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Formulation parameters affecting the performance of coated gelatin capsules with pulsatile release profiles

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Abstract

The objective of this study was to develop and evaluate a rupturable pulsatile drug delivery system based on soft gelatin capsules with or without a swelling layer and an external water-insoluble but -permeable polymer coating, which released the drug after a lag time (rupturing of the external polymer coating). The swelling of the gelatin capsule itself was insufficient to rupture the external polymer coating, an additional swelling layer was applied between the capsule and the polymer coating. Croscarmellose sodium (Ac-Di-Sol) was more effective as a swelling agent than low and high molecular weight hydroxypropylmethyl cellulose (HPMC; E5 or K100M). Brittle polymers, such as ethyl cellulose (EC) and cellulose acetate propionate (CAPr), led to a better rupturing and therefore more complete drug release than the flexible polymer coating, Eudragit RS. The lag time of the release system increased with higher polymer coating levels and decreased with the addition of a hydrophilic pore-former, HPMC E5 and also with an increasing amount of the intermediate swelling layer. The water uptake of the capsules was linear until rupture and was higher with CAPr than with EC. Soft gelatin capsule-based systems showed shorter lag times compared to hard gelatin capsules because of the higher hardness/filling state of the soft gelatin capsules. The swelling pressure was therefore more directed to the external polymer coating with the soft gelatin capsules. Typical pulsatile drug release profiles were obtained at lower polymer coating levels, while the release was slower and incomplete at the higher coating levels. CAPr-coated capsules resulted in a more complete release than EC-coated capsules.

Keywords: Gelatin capsules; Lag time; Mechanical properties; Oral drug delivery; Polymeric films; Pulsatile release; Swelling agents

1. Introduction

Most oral extended release drug delivery systems (DDS) release the drug continuously in a linear or non-linear fashion. Pulsatile drug release profiles are interesting for the treatment of several diseases including hypertension, bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, and ulcer disease (Bussemer et al., 2001; Ritschel and Forusz, 1994). Pulsatile release DDS allow the adaptation of drug therapies to chronopharmacological needs (Lemmer, 1991, 1999).

Pulsatile drug release was obtained with drug-containing cores layered with erodible coatings, which released the drug after erosion of the coating (Gazzaniga et al., 1994). Alternatively, rupturable dosage forms, such as the time-explosion system, were investigated, whereby pellets with a swellable hydroxypropylcellulose layer were coated with a water-insoluble polymer layer, which ruptured after a lag-time and then released

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the drug (Ueda et al., 1994a,b,c). However, the drug loading of pellets is limited and liquid fillings are not possible.

Various capsule-shaped pulsatile delivery systems have been described using insoluble/impermeable and hard capsule halves with swellable plugs, e.g. the Pulsincap system (Binns et al., 1996; McNeill et al., 1990; Wilding et al., 1992). One drawback of this system was the use of a non-approved plug material, which was overcome, e.g. by the use of erodible plugs (Krögel and Bodmeier, 1998) or biocompatible materials (Krögel and Bodmeier, 1999a,b; Tsume et al., 2000). The manufacturing process was still difficult and was conducted manually.

Capsules are pharmaceutically elegant dosage forms offering an improved drug stability, because the content is tightly enclosed by the capsule shell and thus protected from oxygen, moisture and light, and also from physiological fluids until the drug is released. Hard capsules are usually filled with solid materials (Fahrig and Hofer, 1998), but some drugs require a liquid formulation for solubility or bioavailability reasons (Savio et al., 1998). The filling of semisolids or liquids into hard gelatin capsules is possible (Bowtle, 1998; Stegemann, 1999).

A pulsatile delivery system based on hard gelatin capsules with a solid content has been recently described (Bussemer et al., 2003a). The capsules were coated with a swelling layer followed by an external polymer coating, which ruptured after a certain lag time, induced by the water uptake/swelling pressure of the swelling layer.

The objective of this study was to develop and evaluate a soft gelatin capsule-based pulsatile release system for the delivery of liquid drug contents. The performance was compared to the pulsatile hard capsules.

2. Materials and methods

Ammonio methacrylate copolymer type B, USP 25 (Eudragit® RS, Röhm Pharma, Darmstadt, Germany), ethyl cellulose (EC; Ethocel® Standard 10, Dow Chemical Company, Midland, MI, USA), cellulose acetate propionate (CAPr; CAP 504-0.2, Eastman Chemical Company, Kingsport, TN, USA), hydroxypropylmethyl cellulose (HPMC; Methocel® E5 or K100M, Colorcon, Orpington, UK), triethyl citrate (TEC; Morflex, Greensboro, NC, USA), croscarmellose sodium (Ac-Di-Sol®, FMC, Newark, DE, USA), polyvinyl pyrrolidone (Kollidon® 30, BASF, Ludwigshafen, Germany), soft gelatin capsules (length 12.6 mm, width 8 mm, filled with 50 mg methylene blue in PEG 400) (R.P. Scherer, Eberbach, Germany).

All other reagents were of analytical grade and were used without further purification.

2.1. Preparation of polymer films

Polymer films were produced by casting of 10% (w/w) polymer solutions in 90 vol.% ethanol onto a Teflon plate using a casting knife (Multicator 411, Erichsen, Hemer, Germany). After drying for 24 h under a special cover to reduce solvent evaporation in order to obtain smooth homogeneous film surfaces, the films were removed and the film thickness was measured at five points with a thickness gauge Minitest 600 (Erichsen, Hemer, Germany).

2.2. Mechanical properties of polymer films in the dry and wet state

Polymer film samples of 6.5 cm × 6.7 cm were fixed in a special Teflon holder with several holes ($n = 3$). The holder with the film was then immersed into 0.1 N HCl at 37 °C. The puncture strength of films was measured with an Instron 4466 (Instron Wolpert, Darmstadt, Germany). A metal probe, diameter 5 mm, length 15 cm, was driven with a speed of 5 mm/min through a hole either in the dry state (initial puncture strength) or after 60 min on films immersed in the release medium. Force (N)–displacement (mm) curves were recorded with an Instron load cell. The following parameters were calculated:

$$\text{Puncture strength} = \frac{\text{force at film break}}{\text{area of the cross-section of the film within the holder}}$$

$$\text{Modulus} = \text{slope of the force–displacement curve before film break}$$

$$\text{Strain} = \frac{\text{maximum elongation}}{\text{initial length of the film}}$$

$$\text{Energy} = \frac{\text{area under the force–displacement curve}}{\text{volume of the film within the holder}}$$

A detailed description of the puncture test has been described (Bodmeier and Paeratakul, 1993, 1994).

2.3. Preparation of the pulsatile release soft gelatin capsules

Pulsatile capsules were prepared by layering of a 12% (w/w) suspension of Ac-Di-Sol in a 4% (w/w) solution of Kollidon 30 in isopropanol onto soft gelatin capsules in a GC-300 Glatt drum coater (swelling layer) (prewarming of capsules at 40 °C for 10 min, spray nozzle diameter 1.2 mm, atomizing air pressure 0.8 bar, air flow rate 110 m^3/h, inlet air temperature 40 °C, product temperature 25–28 °C, spray rate 10–12 g/min, rotational pan speed 15 rpm, post-coating drying at 35 °C for 10 min). In a second step, the polymer coating was applied from a 4% (w/w) polymer solution in 90 vol.% ethanol. With HPMC as a pore former, EC was first dissolved in 96 vol.% ethanol, then HPMC was dispersed, and finally water was added slowly under stirring until a clear solution was obtained. The EC solutions were applied in the GC-300 Glatt drum coater under the conditions described above.

2.4. Lag time and drug release

The lag time was determined by visual observation of the pulsatile capsules in a USP 25 paddle apparatus (medium: phosphate buffer USP, pH 7.4, 37 °C, rotation speed 100 rpm) and was defined as the time point, when the outer coating ruptured ($n = 5$). The amount of methylene blue released was studied by withdrawing 3 ml samples at predetermined time points. The samples were measured after appropriate dilution with a Shimadzu UV-2101PC UV-Vis scanning spectrophotometer (Shimadzu Europe, Duisburg, Germany) at a wavelength of 663 nm.

2.5. Water uptake studies

At predetermined time points after exposure of the pulsatile capsules to phosphate buffer USP, pH 7.4 (37 °C, 50 ml-flask, shaker-incubator at 50 rpm), the capsules were carefully blotted with tissue paper to remove the surface water and then were weighed with an analytical balance ($n = 3$). Water uptake was calculated as follows:

$$\text{Water uptake (\%)} = \frac{(\text{weight of wet sample}) - (\text{weight of dry sample})}{\text{weight of dry sample}} \times 100$$

2.6. Hardness of the pulsatile release soft gelatin capsules

Capsules, optionally after incubation in phosphate buffer USP, pH 7.4 at 37 °C, were fixed on a metal plate. A metal probe connected to the Instron 4466 was positioned on the surface of the capsules. The metal probe was then moved downward at a constant speed of 5 mm/min. The maximum force was the force when the coating of the capsule cracked. It was defined as the hardness of the capsules.

3. Results and discussion

Preliminary studies were needed to select a suitable polymer for the polymer coating of the pulsatile capsules. The outer polymer coating has to be water-permeable and has to rupture completely after the lag time. Besides the water permeability (Rhodes and Porter, 1998), the mechanical properties of the coating are therefore an important characteristic of the system. The mechanical properties of polymer films, which were prepared by casting from ethanolic solutions, were investigated in the dry and the wet state (Table 1). The mechanical parameters—puncture strength, modulus, strain and energy—decreased after incubation of the films in the medium. This could be explained by the uptake of water, which acted as a plasticizer (Bodmeier and Paeratakul, 1993; Tho et al., 1999). The Eudragit RS-film was very flexible and soft, as indicated by a high strain (elongation) and a low modulus in both the dry and wet state. The EC films had a much lower strain with a higher modulus. The most brittle film was an EC/HPMC-combination as indicated by its low puncture strength accompanied with a low strain and low energy required to rupture the film. The mechanical properties of CAPr-containing films could not be investigated in this study. CAPr formed very brittle films, which could not be removed from the Teflon plates without

Table 1
Mechanical properties of polymeric films, cast from ethanolic solutions

Film	Puncture strength (MPa)		Modulus (MPa)		Strain (%)		Energy (MJ/m^3)	
	$\bar{x}$	S.D.	$\bar{x}$	S.D.	$\bar{x}$	S.D.	$\bar{x}$	S.D.
Dry state								
Eudragit RS, 20% TEC	5.05	0.96	0.011	0.001	170.40	27.26	5.296	0.794
EC	18.27	6.72	2.02	0.40	9.05	3.38	1.645	0.813
EC, 20% TEC	11.04	1.97	1.21	0.06	8.11	1.28	1.017	0.255
EC/HPMC (60:40), 20% TEC	1.05	0.13	0.98	0.33	0.99	0.18	0.034	0.004
Wet state								
Eudragit RS, 20% TEC	0.26	0.05	0.006	0.001	54.57	5.46	0.061	0.010
EC	10.15	0.57	1.23	0.21	7.30	1.37	0.893	0.125
EC, 20% TEC	4.65	1.31	0.24	0.05	18.47	4.91	0.649	0.244
EC/HPMC (60:40), 20% TEC	0.23	0.03	0.05	0.02	4.35	1.16	0.018	0.005

$\bar{x}$: mean.

breakage. However, since the mechanical properties of CAPr films were described as brittle (Edgar et al., 2001; Sand, 1990; Schauber et al., 1999), it was included in the coating experiments.

In a first coating experiment, soft gelatin capsules were coated with Eudragit RS. The coated capsules significantly increased in volume after incubation in the release medium (Fig. 1). A big oil droplet was visible inside the capsule, the rest of the capsule was filled with water. The swollen capsules were also very soft. Because of the flexibility of the Eudragit RS coating, the coated capsules ruptured only slightly with very small cracks and did not rupture completely. No significant drug release was determined. Eudragit RS was therefore not suitable as a coating in this application. The less flexible and more brittle polymers, EC and CAPr, were evaluated for future coatings. Both polymers are soluble in ethanol and were directly sprayed on the soft gelatin capsules.

EC- or CAPr-coated soft gelatin capsules did not expand much in size and did therefore also not rupture sufficiently. Only small amounts of the dye, methylene blue, which served as a model drug, was released from the capsules. In addition, the slope of the lag time-coating level profile was relatively steep, which indicated a high sensitivity in the lag time to small changes in the coating level, as shown for an EC/HPMC 80:20-combination (Fig. 2). The lag time

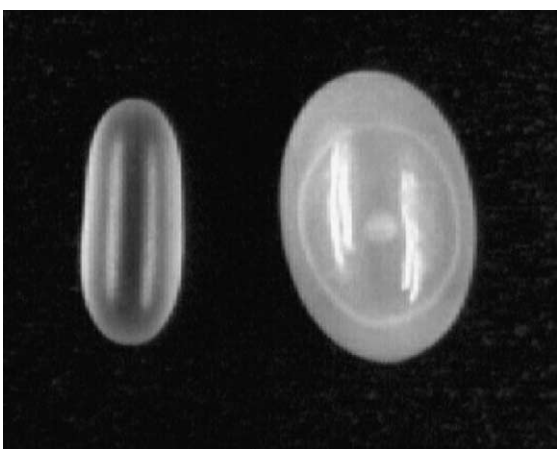

Fig. 1. Eudragit RS-coated soft gelatin capsules. Left: original capsule in the dry state; right: capsule after 4 h of incubation in the release medium (phosphate buffer, pH 7.4).

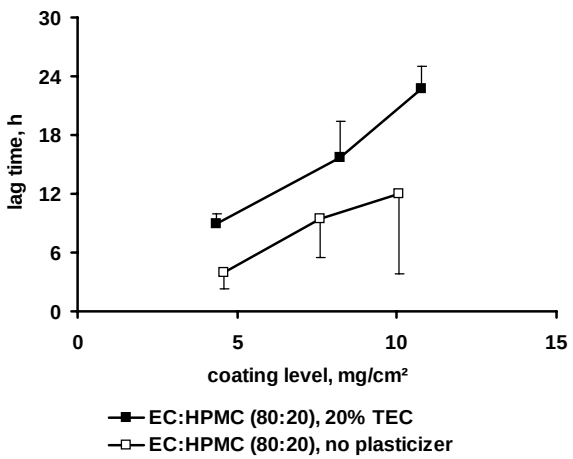

Fig. 2. Lag time of coated soft gelatin capsules without swelling layer.

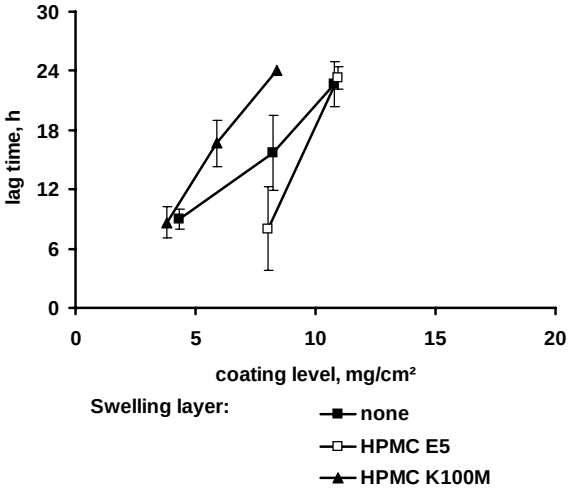

Fig. 3. Lag time of coated soft gelatin capsules with HPMC swelling layer. Polymer coating: EC/HPMC (80:20), 20% TEC, swelling layer: HPMC E5 or K100M, 6–9 mg/cm^2.

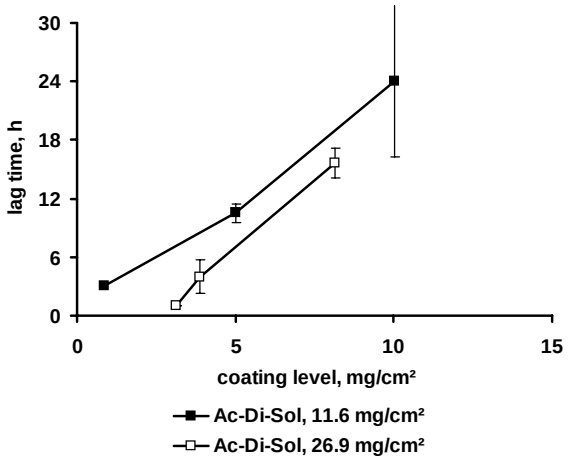

Fig. 4. Lag time of coated soft gelatin capsules with an Ac-Di-Sol swelling layer. Polymer coating: EC/HPMC (80:20), 20% TEC, swelling layer: Ac-Di-Sol:Kollidon 30 (75:25).

prior to drug release increased with increasing coating level (thickness of the polymeric coating). The lag time was lower for plasticizer-free systems compared to capsules coated with EC/HPMC plasticized with 20% (w/w) TEC. The plasticizer-containing coating was more flexible and resisted an increasing inner pressure for a longer time.

The swelling forces developed by the soft gelatin capsule shell were not strong enough to rupture the outer polymer coating completely in order to assure a rapid and complete drug release. Therefore, an additional swelling layer was introduced between the capsule shell and the polymer coating. After contact with release media, the water penetrates through the polymeric coating, the swelling layer hydrates and swells and finally ruptures the outer coating completely. The gelatin shell then disintegrates and releases the drug rapidly.

Various excipients were tested as possible swelling layers. The application of HPMC E5 as a swelling layer reduced the lag time (Fig. 3), but did not improve the rupture behavior enough, the capsules were still incompletely ruptured. The higher molecular weight HPMC K100M resulted in an increase in the lag time because it built a strong gel, which retarded the water uptake, thus prolonging the swelling and rupturing process.

Next, the highly swellable superdisintegrant, Ac-Di-Sol (croscarmellose sodium), was tested. Ac-Di-Sol was chosen because it showed the best swelling performance in a series of superdisintegrants (Bussemer et al., 2003b). Ac-Di-Sol was not soluble in organic solvents, it was therefore sprayed from an ethanolic suspension, containing Kollidon 30 (PVP) as a dissolved binder. The resulting swelling layer was mechanically stable towards attrition.

The Ac-Di-Sol-based swelling layer resulted in good rupturing of the polymer coating. Increasing the amount of swelling layer resulted in reduced lag times at the same external polymer coating level (Fig. 4). As expected, the lag time also increased with increasing coating level because of a reduced permeability of the EC coating for the release medium and the increased mechanical resistance. The extent of rupturing of the outer polymer coating in general decreased at higher polymer coating levels because of the increased mechanical strength of the external polymer coating.

The water permeability of the outer EC layer can be varied by the inclusion of a low molecular weight HPMC. Increasing the HPMC E5 amount in the external coating decreased the lag time (Fig. 5). The water influx increased due to the formation of water-filled channels in the EC-membrane (Gunder et al., 1995; Hjärtstam and Hjertberg, 1998). Water reached the swelling layer faster and the expansion of the swelling layer was accelerated, thus shortening the lag time

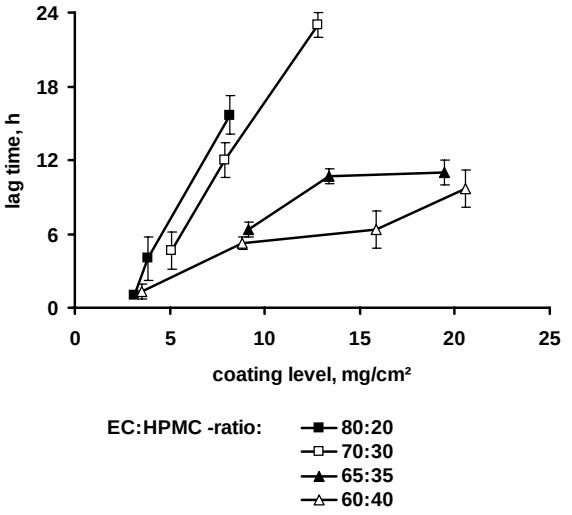

Fig. 5. Lag time of soft gelatin capsules as a function of EC/HPMC ratio. Polymer coating: EC/HPMC, different ratios, 20% TEC, swelling layer: Ac-Di-Sol:Kollidon 30 (75:25), 26.9 mg/cm^2.

prior to rupture. Additionally, the puncture strength as well as the energy, necessary to rupture the film, also decreased with increasing HPMC content (Table 1). The lag time-coating level profile became flatter, indicating a lower sensitivity of the lag time to variations in the coating level and therefore an improved robustness of the system.

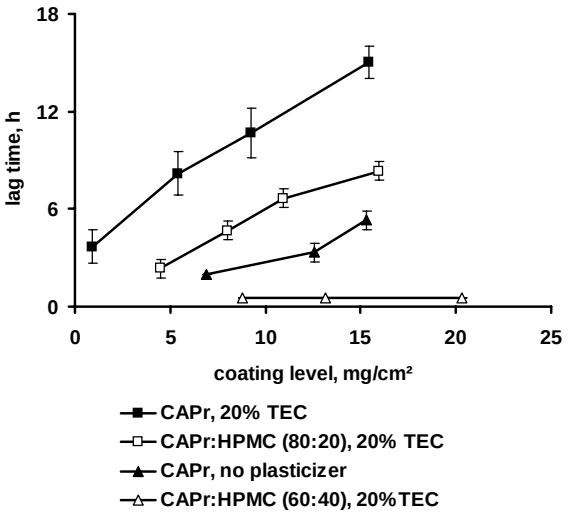

Fig. 6. Lag time of CAPr-coated soft gelatin capsules. Polymer coating: different CAPr-formulations, swelling layer: Ac-Di-Sol: Kollidon 30 (75:25), 23.7–27.9 mg/cm^2.

The trends in the results observed with EC were also obtained with CAPr, another cellulose-based polymer (Fig. 6). The lag time increased with the use of the plasticizer TEC due to the higher flexibility of the coating and it decreased with the addition of the pore-former HPMC. When compared to EC, the lag times were shorter with CAPr, probably because of the higher water permeability of this polymer. For example, at a HPMC level of 40%, the lag phase was very short with CAPr.

Water uptake studies on the coated capsules confirmed the higher water permeability of the CAPr

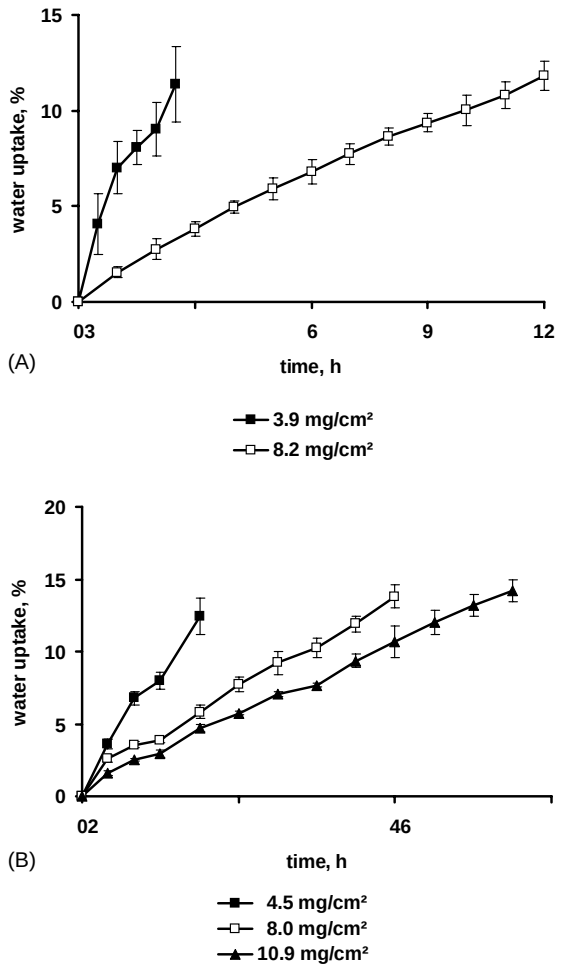

Fig. 7. Water uptake of coated soft gelatin capsules. Polymer coating: (A) EC/HPMC (80:20), 20% TEC; (B) CAPr:HPMC (80:20), 20% TEC, swelling layer: Ac-Di-Sol:Kollidon 30 (75:25), 26.9 mg/cm^2.

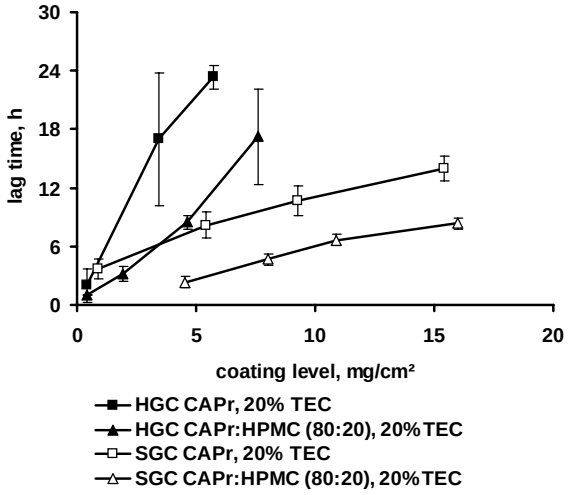

Fig. 8. Comparison of lag times of coated hard (HGC) and soft gelatin capsules (SGC). Polymer coating: CAPr with and without HPMC, 20% TEC, swelling layer: Ac-Di-Sol:Kollidon 30 (75:25), 21.2 mg/cm^2.

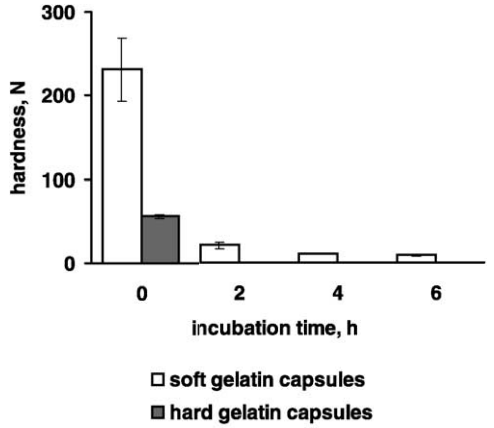

Fig. 9. Hardness of soft and hard gelatin capsules after incubation in the release medium (phosphate buffer, pH 7.4).

coatings compared to the EC coatings (Fig. 7). The curves showed an almost linear water uptake until the polymer coating ruptured. The rate of water uptake decreased with increasing polymer coating level. In all cases, the maximum water uptake was very simi-

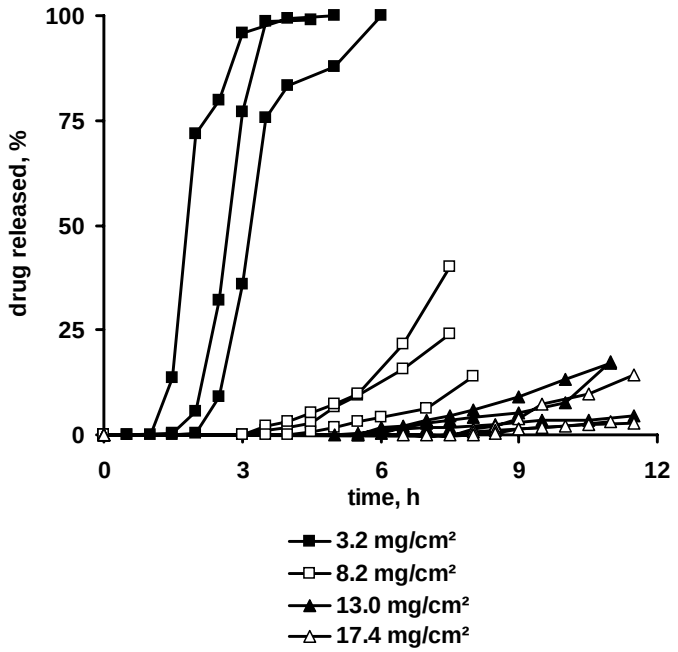

Fig. 10. Drug release from coated soft gelatin capsules as a function of ethyl cellulose coating level. Polymer coating: EC/HPMC (60:40), 20% TEC, swelling layer: Ac-Di-Sol:Kollidon 30 (75:25), 23.2 mg/cm^2.

lar, and was between 11.4 and 11.8% (w/w) for the EC/HPMC-combination (Fig. 7A) and between 12.4 and 14.2% (w/w) for the CAPr/HPMC-combination (Fig. 7B). The maximum water uptake value was slightly higher at the higher coating level because of the higher mechanical resistance of the thicker coatings.

Alternatively to soft gelatin capsules, which are primarily used for the delivery of liquids, hard gelatin capsules were also investigated in this study. The structure of the delivery system was the same in both cases, a soft or hard gelatin capsule core, a swelling layer and a layer of a water-insoluble but -permeable polymer coating.

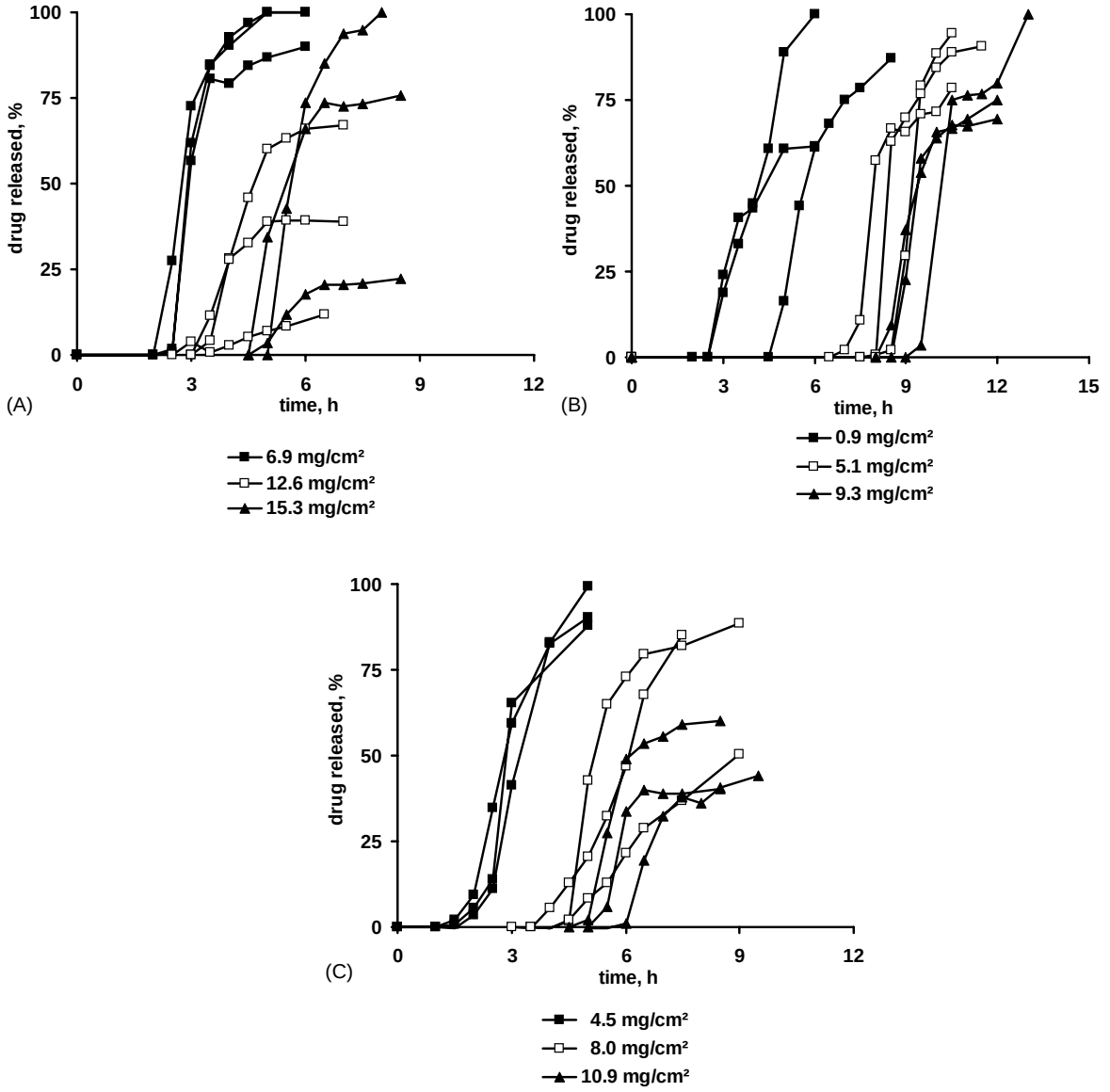

Fig. 11. Drug release from coated soft gelatin capsules as a function of cellulose acetate propionate coating level. Polymer coating: (A) CAPr, (B) CAPr, 20% TEC, (C) CAPr:HPMC (80:20), 20% TEC, swelling layer: Ac-Di-Sol:Kollidon 30 (75:25), 26.7 mg/cm^2.

The lag time was longer with hard gelatin than with soft gelatin capsules at the same coating level, both having the same composition of the swelling and coating layer (Fig. 8). The reason for the shorter lag times with the soft gelatin capsules resides in the different degree of fillings of hard and soft gelatin capsules. Soft gelatin capsules are completely filled with liquid, the pressure developed by the swelling layer is therefore directed primarily towards the outer polymer layer. In comparison, hard gelatin capsules are not completely filled with powder, there is air inside the capsule. The pressure of the swelling layer is therefore also directed towards the capsule core and not exclusively towards the outer coating. More water has therefore to be taken up by the hard gelatin capsules resulting in longer lag times at the same coating level. This was also confirmed with hardness data of soft and hard gelatin capsules (Fig. 9). Soft gelatin capsules were approximately four times harder than the hard capsules (values at time 0). The hardness of the soft gelatin capsules declined with increasing incubation time, while the hardness of the hard gelatin capsules could not be detected in the wet state, because the wet capsules were squeezed under the moving punch without giving a measurable signal. As mentioned above, the higher hardness of soft gelatin capsules was caused by the higher thickness of the gelatin shell as well as by the complete filling and the absence of air when compared with hard gelatin capsules.

Fig. 10 shows the drug release of individual soft gelatin capsules coated with EC/HPMC (60:40), plasticized with 20% TEC. The formulation with a low coating level of 3.2 mg/cm^2 showed distinct pulsatile release profiles, with a rapid and complete drug release after the lag time. However, at a higher coating level, the drug release was not complete. The capsules did not rupture completely, only smaller cracks were visible. This was caused by the higher mechanical resistance of the thicker coatings. This behavior seemed to be more a problem with the soft gelatin capsules than with hard gelatin capsules (Bussemer et al., 2003a) because of the thicker gelatin shell, which had a longer disintegration time when the outer polymeric coating was still partially present, even after it was ruptured. One solution for a better rupturing could also be the use of a thicker swelling layer providing a higher swelling pressure.

With CAPr, the drug release profiles were similar (Fig. 11). Again, at low coating levels, corresponding to lag times up to 3 h, the release was rapid after rupture of the polymer coating. With higher coating levels, the release rate was reduced and in some cases it was incomplete. However, the CAPr-coated capsules performed better than the EC-coated capsules. Another reason for the slow in vitro release could be the lower agitation and the absence of peristaltic movement and destructive forces in the dissolution apparatus, which are present under in vivo conditions and which would result in a more complete drug release after rupturing.

In conclusion, a pulsatile release system based on soft gelatin capsules, was developed with pulsatile drug release profiles, whereby the lag time was primarily controlled by amount and composition of the swelling layer and the coating layer, which affected the swelling pressure of the swelling layer and the water permeability and mechanical properties of the external polymer coating.

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