the pellets, which acts against the film coating. If this hydrostatic pressure exceeds the mechanical stability of the film coating at a given time point, crack formation is induced and drug release will be greatly accelerated (because drug no longer has to diffuse through the polymer membrane).

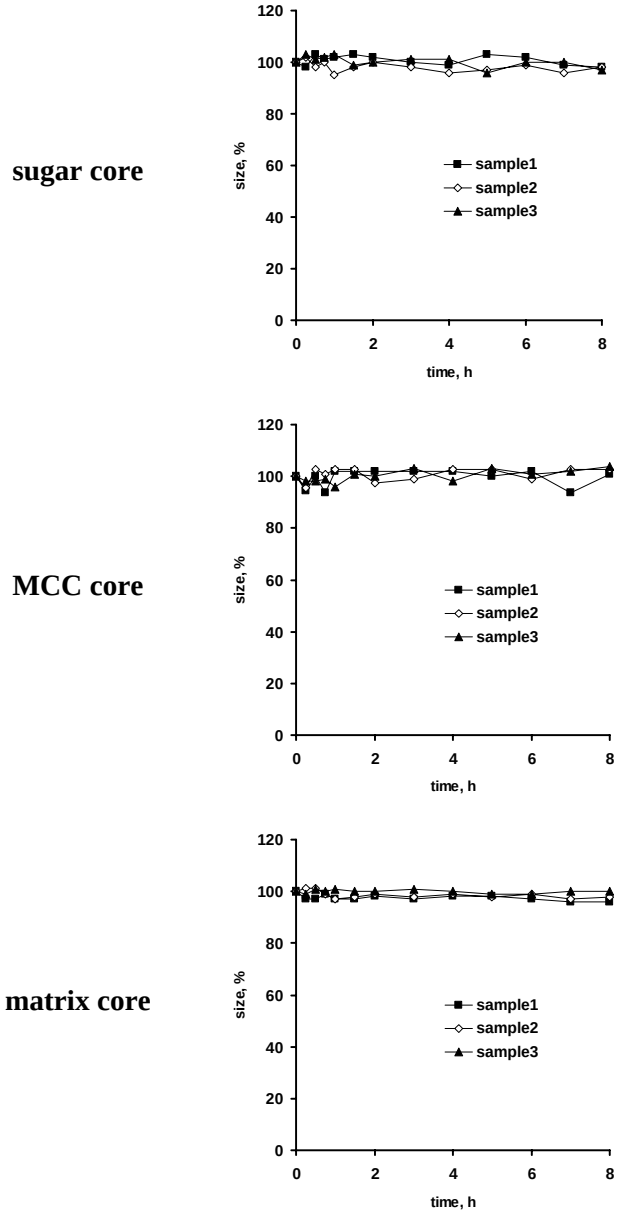


Figure 7.5: Swelling behaviour of theophylline loaded pellets containing different types of starter cores (indicated in the figure), coated with ethylcellulose:PVA-PEG graft copolymer upon exposure to 0.1 N HCl (sugar and MCC cores: polymer polymer blend ratio = 90:10; matrix cores: polymer:polymer blend ratio = 85:15) (coating level = 30 %, single pellets).

This type of phenomenon is often indicated by a steadily increasing pellet diameter, which suddenly levels off and even eventually decreases (since the pellet's content is pushed out of the system due to the pressure gradient) [10]. As it can be seen in Figure 7.5, no such signs are visible in any case, irrespective of the type of starter core. Thus, drug release is likely to be controlled by diffusion through the intact ethylcellulose:PVA-PEG graft copolymer coatings in all cases. This hypothesis was further confirmed by scanning electron microscopy. Figure 7.6 shows surfaces of pellets, which were exposed to 0.1 N HCl for 2 h. No sign of crack formation is visible in any case: theophylline matrix cores, theophylline layered sugar and MCC cores, despite the significantly different osmotic activity of these starter cores.

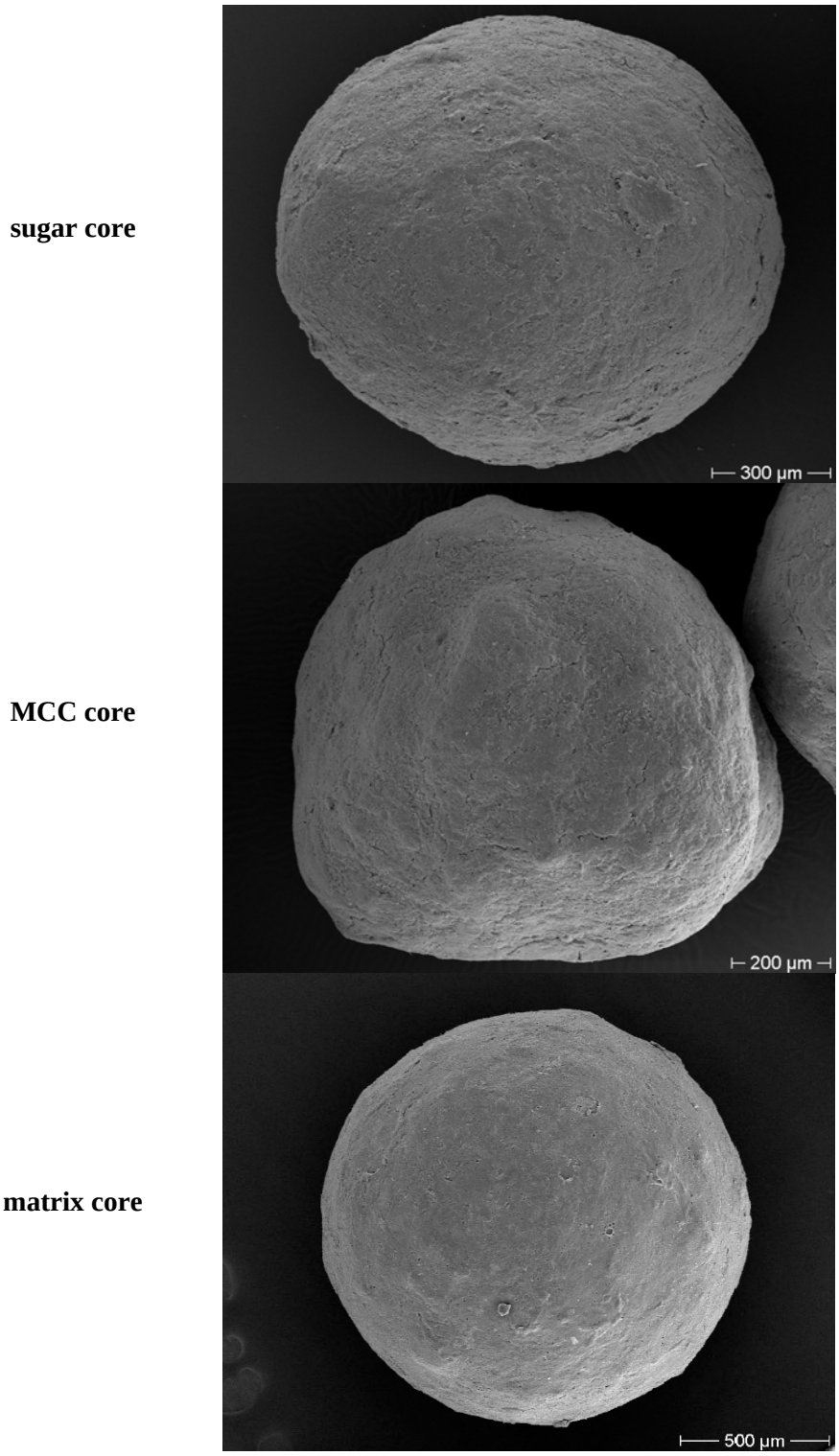


Figure 7.6: Scanning electron microscopy pictures of theophylline loaded pellets containing different types of starter cores (indicated in the figure), coated with ethylcellulose:PVA-PEG graft copolymer upon 2 h exposure to 0.1 N HCl (sugar and MCC cores: polymer polymer blend ratio = 90:10; matrix cores: polymer:polymer blend ratio = 85:15) (coating level = 30 %).

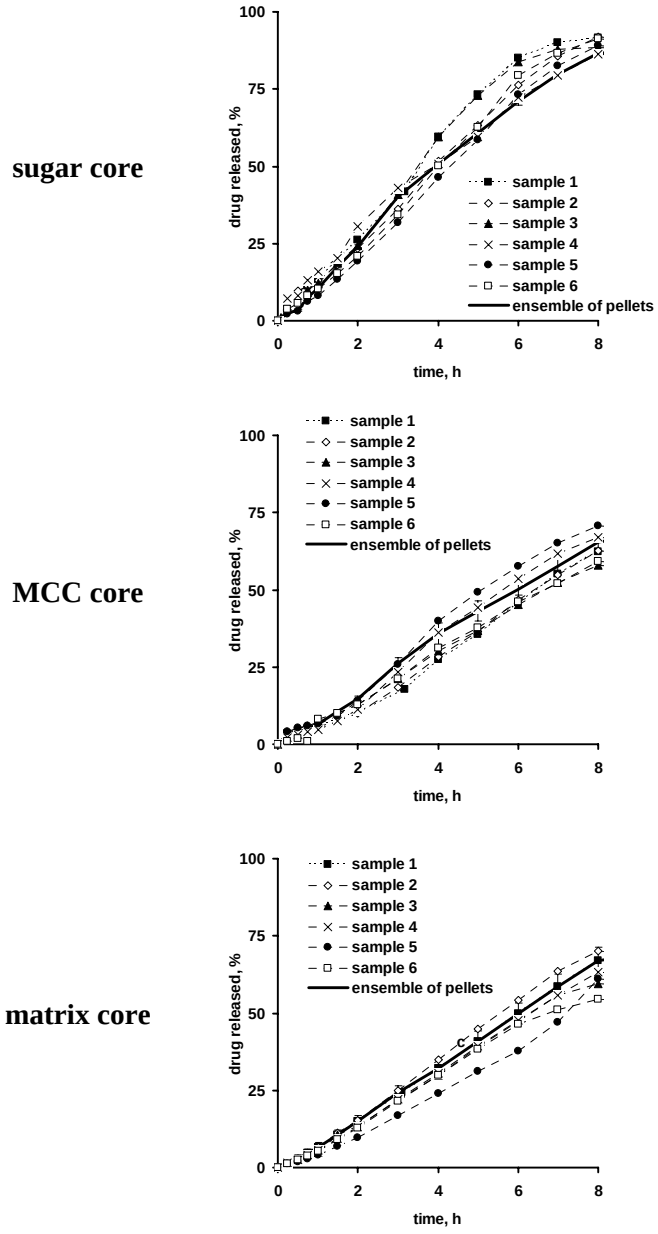


Figure 7.7: Theophylline release from single pellets in 0.1 N HCl from drug layered sugar and MCC cores, coated with ethylcellulose:PVA-PEG graft copolymer 90:10 (coating level: 30 %) as well as from drug matrix cores, coated with ethylcellulose:PVA-PEG graft copolymer 85:15 (coating level: 15 %). For reasons of comparison also drug release from ensembles of pellets is shown.

When studying the underlying drug release mechanisms from coated multiparticulates, drug release should not only be investigated drug from *ensembles* of systems, but also from *single* dosage forms. For instance, an apparent zero order release kinetics observed with an ensemble of pellets might be the result of the summation of individual *pulsatile* drug release patterns with significantly different lag-times, which are homogeneously distributed throughout the observation period. As it can be seen in Figure 7.7, theophylline release from single pellets was very similar to that from ensembles of pellets, irrespective of the type of starter core: drug matrix, sugar or MCC core. These findings are in good agreement with those previously reported on diltiazem HCl layered sugar cores [30], and clearly indicate that the underlying drug release mechanism is uniform and that this type of controlled drug delivery system is very robust.

7.4. Conclusions

Drug release from pellets coated with ethylcellulose containing small amounts of PVA-PEG graft copolymer as release rate modifier and stabilizer is controlled by diffusion through the intact polymer membrane, irrespective of the type of drug and pellet starter core. The impact of the ethylcellulose coating is dominant and effects of the osmolality of the release medium (within the physiological range) and the nature of the starter core composition are negligible. Thus, this type of controlled drug delivery system can be used for very different drugs and is robust.

7.5. References

1. Fukumori, Y., *Coating of Multiparticulates Using Polymeric dispersions*, in *Multiparticulate Oral Drug Delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 79-111.

2. Ghebre-Sellassie, I., *Multiparticulate oral drug delivery*. 1997, New York: Marcel Dekker.

3. McGinity, J.W., *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. 2 ed. 1997, New York: Marcel Dekker.

4. Amighi, K. and A.J. Moes, *Evaluation of thermal and film forming properties of acrylic aqueous polymer dispersion blends: application to the formulation of sustained-release film coated theophylline pellets.* Drug Dev. Ind. Pharm., 1995. **21**(20): p. 2355–2569.

5. Dashevsky, A., et al., *Physicochemical and release properties of pellets coated with Kollicoat(R) SR 30 D, a new aqueous polyvinyl acetate dispersion for extended release*. International Journal of Pharmaceutics, 2005. **290**(1-2): p. 15-23.

6. Siepmann, F., et al., *Polymer blends for controlled release coatings.* Journal of Controlled Release, 2008. **125**(1): p. 1-15.

7. Wade, A. and P.J. Weller, *Handbook of Pharmaceutical Excipients*. 2 ed. 1994, Washington: American Pharmaceutical Association.

8. Banker, G.S., *Film coating theory and practice.* Journal of Pharmaceutical Sciences, 1966. **55**(1): p. 81-89.

9. Eckersley, S.T. and A. Rudin, *Mechanism of film formation from polymer latexes* Journal of Coatings Technology, 1990. **62**(780): p. 89-100.

10. Lecomte, F., et al., *pH-Sensitive Polymer Blends used as Coating Materials to Control Drug Release from Spherical Beads: Importance of the Type of Core.* Biomacromolecules, 2005. **6**(4): p. 2074-2083.

11. Amighi, K. and A.J. Moes, *Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit RS 30D film-coated sustained-release theophylline pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42**(1): p. 29-35.

12. Siepmann, F., et al., *Aqueous HPMCAS coatings: Effects of formulation and processing parameters on drug release and mass transport mechanisms.* European Journal of Pharmaceutics and Biopharmaceutics, 2006. **63**(3): p. 262-269.

13. Wu, C. and J.W. McGinity, *Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer.* European Journal of Pharmaceutics and Biopharmaceutics, 2000. **50**(2): p. 277-284.

14. Siepmann, F., et al., *How to improve the storage stability of aqueous polymeric film coatings.* Journal of Controlled Release, 2008. **126**(1): p. 26-33.

15. Siepmann, F., et al., *How to adjust desired drug release patterns from ethylcellulose-coated dosage forms.* Journal of Controlled Release, 2007. **119**(2): p. 182-189.

16. Chowhan, Z.T., A.A. Amaro, and L.-H. Chi, *Comparative evaluations of aqueous film coated tablet formulations by high humidity aging.* Drug Development and Industrial Pharmacy, 1982. **8**(5): p. 713-737.

17. Bonacucina, G., et al., *Effect of plasticizers on properties of pregelatinised starch acetate (Amprac 01) free films.* International Journal of Pharmaceutics, 2006. **313**(1-2): p. 72-77.

18. Sousa, J.J., et al., *The influence of core materials and film coating on the drug release from coated pellets.* International Journal of Pharmaceutics, 2002. **233**(1-2): p. 111-122.

19. Lecomte, F., et al., *Blends of enteric and GIT-insoluble polymers used for film coating: physicochemical characterization and drug release patterns.* Journal of Controlled Release, 2003. **89**(3): p. 457-471.

20. Gunder, W., B.H. Lippold, and B.C. Lippold, *Release of drugs from ethyl cellulose microcapsules (diffusion pellets) with pore formers and pore fusion.* European Journal of Pharmaceutical Sciences, 1995. **3**(4): p. 203-214.

21. Schultz, P. and P. Kleinebudde, *A new multiparticulate delayed release system.Part I: Dissolution properties and release mechanism.* Journal of Controlled Release, 1997. **47**(2): p. 181-189.

22. Marucci, M., et al., *Mechanistic model for drug release during the lag phase from pellets coated with a semi-permeable membrane.* Journal of Controlled Release, 2008. **127**(1): p. 31-40.

23. Borgquist, P., et al., *Simulation of the release from a multiparticulate system validated by single pellet and dose release experiments.* Journal of Controlled Release, 2004. **97**(3): p. 453-465.

24. Borgquist, P., et al., *Simulation and parametric study of a film-coated controlled-release pharmaceutical.* Journal of Controlled Release, 2002. **80**(1-3): p. 229-245.

25. Strübing, S., H. Metz, and K. Mäder, *Mechanistic analysis of drug release from tablets with membrane controlled drug delivery.* European Journal of Pharmaceutics and Biopharmaceutics, 2007. **66**(1): p. 113-119.

26. Strübing, S., H. Metz, and K. Mäder, *Characterization of poly(vinyl acetate) based floating matrix tablets.* Journal of Controlled Release, 2008. **126**(2): p. 149-155.

27. Katzhendler, I., K. Mader, and M. Friedman, *Structure and hydration properties of hydroxypropyl methylcellulose matrices containing naproxen and naproxen sodium.* International Journal of Pharmaceutics, 2000. **200**(2): p. 161-179.

28. Lindahl, A., et al., *Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women.* Pharmaceutical Research, 1997. **14**(4): p. 497-502.

29. Ladas, S.D., P.E. Isaacs, and G.E. Sladen, *Post-prandial changes of osmolality and electrolyte concentration in the upper jejunum of normal man.* Digestion, 1983. **26**(4): p. 218-23.

30. Muschert, S., et al., *Predictability of Drug Release from Ethylcellulose Coated Pellets.* Journal of Controlled Release, 2008. **submitted**.

8. OPTIMIZATION OF THE CURING CONDITIONS

Abstract: The curing conditions required to provide appropriate film formation in aqueous ethylcellulose dispersions containing small amounts of PVA-PEG graft copolymer could successfully be optimized. For instance, in the case of ethylcellulose:PVA-PEG graft copolymer 85:15 blends 2 h at 60 °C or 8 h at 50 °C were shown to be sufficient (instead of 48 h at 60 °C) in order to obtain stable film coatings. Open long term storage for up to 12 months showed no changes in the resulting drug release kinetics.

8. Optimization of the curing conditions

8.1. Introduction

Latex and pseudolatex dispersions are frequently used for the coating of multiparticulates since they offer various advantages compared to organic solutions, including reduced toxicity and environmental concerns [1]. However, generally a thermal after treatment (curing step) is required to assure appropriate film formation. This is due to the underlying film formation mechanism, which is fundamentally different from that of films formed from organic solutions. Upon water evaporation the discrete polymer particles are driven together and particle fusion occurs [2, 3]. Importantly, this step is time and temperature dependent [4-7]. Generally, it is completed during the curing step. The addition of appropriate types and amounts of plasticizers can help facilitating polymer particle fusion [8.] They decrease the glass transition temperature and, thus, increase polymer chain mobility. In some extreme case it has been shown that by increasing the plasticizer level the Tg can be lowered to a point that the curing step can be performed by simply storing the pellets for a short period of time at room temperature [9]. The curing step can also lead to a more homogeneous distribution of the plasticizer within the film coating [10.]. Also the drug might act as a plasticizer for the polymer, in example ibuprofen plasticizes ethylcellulose [11]. Due to hydrogen bonding between the drug and polymer groups ibuprofen facilitates polymer particle fusion. It has to be pointed out that exposure to elevated temperatures for long periods of time can also lead to plasticizer loss and the films might be “overdried” [6, 8, 12]. *Incomplete* film formation can lead to decreasing drug release rates upon long term storage [13-15], because further polymer particles coalescence results in decreased film permeability for the drug. This process is likely to be accelerated at high relative humidity and elevated temperatures (e.g., 75 % RH & 40 °C = stress conditions according to the ICH guidelines): Water acts as a plasticizer for ethylcellulose and an increase in temperature leads to increased macromolecular mobility.

8.2. Experimental section

8.2.1. Materials

Diltiazem hydrochloride (diltiazem HCl; VWR, Fontenay-sous-Bois, France), sugar cores (sugar spheres NF, 710–850 µm; NP Pharm, Bazainville, France), theophylline pellets (70 % w/w drug content; FMC, Philadelphia, PA), Ethylcellulose Aqueous Dispersion NF (Aquacoat ECD; FMC Biopolymer, Philadelphia, USA), poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer, Kollicoat IR; BASF, Ludwigshafen, Germany), triethyl citrate (TEC; Morflex, Greensboro, USA), hydroxypropyl methylcellulose (HPMC, Methocel E 5; Colorcon, Dartford, UK).

8.2.2. Preparation of coated pellets

Drug layered starter cores: Sugar cores were coated with an aqueous solution of diltiazem HCl (18.2 % w/w) and HPMC (0.9 % w/w) in a fluidized bed coater (Strea 1, Wurster insert, Niro; Aeromatic-Fielder, Bubendorf, Switzerland). The process parameters were as follows: inlet temperature = 40 °C, product temperature = 40±2 °C, spray rate = 1-3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. The final drug loading was 10 % w/w.

Controlled release pellets: The drug layered sugar cores and theophylline matrix cores (70 % w/w drug content) were coated with aqueous ethylcellulose dispersion containing 10 % (w/w) PVA-PEG graft copolymer in a fluidized bed coater (Strea 1, Wurster insert) until a weight gain of 5 to 30 % (w/w) was achieved. The aqueous ethylcellulose dispersion was plasticized with 25 % w/w TEC (based on the ethylcellulose content; overnight stirring) and blended with aqueous PVA-PEG graft copolymer solution (6.6 % w/w) 30 min prior to coating (under gentle stirring). The process parameters were as follows: inlet temperature = 38 °C, product temperature = 38 ± 2 °C, spray rate = 2-3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. After coating the pellets were further fluidized for 10 min

and subsequently cured for 1 to 48 h at 40 °C, 50 °C and 60 °C at ambient relative humidity (RH) or 75 % RH (in the latter case followed by an additional drying step of 24 h at 60 °C/ambient RH), as indicated.

8.2.3. Drug release from coated pellets

Drug release from the pellets was measured in 0.1 M HCl and phosphate buffer pH 7.4 (USP XXIX) using the paddle apparatus (USP XXIX; Sotax, Basel, Switzerland) (900 mL; 37 °C, 100 rpm; n = 3). At pre-determined time intervals, 3 mL samples were withdrawn and analyzed UV-spectrophotometrically (diltiazem HCl: λ = 236.9 nm in 0.1 N HCl and λ = 237.4 nm in phosphate buffer pH 7.4; theophylline: λ = 270.4 nm in 0.1 N HCl and λ = 272.2 nm in phosphate buffer pH 7.4; UV-1650PC, Shimadzu, Champs-sur-Marne, France).

8.2.4. Storage stability

Coated pellets were stored in *open* glass vials at room temperature/ambient RH as well as under stress conditions: 40°C/75 % RH. Theophylline and diltiazem HCl release from the pellets was measured before and after 3, 6 and 12 months storage as described in section 8.2.3.

8.3. Results and discussion

It has previously been shown that curing for 2 d at 60 °C and 75 % RH is sufficient to assure appropriate film formation in the case of ethylcellulose:PVA-PEG graft copolymer 85:15 coatings [3]. It was the aim of this study to evaluate to which extent these conditions can be reduced, while still assuring appropriate film formation and long term stability.

As it can be seen in Figures 8.1 and 8.2, the resulting drug release profiles were very similar for diltiazem HCl layered sugar cores as well as for theophylline matrix pellets coated with

ethylcellulose:PVA-PEG graft copolymer 85:15 coatings, irrespective of the investigated curing conditions:

(i) 1 d at 60°C/ambient relative humidity (RH);

(ii) 2 d at 60°C/ambient RH;

(iii) 1 d at 60°C/75 %RH (followed by an additional drying step of 1 d at 60 °C/ambient RH); and

(iv) 2 d at 60°C/75 %RH (followed by an additional drying step of 1 d at 60 °C/ambient RH).

Diltiazem HCl is freely water soluble, theophylline is slightly water soluble.

Figure 8.3 illustrates that the obtained drug release patterns were stable during *open* long term storage under stress conditions (40 ° C and 75 % RH), irrespective of the type of drug release medium and type of investigated curing conditions.

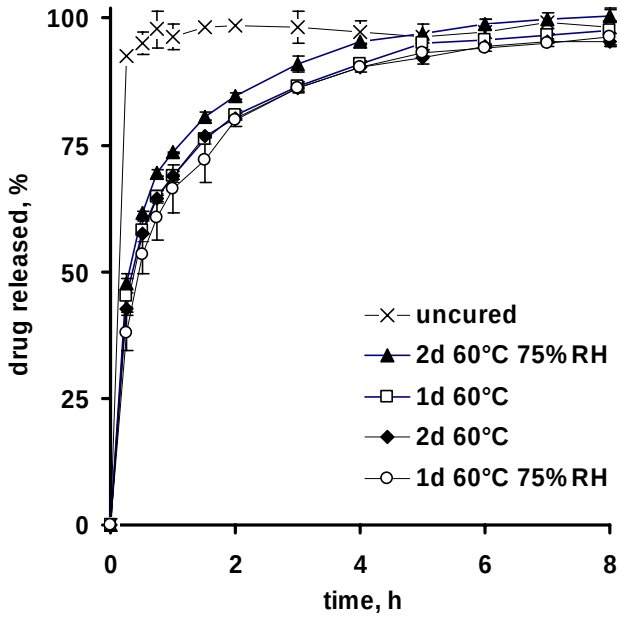


Figure 8.1: Influence of curing conditions (indicated in the figure) on drug release from diltiazem HCl layered sugar cores coated with ethylcellulose:PVA-PEG graft copolymer 85:15 in phosphate buffer pH 7.4 (drug loading: 10%; coating level: 15 %).

(a) (b)

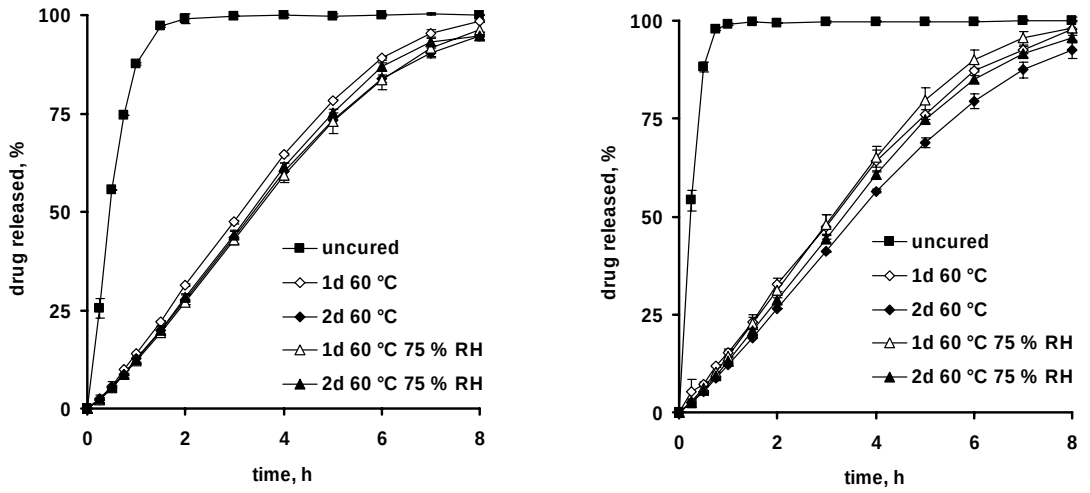


Figure 8.2: Effects of the curing conditions (indicated in the figures) on drug release from theophylline matrix cores coated with ethylcellulose:PVA-PEG graft copolymer 85:15 in: (a) 0.1 N HCl and (b) phosphate buffer pH 7.4 (coating level: 10 %).

(a) (b)

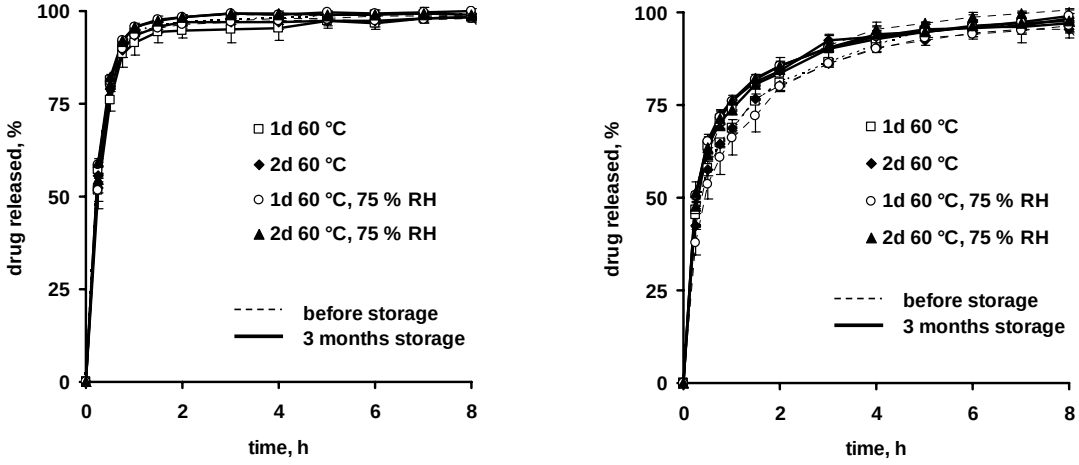


Figure 8.3: Diltiazem HCl release from drug layered sugar cores coated with ethylcellulose:PVA-PEG graft copolymer 85:15 before and after 3 months storage at 40 °C and 75 % relative humidity in: (a) 0.1 N HCl and (b) phosphate buffer pH 7.4 (curing conditions as indicated in the figures; drug loading: 10%; coating level: 15 %).

8.3.1. Optimization of the curing temperature

As it can be seen in Figure 8.4, the curing temperature can be decreased to only 50 °C at a curing time of 24 h in the case of theophylline matrix pellets coated with ethylcellulose:PVA-PEG graft copolymer 85:15: The resulting release profiles are overlapping in 0.1 N HCl as well as in phosphate buffer pH 7.4. However, curing at only 40 ° C for 24 h led to insufficient film formation and much higher drug release rates.

(a) (b)

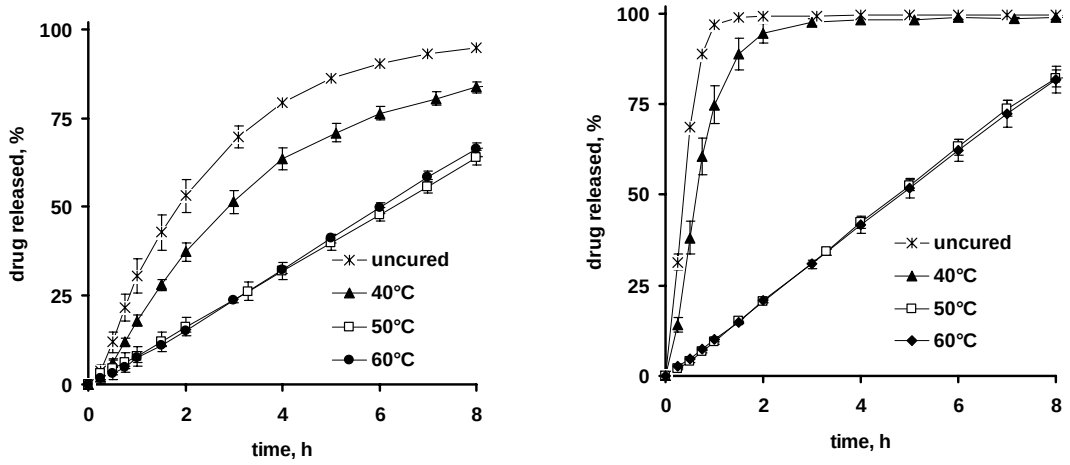


Figure 8.4: Influence of the curing temperature (indicated in the figures) on theophylline release from ethylcellulose:PVA-PEG graft copolymer 85:15 coated drug matrix cores in: (a) 0.1 N HCl and (b) phosphate buffer pH 7.4 (curing time: 24 h, coating level: 15 %).

8.3.2. Effect of the curing time

Figure 8.5 shows that also the curing time can significantly be reduced, while assuring adequate film formation. The release of theophylline from drug matrix pellets coated with ethylcellulose:PVA-PEG graft copolymer 85:15 are shown. The curing temperature was constant: (a) 60 °C and (b) 50 °C, while the curing time was varied. Clearly, overlapping drug release patterns were obtained if the curing time exceeded 2 h at 60 °C and 8 h at 50 °C.

(a) (b)

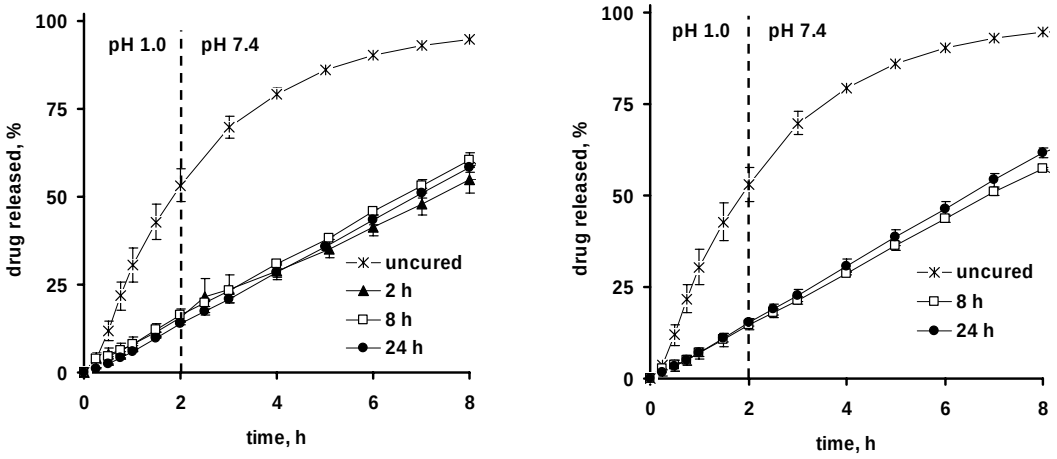
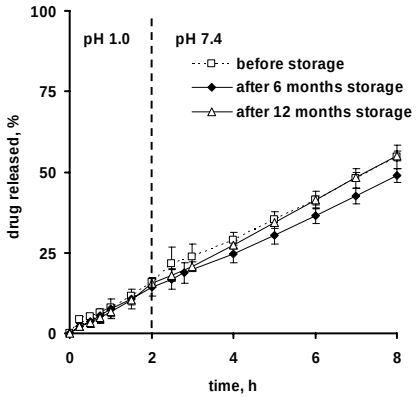


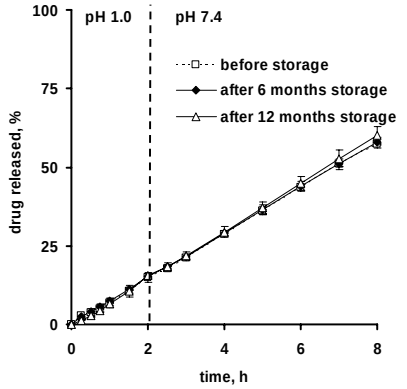
Figure 8.5: Influence of the curing time (indicated in the figure) on theophylline release from ethylcellulose:PVA-PEG graft copolymer 85:15 coated drug matrix cores cured at: (a) 60 °C and (b) 50 °C in: 0.1 M HCl for 2 h, followed by phosphate buffer pH 7.4 (coating level: 15 %).

These results were confirmed by long term stability trials: Figure 8.6 shows theophylline release from pellets coated with ethylcellulose:PVA-PEG graft copolymer 85:15 at a coating level of 15 % before and after 6 and 12 months open storage at ambient conditions. In the first 2 h the pellets were exposed to 0.1 N HCl, then to phosphate buffer pH 7.4. Clearly, drug release before and after storage was very similar in all cases.

2 h 60 °C



8 h 50°C



24 h 60°C

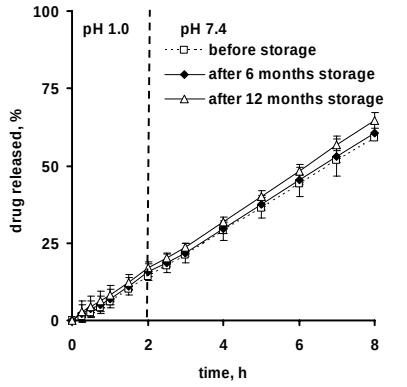


Figure 8.6: Storage stability of ethylcellulose:PVA-PEG graft copolymer 85:15 coated theophylline matrix cores cured under different conditions (indicated in the figure) before and after 12 months open storage under ambient conditions (coating level: 15 %): Drug release in 0.1 M HCl for 2 h, followed by phosphate buffer pH 7.4.

8.4. Conclusions

When coating pellets with ethylcellulose:PVA-PEG graft copolymer 85:15, the curing temperature and curing time required to provide appropriate film formation can be reduced to only 2 h (at 60 ° C) and to only 50 °C (at 8 h) in the investigated cases. These conditions can serve as suitable guidelines also for other types of systems.

8.5. References

1. Wesseling, M. and R. Bodmeier, *Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat(R), or an organic ethylcellulose solution.* European Journal of Pharmaceutics and Biopharmaceutics, 1999. **47**(1): p. 33-38.
2. Wesseling, M., *Preparation and investigation of coated multiparticulate drug delivery systems*. 1999, Freie Universitaet Berlin: Berlin.
3. Siepmann, F., et al., *How to improve the storage stability of aqueous polymeric film coatings.* Journal of Controlled Release, 2008. **126**(1): p. 26-33.
4. Millili, G.P., R.J. Wigent, and J.B. Schwartz, *Autohesion in Pharmaceutical Solids.* Drug Development and Industrial Pharmacy, 1990. **16**(16): p. 2383 - 2407.
5. Miller, R.A. and E.B. Vadas, *The Physical Stability of Tablets Coated using an Aqueous Dispersion of Ethylcellulose.* Drug development and Industrial pharmacy, 1984. **10**(10): p. 1565 – 1585.
6. Wurster, D.E., S. Bhattacharjya, and D.R. Flanagan, *Effect of Curing on Water Diffusivities in Acrylate Free Films as Measured via a Sorption Technique.* AAPS PharmSciTech., 2007. **8**(3): p. Article 71.
7. Hutchings, D., B. Kuzmak, and A. Sakr, *Processing Considerations for an EC Latex Coating System: Influence of Curing Time and Temperature.* Pharmaceutical Research, 1994. **11**(10): p. 1474-1478.
8. Bodmeier, R., X. Guo, and O. Paeratakul, *Process and formulation variables affecting the drug release from pellets coated with the ethylcellulose-pseudolatex Aquacoat*, in *Aqueous polymeric coatings for pharmaceutical dosage forms*, J. McGinity, Editor. 1997, Marcel Dekker: New York. p. 55-80.

9. Bodmeier, R. and O. Paeratakul, *The Effect of Curing on Drug Release and Morphological Properties of Ethylcellulose Pseudolatex-Coated Beads.* Drug Development and Industrial Pharmacy, 1994. **20**(9): p. 1517 - 1533.

10. Lippold, B.H., B.K. Sutter, and B.C. Lippold, *Parameters controlling drug release from pellets coated with aqueous ethyl cellulose dispersion.* International Journal of Pharmaceutics, 1989. **54**(1): p. 15-25.

11. Brabander, C.d., et al., *Characterization of ibuprofen as a nontraditional plasticizer of ethyl cellulose.* Journal of Pharmaceutical Sciences, 2002. **91**(7): p. 1678-1685.

12. Guma, N.C., K. Kale, and K.R. Morris, *Investigation of film curing stages by dielectric analysis and physical characterization.* Journal of Pharmaceutical Sciences, 1997. **86**(3): p. 329-334.

13. Amighi, K. and A.J. Moes, *Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit RS 30D film-coated sustained-release theophylline pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42**(1): p. 29-35.

14. Lippold, B.C. and R. Monells Pages, *Film formation, reproducibility of production and curing with respect to release stability of functional coatings from aqueous polymer dispersions.* Pharmazie, 2001, Pages 5-17. **56**(1): p. 5-17.

15. Hoffart, V., et al., *Storage stability of pellets coated with the aqueous ethylcellulose dispersion-Aquacoat ECD at elevated temperature and humidity*, in *2005 AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists*. 2005: Nashville, USA.

9. SUMMARY

The major aims of this work included: (i) the preparation of different types of ethylcellulose coated dosage forms using aqueous dispersions, (ii) the thorough physico-chemical characterization of the systems in vitro, (iii) the development of novel strategies allowing for an easy adjustment of desired drug release patterns and long term stable film coatings, and (iv) a better understanding of the underlying drug release mechanisms. Ethylcellulose is a highly suitable polymer for controlled release coatings. However, drug permeability through the intact polymeric networks might be low and incomplete film formation during coating and curing might lead to further polymer particle coalescence during long term storage. To overcome these restrictions, small amounts of carrageenan, propylene glycol alginate or poly(vinyl acetate)-poly(propylene) glycol graft copolymer were added. The presence of these hydrophilic compounds attracts water within the coatings during film formation and facilitates polymer particle coalescence: water acts as a plasticizer and is mandatory for the capillary forces driving the colloidal particles together. Furthermore, the permeability of the resulting polymeric membranes is significantly increased, which can at least partially be explained by increased water uptake and dry mass loss rates and extents upon exposure to aqueous media. Importantly, the addition of these hydrophilic compounds does not cause coagulation of the coating formulations. This is in contrast to the previously proposed additive HPMC (hydroxypropyl methylcellulose). It could be shown that the resulting drug release kinetics can be easily adjusted by varying the additive's content and that long term stable drug release profiles can be provided upon appropriate coating and curing, even upon 6 months open storage under stress conditions. Furthermore, new insight into the underlying drug release mechanisms could be gained and the importance of the type of drug, starter core and release medium for the resulting drug release kinetics be elucidated. This knowledge can help to facilitate the optimization of this type of advanced drug delivery systems and to face challenges encountered during product development and production.

10. RÉSUMÉ

Les principaux objectifs de ces travaux incluent : (i) la préparation de différents types de formes pelliculées avec des dispersions aqueuses d'éthyle cellulose, (ii) la caractérisation physicochimique détaillée de ces systèmes in vitro, (iii) le développement de nouvelles stratégies permettant d'ajuster facilement les cinétiques de libération et d'assurer la stabilité à long terme des pelliculages, et (iv) de mieux comprendre les mécanismes de libération sous-jacents. L'éthyle cellulose est un polymère très approprié pour les pelliculages permettant de contrôler la libération de principes actifs. Cependant, la perméabilité du principe actif à travers les réseaux polymériques peut être faible et une formation incomplète du film polymérique pendant le pelliculage ou l'étape de traitement thermique peut laisser place a des phénomènes de coalescence des particules de polymère lors du stockage à long terme. Pour surmonter ces restrictions, de faibles quantités de carraghénane, d'alginate de propylène glycol et de copolymère d'acide polyvinylique et de polyéthylène glycol ont été ajoutées. La présence de ces composés hydrophiles attire l'eau dans le pelliculage au cours de la formation du film et facilite la coalescence des particules de polymère : l'eau joue le rôle de plastifiant et est nécessaire aux forces capillaires qui forcent les particules colloïdales entre elles. De plus, l'ajout de ces composés permet d'augmenter la perméabilité des membranes polymériques. Ceci peut être attribué à une augmentation de la prise en eau et de perte en masse des membranes exposées à des milieux aqueux. Il est également important de noter que ces composés hydrophiles n'entraînent pas de coagulation des formules de pelliculage contrairement à l'hydroxypropyle méthyle cellulose (HPMC) proposée précédemment. Il a été montré que les cinétiques de libération résultantes peuvent être facilement ajustées en variant la teneur en additif et les profils restent stables à long terme avec des conditions de pelliculage et de traitement thermique appropriés, et ce même après 6 mois de stockage dans des conditions stress. En outre, les connaissances sur les mécanismes de libération ont pu être approfondies et l'importance du type de principe actif, de noyau de départ et de milieu de

libération pour les cinétiques de libération résultantes élucidées. Ces informations peuvent aider à faciliter l'optimisation de ce type de médicaments avancés et à relever les défis rencontrés lors du développement et de la production d'un produit.

11. References

Amighi, K. and A.J. Moes, *Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit RS 30D film-coated sustained-release theophylline pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 1996. **42**(1): p. 29-35.

Banker, G.S., *Film coating theory and practice.* Journal of Pharmaceutical Sciences, 1966. **55**(1): p. 81-89.

BASF, *Kollicoat IR*, in *Technical Information*. 2001, BASF Aktiengesellschaft.

Bauer, K.H., K.-H. Froemming, and C. Fuehrer, *Lehrbuch der Pharmazeutischen Technologie*. 7 ed. 2002, Stuttgart: Wissenschaftliche Verlagsgesellschaft.

Bodmeier, R. and H. Chen, *Evaluation of biodegradable poly(lactide) pellets prepared by direct compression.* International Journal Pharmaceutics, 1989. **78**: p. 819-822.

Bodmeier, R., X. Guo, and O. Paeratakul, *Process and formulation factors affecting the drug release from pellets coated with the ethylcellulose-pseudolatex Aquacoat*, in *Aqueous polymeric coatings for pharmaceutical dosage forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York.

Bodmeier, R. and O. Paeratakul, *Process and formulation variables affecting the drug release from chlorpheniramine maleate-loaded beads coated with commercial and self-prepared aqueous ethyl cellulose pseudolatexes.* International Journal of Pharmaceutics, 1991. **70**(1-2): p. 59-68.

Bodmeier, R. and O. Paeratakul, *The Effect of Curing on Drug Release and Morphological Properties of Ethylcellulose Pseudolatex-Coated Beads.* Drug Development and Industrial Pharmacy, 1994. **20**(9): p. 1517 - 1533.

Borgquist, P., et al., *Simulation of the release from a multiparticulate system validated by single pellet and dose release experiments.* Journal of Controlled Release, 2004. **97**(3): p. 453-465.

11. References

Borgquist, P., et al., *Simulation and parametric study of a film-coated controlled-release pharmaceutical.* Journal of Controlled Release, 2002. **80**(1-3): p. 229-245.

Brabander, C.d., et al., *Characterization of ibuprofen as a nontraditional plasticizer of ethyl cellulose.* Journal of Pharmaceutical Sciences, 2002. **91**(7): p. 1678-1685.

Brown, G., *Formation of films from polymer dispersions.* J. Polymer Sci., 1956. **22**(102): p. 423-434.

Buscall, R. and R.H. Ottewill, *The stability of polymer latices,* in *Polymer Colloids,* T.C. R. Buscall, J.F. Stageman, Editor. 1985, Elsevier: London.

Carslaw, H.S. and J.C. Jaeger, *Conduction of Heat in Solids*. 1959, Oxford: Clarendon Press.

Chan, L.W., K.T. Ong, and P.W.S. Heng, *Novel Film Modifiers to Alter the Physical Properties of Composite Ethylcellulose Films.* Pharmaceutical Research, 2005. **22**(3): p. 476-489.

Chevalier, Y., et al., *Film formation with latex particles.* Colloid Polym. Sci., 1992. **270**: p. 806-821.

Crank, J., *The Mathematics of Diffusion*. 2 ed. 1975, Oxford: Clarendon Press.

Csaba, N., et al., *PLGA:Poloxamer and PLGA:Poloxamine Blend Nanoparticles: New Carriers for Gene Delivery*. Biomacromolecules 2005. **6**(1): p. 271-278.

Dashevsky, A., K. Kolter, and R. Bodmeier, *pH-independent release of a basic drug from pellets coated with the extended release polymer dispersion Kollicoat® SR 30 D and the enteric polymer dispersion Kollicoat® MAE 30 DP*. European Journal of Pharmaceutics and Biopharmaceutics, 2004. **58**(1): p. 45-49.

Dashevsky, A. and A. Mohamad, *Development of pulsatile multiparticulate drug delivery system coated with aqueous dispersion Aquacoat(R) ECD.* International Journal of Pharmaceutics, 2006. **318**(1-2): p. 124-131.

DeMerlis, C.C., D.R. Schoneker, and J.F. Borzelleca, *A subchronic toxicity study in rats and genotoxicity tests with an aqueous ethylcellulose dispersion.* . Food and Chemical Toxicology, 2005. **43**: p. 1355-1364.

Dillon, R.E., L.A. Matheson, and E.B. Bradford, *Sintering of synthetic latex particles.* Journal of Colloid Science, 1951. **6**(2): p. 108-117.

Dressman, J.B., et al., *Mechanisms of release from coated pellets,* in *Multiparticulate Oral Drug delivery,* I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 285-306.

Eckersley, S.T. and A. Rudin, *Mechanism of film formation from polymer latexes* Journal of Coatings Technology, 1990. **62**(780): p. 89-100.

Ensslin, S., et al., *New insight into modified release pellets - Internal structure and drug release mechanism.* Journal of Controlled Release, 2008. **128**(2): p. 149-156.

Fan, L.T. and S.K. Singh, *Controlled Release: A Quantitative Treatment*. 1989, Berlin: Springer-Verlag.

FMC, *Aquacoat ECD sales brochure*. 2008, FMC Biopolymer.

Francis, M.F., et al., *In Vitro Evaluation of pH-Sensitive Polymer/Niosome Complexes.* Biomacromolecules, 2001. **2**(3): p. 741-749.

Frohoff-Hülsmann, M.A., B.C. Lippold, and J.W. McGinity, *Aqueous ethyl cellulose dispersion containing plasticizers of different water solubility and hydroxypropyl methyl-cellulose as coating material for diffusion pellets II: properties of sprayed films.* Eur. J. Pharm. Biopharm., 1999. **48**(1): p. 67-75.

Frohoff-Hülsmann, M.A., B.C. Lippold, and J.W. McGinity, *Aqueous ethyl cellulose dispersion containing plasticizers of different water solubility and hydroxypropyl methyl cellulose as coating material for diffusion pellets I: Drug release rates from coated pellets.* International Journal of Pharmaceutics, 1999. **177**: p. 69-82.

11. References

Fukumori, Y., *Coating of Multiparticulates Using Polymeric dispersions*, in *Multiparticulate Oral Drug Delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 79-111.

Ghebre-Sellassie, I., *Pellets: A general overview*, in *Pharmaceutical Pelletization Technology*, I. Ghebre-Sellassie, Editor. 1989, Marcel Dekker: New York. p. 1-13.

Ghebre-Sellassie, I., *Multiparticulate oral drug delivery*. 1997, New York: Marcel Dekker.

Ghebre-Sellassie, I., et al., *Evaluation of acrylic-based modified-release film coatings.* International Journal of Pharmaceutics, 1987. **37**(3): p. 211-218.

Ghebre-Sellassie, I., et al., *Characterization of a new water-based coating for modified-release preparations.* Pharm. Technol., 1988. **12**: p. 96-106.

Glatt. *Fluid Bed Coating*. Technologies 2004-2008 [cited; Available from: http://www.glatt.com/e/01_technologien/01_04_08.htm.

Guma, N.C., K. Kale, and K.R. Morris, *Investigation of film curing stages by dielectric analysis and physical characterization.* Journal of Pharmaceutical Sciences, 1997. **86**(3): p. 329-334.

Gunder, W., B.H. Lippold, and B.C. Lippold, *Release of drugs from ethyl cellulose microcapsules (diffusion pellets) with pore formers and pore fusion.* European Journal of Pharmaceutical Sciences, 1995. **3**(4): p. 203-214.

Hamdani, J., A.J. Moës, and K. Amighi, *Development and in vitro evaluation of a novel floating multiple unit dosage form obtained by melt pelletization.* International Journal of Pharmaceutics, 2006. **322**(1-2): p. 96-103.

Hardy, J.G., S.S. Davis, and C.G. Wilson, *Drug delivery to the gastrointestinal tract*. 1989, Chichester: Ellis Horwood

11. References

Harris, M.R. and I. Ghebre-Sellassie, *Aqueous polymeric coating for modified release oral dosage forms*, in *Aqueous polymeric film coatings for pharmaceutical dosage forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York.

Hoffart, V., et al., *Storage stability of pellets coated with the aqueous ethylcellulose dispersion-Aquacoat ECD at elevated temperature and humidity*, in *2005 AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists*. 2005: Nashville, USA.

Hoffart, V., et al., *Effect of unconventional curing conditions on storage stability of pellets coated with Aquacoat ECD*, in *2005 AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists*. 2005: Nashville, USA.

Hoffman, A., M. Donbrow, and S. Benita, *Direct measurements on individual microcapsule dissolution as a tool for determination of release mechanism.* J Pharm Pharmacol. , 1986. **38**(10): p. 764-766.

Hutchings, D., B. Kuzmak, and A. Sakr, *Processing Considerations for an EC Latex Coating System: Influence of Curing Time and Temperature.* Pharmaceutical Research, 1994. **11**(10): p. 1474-1478.

Iyer, R.M., L.L. Augsburger, and D.M. Parikh, *Evaluation of drug layering and coating: Effect of process mode and binder level.* Drug Dev. Ind. Pharm., 1993. **19**: p. 981-998.

Keshikawa, T. and H. Nakagami, *Film formation with coating systems of aqueous susoensions and latex dispersions of ethylcellulose.* Chemical Pharmaceutical Bulletin, 1994. **42**(3): p. 656-662.

Kucera, S., *Physical and chemical properties of acrylic polymers influencing physical aging.* 2007, University of Texas: Austin.

Ladas, S.D., P.E. Isaacs, and G.E. Sladen, *Post-prandial changes of osmolality and electrolyte concentration in the upper jejunum of normal man.* Digestion, 1983. **26**(4): p. 218-23.

Lecomte, F., *pH-sensitive polymer blends used as coating materials in controlled drug delivery systems*. 2004, Freie Universität Berlin: Berlin.

Lecomte, F., et al., *Polymer blends used for the coating of multiparticulates: comparison of aqueous and organic coating techniques.* Pharm. Res., 2004. **21**: p. 882-890.

Lecomte, F., et al., *pH-Sensitive Polymer Blends used as Coating Materials to Control Drug Release from Spherical Beads: Importance of the Type of Core.* Biomacromolecules, 2005. **6**(4): p. 2074-2083.

Lecomte, F., et al., *pH-sensitive film blends used as coating materials to control drug release from spherical beads: elucidation of the underlying mass transport mechanisms.* Pharmaceutical Research, 2005. **22**: p. 1129-1141.

Lehmann, K., *Coating of multiparticulates using organic solutions - Formulation and process considerations*, in *Multiparticulate drug delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 51-78.

Lehmann, K., *Chemistry and application properties of polymethacrylate coating systems*, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage forms*, J.W. McGinity, Editor. 1997, Marcel Dekker: New York. p. 101-176.

Lightfood, D.K., *Multiparticulate Encapsulation equipment and process*, in *Multiparticulate Oral Drug Delivery*, I. Ghebre-Sellassie, Editor. 1997, Marcel Dekker: New York. p. 159-180.

Lindahl, A., et al., *Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women.* Pharmaceutical Research, 1997. **14**(4): p. 497-502.

11. References

Lippold, B.C. and R. Monells Pages, *Film formation, reproducibility of production and curing with respect to release stability of functional coatings from aqueous polymer dispersions.* Pharmazie, 2001, Pages 5-17. **56**(1): p. 5-17.

Lippold, B.H., B.K. Sutter, and B.C. Lippold, *Parameters controlling drug release from pellets coated with aqueous ethyl cellulose dispersion.* International Journal of Pharmaceutics, 1989. **54**(1): p. 15-25.

Marucci, M., G. Ragnarsson, and A. Axelsson, *Evaluation of osmotic effects on coated pellets using a mechanistic model.* International Journal of Pharmaceutics, 2007. **336**(1): p. 67-74.

Marucci, M., et al., *Mechanistic model for drug release during the lag phase from pellets coated with a semi-permeable membrane.* Journal of Controlled Release, 2008. **127**(1): p. 31-40.

McGinity, J.W., *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms.* 2 ed. 1997, New York: Marcel Dekker.

Miller, R.A. and E.B. Vadas, *The Physical Stability of Tablets Coated using an Aqueous Dispersion of Ethylcellulose.* Drug development and industrial pharmacy, 1984. **10**(10): p. 1565 – 1585.

Millili, G.P., R.J. Wigent, and J.B. Schwartz, *Autohesion in Pharmaceutical Solids.* Drug Development and Industrial Pharmacy, 1990. **16**(16): p. 2383 - 2407.

Morflex, *Influence of plasticizers on the dissolution and physical properties of ethylcellulose films and coated beads*, in *Pharmaceutical Coatings Bulletin*. 1995, Morflex Inc.

Munday, D.L. and A.R. Fassihi, *Controlled release delivery: Effect of coating composition on release characteristics of mini-tablets.* International Journal of Pharmaceutics, 1989. **52**(2): p. 109-114.

Muschert, S., et al., *Improved long term stability of ethyl cellulose film coatings: Importance of the type of drug and starter core.* International Journal of Pharmaceutics 2008 **accepted**.

Muschert, S., et al., *Predictability of Drug Release from Ethylcellulose Coated Pellets.* Journal of Controlled Release, 2008 **submitted.**

Naelapää, K., et al. *Dealing with complex interactions in experimental data*. in *2nd Pharmaceutical Solid State Research Cluster (PSSRC) Symposium*. 2008. Gent, Belgium.

Naelapää, K., et al., *Coating of potassium chloride with ethylcellulose aqueous dispersion--Effects of processing parameters on film formation and film properties.* European Journal of Pharmaceutical Sciences, 2007. **32**(1, Supplement 1): p. S20-S20.

Nagakami, H., et al., *Application of aqueous suspensions and latex dispersions of water-insoluble polymers for tablets and granule coatings.* . Chem. Pharm. Bull., 1991. **39** p. 1837-1842.

Okarter, T.U. and K. Singla, *The effects of plasticizers on the release of metoprolol tartrate from granules coated with a polymethacrylate film.* Drug Dev. Ind. Pharm., 2000. **26**: p. 323-329.

Okhamafe, A.O. and P. York, *Studies of interaction phenomena in aqueous-based film coatings containing soluble additives using thermal analysis techniques.* J. Pharm. Sci., 1988. **77**(5): p. 438-443.

Onions, A., *Films from water-based colloidal dispersions.* Manuf. Chem., 1986. **57**(4): p. 66-67.

Ozturk, A.G., et al., *Mechanism of release from pellets coated with an ethylcellulose-based film.* Journal of Controlled Release, 1990. **14**(3): p. 203-213.

Paeratakul, O., *Pharmaceutical applications of aqueous colloidal polymer dispersions*. 1993, University of Texas: Austin.

Pearnchob, N., *Evaluation of new film coating processes and materials*. 2002, Freie Universitaet Berlin: Berlin.

Petereit, H.U. and W. Weisbrod, *Formulation and process considerations affecting the stability of solid dosage forms formulated with methacrylate copolymers.* Eur. J. Pharm. Biopharm., 1999. **47**(1): p. 15-25.

Porter, S.C., *Controlled-Release Film Coatings Based on Ethylcellulose.* Drug Development and Industrial Pharmacy, 1989. **15**(10): p. 1495 - 1521.

Proikakis, C.S., P.A. Tarantili, and A.G. Andreopoulos, *The role of polymer/drug interactions on the sustained release from poly(dl-lactic acid) tablets.* European Polymer Journal, 2006. **42**(12): p. 3269-3276.

Ragnarsson, G., et al., *In vitro release characteristics of a membrane-coated pellet formulation -- influence of drug solubility and particle size.* International Journal of Pharmaceutics, 1992. **79**(1-3): p. 223-232.

Rohera, B.D. and N.H. Parikh, *Influence of type and level of water-soluble additives on drug release and surface and mechanical properties of Surelease films.* Pharm Dev Technol. , 2002. **7**(4): p. 421-432.

Ronsse, F., J.G. Pieters, and K. Dewettinck, *Modelling heat and mass transfer in batch, top-spray fluidised bed coating processes.* Powder Technology, 2008. **in press**.

Roux, E., et al., *On the Characterization of pH-sensitive Liposome/Polymer Complexes.* Biomacromolecules, 2003. **4**(2): p. 240-248.

Rowland, M. and T.N. Tozer, *Clinical Pharmacokinetics: Concepts and Applications*. 3 ed, ed. M. Rowland and T.N. Tozer. 1995, Baltimore: Lippincott Williams & Wilkins. 601.

Sadeghi, F., J.L. Ford, and A. Rajabi-Siahboomi, *The influence of drug type on the release profiles from Surelease-coated pellets.* International Journal of Pharmaceutics, 2003. **254**(2): p. 123-135.

Sadeghi, F., et al., *Comparative Study of Drug Release from Pellets Coated with HPMC or Surelease.* Drug Development and Industrial Pharmacy, 2000. **26**(6): p. 651-660.

Sakellariou, P. and R.C. Rowe, *The morphology of blends of ethylcellulose with hydroxypropyl methylcellulose as used in film coating.* International Journal of Pharmaceutics, 1995. **125**(2): p. 289-296.

Sakellariou, P., R.C. Rowe, and E.F.T. White, *Polymer/polymer interaction in blends of ethyl cellulose with both cellulose derivatives and polyethylene glycol 6000.* International Journal of Pharmaceutics, 1986. **34**(1-2): p. 93-103.

Schmidt, C., *Multiparticulate Oral Drug Delivery Systems*. 2000, Freie Universität Berlin: Berlin.

Schultz, P. and P. Kleinebudde, *A new multiparticulate delayed release system.Part I: Dissolution properties and release mechanism.* Journal of Controlled Release, 1997. **47**(2): p. 181-189.

Schultz, R.K. and R.R. Myers, *Acrylic latex film formation in the critical temperature range.* Journal of Applied Polymer Science, 1964. **8**(2): p. 755 - 764.

Shao, Z.J., et al. (2002) *Drug release from Kollicoat SR 30D-coated nonpareil beads: evaluation of coating level, plasticizer type, and curing condition*. AAPS PharmSciTech **Volume**, E15

Siepmann, F., et al., *How to adjust desired drug release patterns from ethylcellulose-coated dosage forms.* Journal of Controlled Release, 2007. **119**(2): p. 182-189.

Siepmann, F., et al., *How to improve the storage stability of aqueous polymeric film coatings.* Journal of Controlled Release, 2008. **126**(1): p. 26-33.

11. References

Siepmann, F., et al., *Carrageenan as an Efficient Drug Release Modifier for Ethylcellulose-Coated Pharmaceutical Dosage Forms.* Biomacromolecules, 2007. **8**(12): p. 3984-3991.

Siepmann, F., et al., *Aqueous HPMCAS coatings: Effects of formulation and processing parameters on drug release and mass transport mechanisms.* European Journal of Pharmaceutics and Biopharmaceutics, 2006. **63**(3): p. 262-269.

Siepmann, F., et al., *pH-sensitive film coatings: Towards a better understanding and facilitated optimization.* European Journal of Pharmaceutics and Biopharmaceutics, 2008. **68**(1): p. 2-10.

Siepmann, J., *Polymeric controlled drug delivery systems : Elucidation of transport mechanisms and optimization of release patterns*. 1999, Freie Universitaet Berlin: Berlin.

Siepmann, J., *Neue Arzneiformen - Seminar*, F.U. Berlin, Editor. 2002: Berlin.

Siepmann, J. *Understanding drug release mechanisms*. in *Coating Workshop*. 2008. Lille, France.

Siepmann, J., et al., *How Autocatalysis Accelerates Drug Release from PLGA-Based Microparticles: A Quantitative Treatment.* Biomacromolecules 2005. **6**(4): p. 2312-2319.

Siepmann, J. and A. Göpferich, *Mathematical modeling of bioerodible, polymeric drug delivery systems.* Adv. Drug Deliver. Rev., 2001. **48**(2-3): p. 229-247.

Siepmann, J. and N. Peppas, *Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC).* Adv. Drug Deliver. Rev., 2001. **48**(2-3): p. 139-157.

Stafford, J.W., *Enteric film coating using completely aqueous dissolved hydroxypropyl methyl cellulose phtalate spray solutions.* Drug Dev. Ind. Pharm., 1982. **8**(4): p. 513-530.

Stenekes, R.J.H., et al., *Pore Sizes in Hydrated Dextran Microspheres.* Biomacromolecules, 2000. **1**(4): p. 696-703.

Strübing, S., H. Metz, and K. Mäder, *Mechanistic analysis of drug release from tablets with membrane controlled drug delivery.* European Journal of Pharmaceutics and Biopharmaceutics, 2007. **66**(1): p. 113-119.

Stubbe, B.G., et al., *Tailoring the Swelling Pressure of Degrading Dextran Hydroxyethyl Methacrylate Hydrogels.* Biomacromolecules 2003. **4**(3): p. 691-695.

Tang, L., et al., *Drug Release from Film-Coated Chlorpheniramine Maleate Nonpareil Beads: Effect of Water-Soluble Polymer, Coating Level, and Soluble Core Material.* Pharmaceutical Development and Technology, 2000. **5**(3): p. 383 - 390.

Theeuwes, F., *Elementary osmotic pump.* Journal of Pharmaceutical Sciences 1975. **64**(12): p. 1987-1991.

Timmins, P., A.M. Delargy, and J.R. Howard, *Optimization and characterization of a pH-independent extended-release hydrophilic matrix tablet.* Pharmaceutical Development and Technology, 1997. **2**(1): p. 25-31.

Vanderhoff, J.W., et al., *Theoretical consideration of the interfacial forces involved in the coalescence of latex particles.* Macromol. Chem. , 1966. **1**: p. 361-397.

Venkatraman, S., et al., *An overview of controlled release systems.*, in *In Handbook of pharmaceutical controlled release technology*, D.L. Wise, Editor. 2000, Marcel Dekker: New York. p. 431-463.

Vergnaud, J.M., *Controlled Drug Release of Oral Dosage Forms*. 1993, Chichester: Ellis Horwood.

Verma, R.K. and S. Garg (2001) *Current status of drug delivery technologies and future directions*. Pharm. Technol. On Line **Volume**, 1-14

Vidmar, V., I. Jalsenjak, and T. Kondo, *Volume of waterfilled pores in the ethyl cellulose membrane and the permeability of microcapsules.* J. Pharm. Pharmacol, 1982. **34** (7): p. 411-414.

Wade, A. and P.J. Weller, *Handbook of pharmaceutical excipients*. 2 ed. 1994, Washington: American Pharmaceutical Association.

Wagner, K., *Aqueous polymer dispersions for extended release dosage forms*. 2002, Freie Universitaet Berlin: Berlin.

Wallace, J.W., *Cellulose derivatives and natural products utilized in pharmaceutics,* in *Encyclopedia of Pharmaceutical Technology*, J.S.a.J.C. Boylan, Editor. 1990, Marcel Dekker: New York. p. 319-339.

Wesseling, M., *Preparation and investigation of coated multiparticulate drug delivery systems*. 1999, Freie Universitaet Berlin: Berlin.

Wesseling, M. and R. Bodmeier, *Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat(R), or an organic ethylcellulose solution.* European Journal of Pharmaceutics and Biopharmaceutics, 1999. **47**(1): p. 33-38.

Wheatley, T.A. and C.R. Steuernagel, *Latex emulsion for controlled drug delivery,* in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms,* J.W. McGinity, Editor. 1997, Marcel Dekker: New York. p. 1-54.

Wong, D. and R. Bodmeier, *The impact of the use of flocculated colloidal dispersions on the drug release from drug-containing films and coated tablets.* Pharm. Res., 1994. **11**: p. S-185.

Wong, D. and R. Bodmeier, *Flocculation of an aqueous colloidal ethyl cellulose dispersion (Aquacoat) with a water-soluble polymer, hydroxypropyl methyl cellulose.* Eur. J. Pharm. Biopharm., 1996. **42**(1): p. 12-15.

Wu, C. and J.W. McGinity, *Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer.* European Journal of Pharmaceutics and Biopharmaceutics, 2000. **50**(2): p. 277-284.

Wurster, D.E., S. Bhattacharjya, and D.R. Flanagan, *Effect of Curing on Water Diffusivities in Acrylate Free Films as Measured via a Sorption Technique.* AAPS PharmSciTech., 2007. **8**(3): p. Article 71.

Ye, Z.-w., et al., *Correlation between the permeability of metoprolol tartrate through plasticized isolated ethylcellulose/hydroxypropyl methylcellulose films and drug release from reservoir pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 2007. **67**(2): p. 485-490.

Yilmaz, G., et al., *Modulated Release of a Volatile Compound from Starch Matrixes via Enzymatically Controlled Degradation.* Biomacromolecules, 2002. **3**(2): p. 305-311.

Zentner, G.M., G.S. Rork, and K.J. Himmelstein, *Osmotic flow through controlled porosity films: An approach to delivery of water soluble compounds.* Journal of Controlled Release, 1985. **2**(3): p. 217-229.

Zimehl, R. and G. Lagaly, *Coagulation of latex dispersions in the presence of some organic compounds.* Colloids and Surfaces, 1987. **22**(2): p. 215-224.

12. LISTE DE PUBLICATIONS DANS LE CADRE DE CETTE THÈSE

Articles :

2007 Siepmann, F ; Muschert, S ; Zach, S ; Leclercq, B ; Carlin, B ; Siepmann, J. Carrageenan as an efficient drug release modifier for ethylcellulose-coated pharmaceutical dosage forms. *Biomacromolecules* 8, 3984-3991.

2008 Siepmann, F ; Muschert, S ; Leclercq, B ; Carlin, B ; Siepmann, J. How to improve the storage stability of aqueous polymeric film coatings. *Journal of Controlled Release* 126, 26-33.

2008 Muschert, S ; Cuppok, Y ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J. Improved long term stability of ethyl cellulose film coatings: Importance of the type of drug and starter core. *International Journal of Pharmaceutics* accepté.

2008 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J. Predictability of drug release from ethyl cellulose coated pellets. *Journal of Controlled Release* soumis.

2008 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J. Drug release mechanisms from ethyl cellulose:PVA-PEG graft copolymer coated pellets. *European Journal of Pharmaceutics and Biopharmaceutics* soumis.

12. Liste de publications dans le cadre de cette thèse

Poster :

2007 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J.
How to improve the storage stability of aqueous controlled release film coatings.
3rd Pharmaceutical Sciences World Congress (PSWC), Amsterdam, Pays-Bas, # DD-T-108.

2007 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J.
Adjustment of desired drug release patterns from pellets coated with aqueous ethylcellulose dispersions: Importance of the type of core and drug solubility.
34th International Symposium on Controlled Release of Bioactive Materials, Controlled Release Society, Long Beach, États-Unis, # 647.

2007 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J.
The stability of ethylcellulose film coatings containing PG alginate or carrageenan.
34th International Symposium on Controlled Release of Bioactive Materials, Controlled Release Society, Long Beach, États-Unis, # 758.

2007 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J.
Improved storage stability of controlled release pellets coated with aqueous ethylcellulose dispersion.
144th British Pharmaceutical Conference (BPC), Manchester, Royaume-Uni, # 95.

2007 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J.
How to provide broad spectra of release patterns from ethylcellulose-coated pellets, irrespective of the type of drug and type of core.
AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists, San Diego, États-Unis. # T2103.

12. Liste de publications dans le cadre de cette thèse

2008 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J.
Importance of the curing conditions for ethylcellulose-PVA-PEG-graft-copolymer coatings.
APV, APGI, ADRITELF World Meeting, Barcelone, Espagne, # 76.

2008 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J.
Improved Storage stability of aqueous ethylcellulose-based film coatings for controlled drug delivery.
APV, APGI, ADRITELF World Meeting, Barcelone, Espagne, # 167.

2008 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J.
Drug Release Mechanisms from Pellets Coated with Ethylcellulose:PVA-PEG-graft-copolymer.
35th International Symposium on Controlled Release of Bioactive Materials, Controlled Release Society, New York, États-Unis, # 479.

2008 Muschert, S ; Barthélémy, C ; Cuppok, Y ; Aguilar, B ; Flament, MP ; Odou, P ; Siepmann, F ; Siepmann. J.
How the Experimental Setup can Affect Drug Release Patterns from Oral Dosage Forms.
35th International Symposium on Controlled Release of Bioactive Materials, Controlled Release Society, New York, États-Unis, # 500.

2008 Muschert, S ; Marucci, M ; Cuppok, Y ; Hjaertstam, J ; Siepmann, F ; Siepmann, J ; Axelsson A.
Kollicoat SR:Eudragit NE Blends used for Film Coating.
35th International Symposium on Controlled Release of Bioactive Materials, Controlled Release Society, New York, États-Unis, # 519.

2008 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J.
Osmotic effects on release from coated pellets: Impact of substrate core composition.
145th British Pharmaceutical Conference (BPC), Manchester, Royaume-Uni, # 156.

12. Liste de publications dans le cadre de cette thèse

2008 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J.
Polymeric coatings for solid dosage forms : Characterization and optimization.
Colloque annuel des Doctorants - Journée André Verbert, Lille, France. # 42.

2008 Muschert, S ; Siepmann, F ; Leclercq, B ; Carlin, B ; Siepmann, J.
Optimization of the curing conditions for aqueous ethylcellulose-based film coatings.
AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists, Atlanta, États-Unis. accepté.

Communications orales

2007 Siepmann, F ; Muschert, S ; Leclercq, B ; Carlin, B ; Siepmann, J.
Aquacoat ECD-based film coatings: How to adjust drug release profiles.
FMC Technical Webcast New Research.

13. CURRICULUM VITAE

Nom, prénom	Muschert, Susanne
Date de naissance	22 Février 1980
Lieu de naissance	Lutherstadt Wittenberg, Allemagne
Nationalité	Allemande

Etudes universitaires et examens

1998	Baccalauréat C
1999-2005	Etudes de Pharmacie à Freie Universität Berlin, Berlin, Allemagne Premier Examen d'Etat le 28.08.2001 Deuxième Examen d'Etat le 20.01.2004 Troisième Examen d'Etat le 12.05.2005 Approbation le 08.06.2005

Formation et stages

Recherche

2006	Depuis 04/2006 Doctorat « Enrobages polymériques pour des formes orales solides : Caractérisation et optimisation », Jeune Equipe JE 2491 : « Médicament à libération contrôlée du principe actif : Mécanismes et optimisation », Ecole doctorale de Biologie et Santé de Lille, (directeur de thèse : Pr. J. Siepmann)
2004	6 Mois de stage en recherche Laboratoire de Pharmacotechnie Industrielle, Faculté de Pharmacie, Université Lille2, Lille, France, Titre : « Microparticules biodégradables à libération contrôlée du principe actif », Responsable : Pr. J. Siepmann

13. Curriculum vitae

Officine

07/2005-03/2006

Pharmacienne à la Panther-Apotheke à Berlin, Allemagne

(Avec encadrement d'une stagiaire)

05/2005-06/2005

Pharmacienne à la Nord-Apotheke à Berlin, Allemagne

02/2005-04/2005

Stage à la Storch-Apotheke à Berlin, Allemagne

02/2004-04/2004 et 11/2004-01/2005

Stage à la Panther-Apotheke à Berlin, Allemagne

Hôpital

06/1999-09/1999

4 Semaines de stage à la Pharmacie Hospitalière de l'Hôpital Paul-Gerhardt Stift ; Wittenberg, Allemagne ; responsable : Mme Hahn

Enseignements

Depuis 10/2007

Vacataire d'enseignement et de surveillance

Travaux pratiques Technologie pharmaceutique et cosmétologique 2ème année DEUST Santé environnement

Travaux pratiques de Pharmacie Galénique et Biopharmacie 3ème année

Travaux pratiques de Dermopharmacie et Cosmétologie O4 5ème année (filière Officine)

Enseignements dirigés de Pharmacotechnie industrielle 2ème année

Enseignements dirigés de Pharmacotechnie industrielle UV I 1 5ème année (filière Industrie)

Enseignements dirigés de Pharmacotechnie industrielle UV I 4 5ème année (filière Industrie)

Surveillance des examens Masters II (Pharmacotechnie Industrie)

Surveillance des examens UE I 1 5ème année (filière Industrie)

13. Curriculum vitae

Langues

Allemand, anglais, français