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Research paper

Evaluation of the swelling, hydration and rupturing properties of the swelling layer of a rupturable pulsatile drug delivery system

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Abstract

The objective of this study was to investigate the swelling characteristics of various swellable polymers in swelling layers that induce the rupturing of an outer polymer coating in pulsatile drug delivery systems (DDS). An apparatus was designed to measure simultaneously the swelling energy/force and water uptake of discs, made of polymers. The swelling energy of several excipients decreased in the following order: croscarmellose sodium (Ac-Di-Sol®) > low-substituted hydroxypropyl cellulose (L-HPC) > sodium starch glycolate (Explotab®) > crospovidone (Kollidon® CL) > hydroxypropyl methylcellulose (Methocel® K100M). A linear correlation existed between the swelling energy and the water uptake. The swelling behavior of Ac-Di-Sol® depended on the ionic strength and the pH of the medium due to a competition for free water and the acidic nature of this polymer. Analysis of the time-dependent swelling force data with a previously developed exponential equation confirmed a diffusion-controlled swelling force development, predominantly controlled by the penetration rate of the medium. The swelling behavior and the rupture of the outer polymeric coating of a pulsatile DDS were demonstrated in simulation tests.

Keywords: Croscarmellose sodium; Hydroxypropyl cellulose; Swelling force; Swelling energy; Pulsatile release

1. Introduction

Traditionally, drugs are released in an immediate or extended fashion. However, in recent years, pulsatile drug release systems are gaining growing interest. A pulsatile drug release, where the drug is released rapidly after a well-defined lag-time, could be advantageous for many drugs or therapies [1–3]. Pulsatile release systems can be classified in multiple-pulse and single-pulse systems [4]. A popular class of single-pulse systems is that of rupturable dosage forms. Baker proposed a core with osmotically active agents, e.g. drugs, covered with a semipermeable membrane [5]. Other systems consist of a drug-containing core, covered by a swelling layer and an outer insoluble, but semipermeable polymer coating or membrane [6–8]. We developed a capsule-based system, whereby drug-filled hard or soft gelatin capsules were coated with a swelling layer followed by the coating with a water-insoluble but permeable polymer layer. Upon contact with gastrointestinal fluids, water penetrates through the outer polymer coating and hydrates the swelling layer. This, in turn, develops a swelling pressure responsible for the rupture of the external polymer coating, leading to rapid drug release. The lag time prior to the rupture is mainly controlled by: (i) the permeation and mechanical properties of the polymer coating and (ii) the swelling behavior of the swelling layer, which is investigated in the present study.

The swelling of superdisintegrants (swellable polymers with a high potential for swelling) was previously determined on individual particles, which were able to swell freely in the medium [9,10]. The increase in particle volume was measured microscopically. In addition to free superdisintegrant particles, the swelling of pure superdisintegrant tablets has also been investigated [11,12]. However, both

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the free swelling of single particles or compressed superdisintegrants are not optimal models to evaluate the developed forces. A large increase in volume of freely swelled particles does not necessarily result in high swelling pressure. Thus, various tests have been developed to determine the swelling under a load [13–16].

Swelling and hydration of superdisintegrants could be influenced by several physicochemical properties of the particles [17]. A larger particle size and hence, increased porosity lead to a faster wicking and swelling with different grades of crospovidone. A sponge-like surface morphology of the particles increased the intraparticle porosity.

Besides pure disintegrant particles or tablets, the disintegration force of several superdisintegrants in the presence of other excipients have been investigated with various tablet formulations [18–20]. In a typical experiment, the tablet exerted a swelling force against a fixed barrier, which was then recorded.

These previous reports described the swelling behavior of tablets with a relatively low content of disintegrants and high porosity, which are typical for conventional tablets. In contrast, the swelling layer of the rupturable pulsatile drug delivery systems (DDS) developed by us is less porous and the content of the swellable polymer is high (>75%). The aim of this study was to investigate the swelling behavior of cast discs, containing high amounts of superdisintegrants, using a new apparatus. These discs simulated the swelling layer of a capsule-based rupturable pulsatile DDS designed for oral applications.

2. Materials and methods

2.1. Materials

Croscarmellose sodium (Ac-Di-Sol®, FMC, Newark, DE, USA), sodium starch glycolate (Exlotab®, Penwest Pharmaceuticals, Patterson, NY, USA), crospovidone (Kollidon® CL), polyvinyl pyrrolidone (Kollidon® 30, Kollidon® 90) (BASF, Ludwigshafen, Germany), ethylcellulose (EC, Ethocel® Standard 10, Dow Chemical Company, Midland, MI, USA), hydroxypropyl methylcellulose (Methocel® K100M, Colorcon, Orpington, UK), hydroxypropyl methylcellulose (HPMC, Pharmacoat® 603), low-substituted hydroxypropyl cellulose (L-HPC, LB11), hydroxypropyl cellulose (HPC, Klucel® EF, Hercules, Pendlebury, UK), acetyltributyl citrate (ATBC), triethyl citrate (TEC) (Morflex, Greensboro, NC, USA), and size #0 hard gelatin capsules containing 340 mg acetaminophen (Capsugel, Bornem, Belgium). All other reagents were of analytical grade and were used without further purification.

2.2. Casting of the swellable discs

The swellable polymer (225–600 mg) was suspended in 3 g of a PVP (Kollidon® 30 or 90) solution in isopropanol. These suspensions were poured into special Plexiglas molds (inner diameter 25 mm) and dried in an oven at 40 °C for 12 h. The dried discs were carefully removed and stored in a dessicator until further testing.

2.3. Swelling energy measurement

Swelling energy experiments ($n = 3$) were performed using a self-built swelling device where the sample discs were placed inside a Plexiglas cylinder on a glass filter, porosity grade #1 (Fig. 1). The samples (cast discs) were placed on the glass filter. A tightly fitting punch of predetermined weight was placed on top of the sample. To reduce friction between the punch and the Plexiglas cylinder, paraffin was applied as a lubricant. The swelling medium at 37 °C (purified water, phosphate buffer pH 7.4 (USP 25), 0.9% NaCl solution, or 0.1 N HCl, 37 °C) was added up to the level of the glass filter. All vessels were covered to avoid water evaporation. Upon medium penetration through the filter, the swelling sample started to swell and pushed the punch upwards. The displacement of the punch was followed over time.

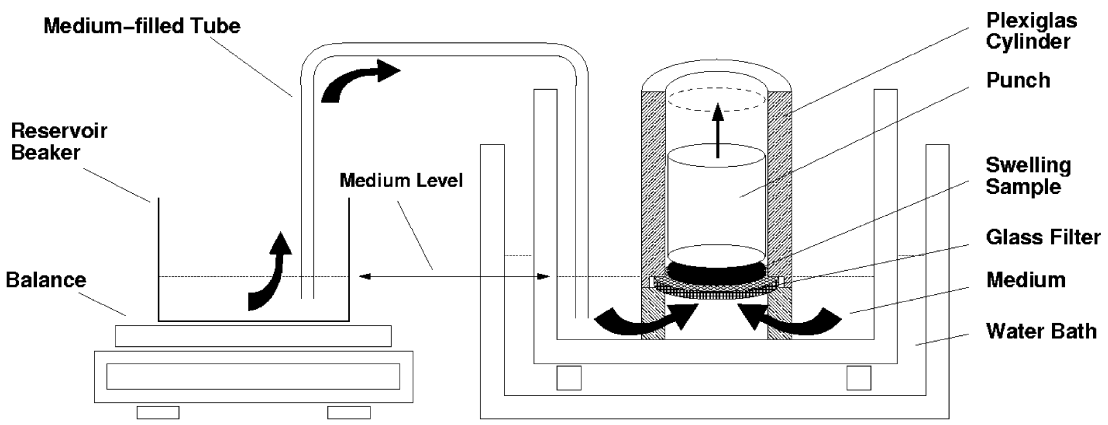

Fig. 1. Swelling-device for the simultaneous measurement of the water uptake and the swelling energy developed by the swelling sample.

The swelling medium, which was taken up by the swelling sample was replaced automatically from the reservoir via the tube. This water flux resulted in a weight change of the reservoir beaker and was recorded with a digital balance as a function of time. The water uptake was calculated as:

$$\%\ \text{water uptake} = (\text{amount of uptaken water})/(\text{initial weight of the sample disc}) \times 100. \quad (3)$$

2.4. Swelling force measurements

The device (Fig. 1) was modified for the evaluation of the swelling force. A sample disc was placed on the glass filter. The punch was then placed on top of the sample and was connected with an Instron®-load cell. In contrast to the above described swelling energy experiment, where the punch moved during the swelling process, the punch was now kept in a fixed position during the test. The medium (purified water, 0.9% w/w aqueous NaCl solution, phosphate buffer solution pH 7.4 (USP 25), or 0.1 N HCl, 37 °C) was added and the exerted swelling force was recorded as a function of time ($n = 3$).

2.5. Preparation of polymer films

The polymers (ethylcellulose, HPMC) were dissolved in 90% v/v ethanol at a concentration of 10% w/w. The resulting solutions were cast on Teflon plates, 14×14 cm^2, and dried for 24 h at room temperature. The resulting films were carefully removed by hand and weighed with an analytical balance. The weight per area (mg/cm^2) was calculated as:

$$\text{weight per area} = (\text{weight of the film sample})/(\text{area of the sample}). \quad (4)$$

2.6. Simulated rupture test

A sample of swellable polymer was mixed into 1 g of a binder solution in isopropanol and poured into a plastic cell with one orifice, inner diameter 12 mm, outer diameter 32 mm, height 10 mm, and dried for 12 h forming a solid disc fitting tightly into the orifice. Separately, a circular piece of the film (diameter 32 mm) was cut out from the polymer films and was mounted onto the plastic cell (Fig. 2). After the attachment of a stabilizing plastic ring (inner diameter 12 mm), the cell was immersed into the medium at 37 °C ($n = 4$). The time when the film was ruptured by the swellable polymer was measured using a digital stopwatch and was defined as the lag time.

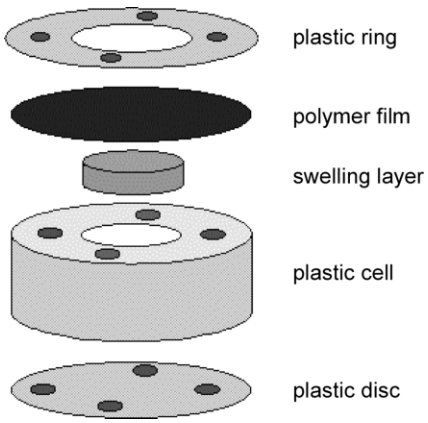

Fig. 2. Rupture cell.

2.7. Preparation of pulsatile drug delivery systems

A 12% w/w suspension of Ac-Di-Sol® in a 4% w/w solution of PVP in isopropanol was layered onto the drug-filled hard gelatin capsules in a GC-300 Glatt drum coater (pre-warming at 40 °C for 10 mm, 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 30 °C, spray rate 10–12 g/min, rotational pan speed 15 rpm, post-coating drying at 35 °C for 30 mm). In the second step, the polymer coating was applied by spray-coating of an EC–HPMC (55:45) solution in 90% v/v ethanol, total polymer concentration 4% w/w in the GC-300 Glatt drum coater under the conditions described above.

2.8. Lag time of the capsule-shaped pulsatile DDS

Pulsatile DDS ($n = 5$) were placed into an USP 25 paddle apparatus, rotation speed 50 rpm, with phosphate buffer USP pH 7.4, 37 °C and observed visually. The lag time was defined as the time point, when the outer coating ruptured due to swelling.

3. Results and discussion

The proposed capsule-shaped pulsatile DDS consisted of a drug-containing gelatin capsule as the core, a swelling layer and an external polymeric coating. The swelling layer was formed from suspensions of the swellable polymer. The addition of a binder (Kollidon® 30 or 90) was necessary to form a film-like swelling layer on the capsule shell. The swelling behavior of cast discs containing the swelling layer and a binder simulating the swelling layer of a rupturable pulsatile DDS was investigated.

3.1. Swelling energy and water uptake measurements

The swelling energy was calculated by:

$$E = F_{\text{weight}} d \quad (1)$$

where E is the swelling energy (mJ), F_{weight} is the predetermined weight force of the punch, and d the displacement of the punch measured with a caliper gauge.

The normalized energy was calculated by Eq. (2),

$$E_{\text{norm}} = E/W_{\text{s}} \quad (2)$$

where w_{s} is the weight of the swellable polymer.

To validate the method, punches of different weight were used to measure the swelling energy. The swelling energy (mJ) was normalized to the amount of the superdisintegrant, Ac-Di-Sol® (g). The normalized energy increased within the first minutes and reached a plateau (Fig. 3A). The

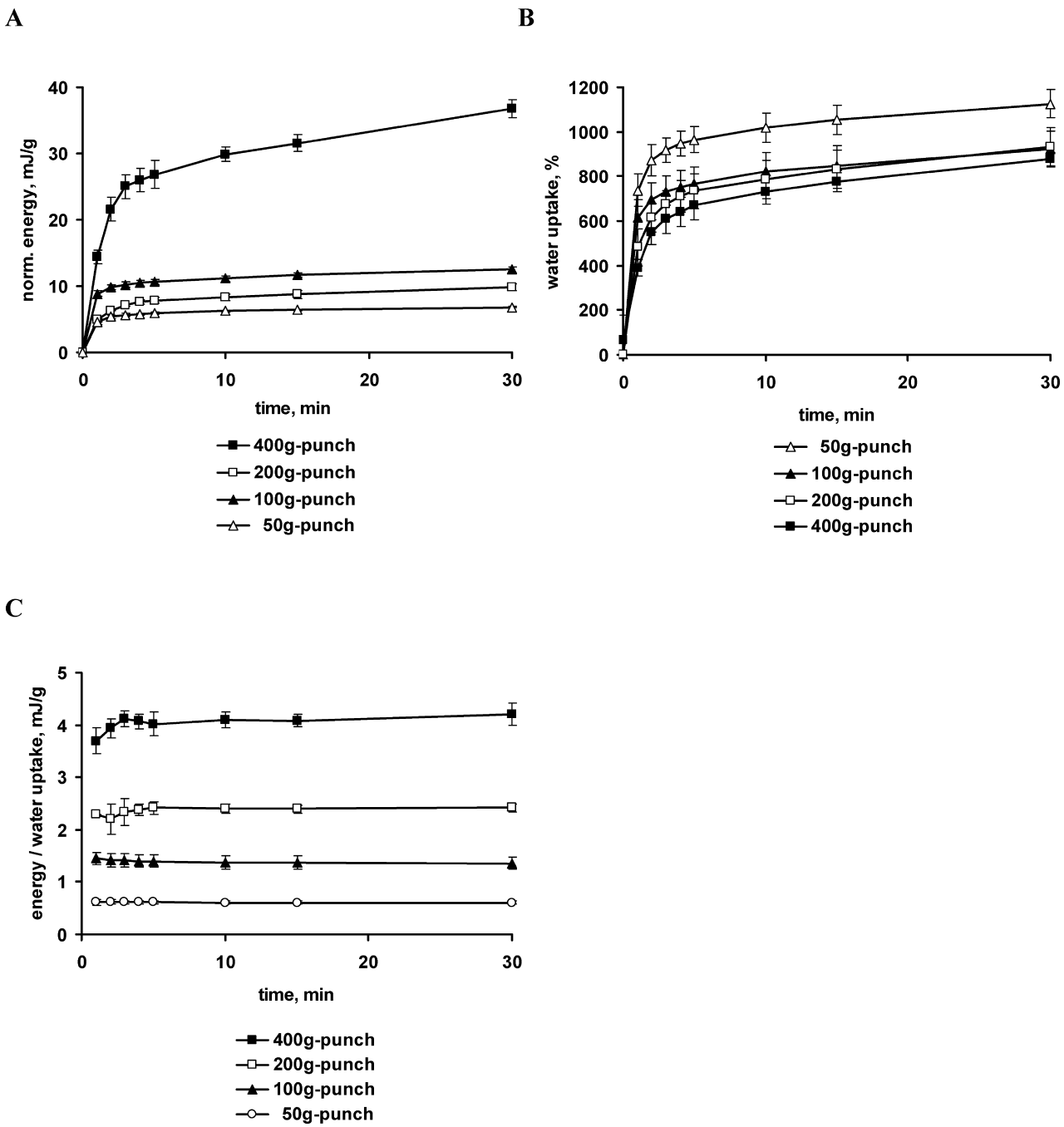

Fig. 3. (A) Normalized swelling energy of discs containing Ac-Di-Sol® (85.7% w/w) and Kollidon® 90 (14.3% w/w) as a function of punch weight, (B) simultaneously measured water uptake, (C) ratio of swelling energy to water uptake; medium: purified water, 37 °C.

calculated energy was higher with a higher punch weight: a heavier punch compressed the gel-like swollen superdisintegrant more than a lighter one, thus creating a higher resistance of the gel against compression. In other words, if a heavier load was pushed upwards by the swelling superdisintegrant, it exerted more mechanical work or swelling energy.

Simultaneously with the swelling energy, the water uptake was also observed in the same experiment (Fig. 3B). The highest amount of water was taken up with the 50 g punch, because the superdisintegrant, Ac-Di-Sol®, can swell more freely under the lowest load, resulting in a lower mechanical work/energy. Interestingly, the ratio of developed swelling energy to the amount of uptaken water was constant over time (Fig. 3C). This constant ratio indicated a linear dependency of the energy to the water taken up and, therefore, suggested that the magnitude of the swelling energy was the result of the uptaken water: the higher the water uptake, the higher the observed swelling energy of the gel-like structure formed under a certain load. This is in agreement with the findings in previously published studies [21–23].

3.2. Effect of the type of the swellable polymer

Different swellable polymers, present in cast sample discs in combination with a binder, were compared to characterize their swelling potential (Fig. 4). The punch did not move with Explotab®, Kollidon® CL, and Methocel® K100M. Therefore, these materials were not suitable for the application in the rupturable DDS due to the insufficient development of swelling energy. In contrast, L-HPC and Ac-Di-Sol® developed a detectable swelling energy and the

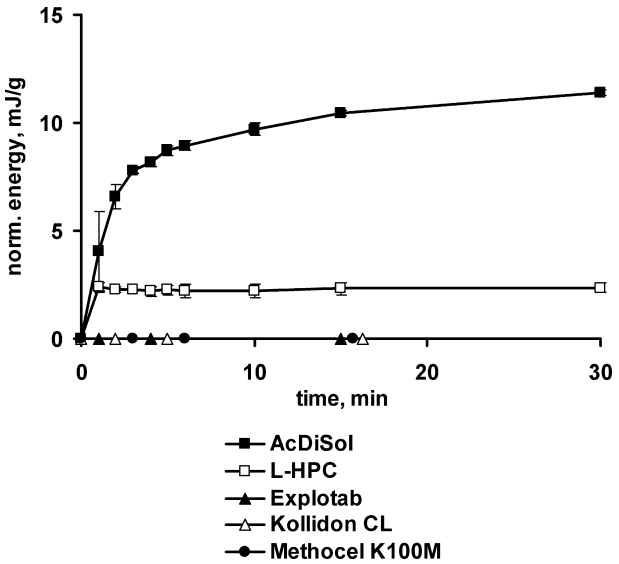

Fig. 4. Normalized swelling energy of discs containing different superdisintegrant (superdisintegrant:Kollidon® 30, 3:1 w/w); punch weight: 100 g; medium: purified water, 37 °C.

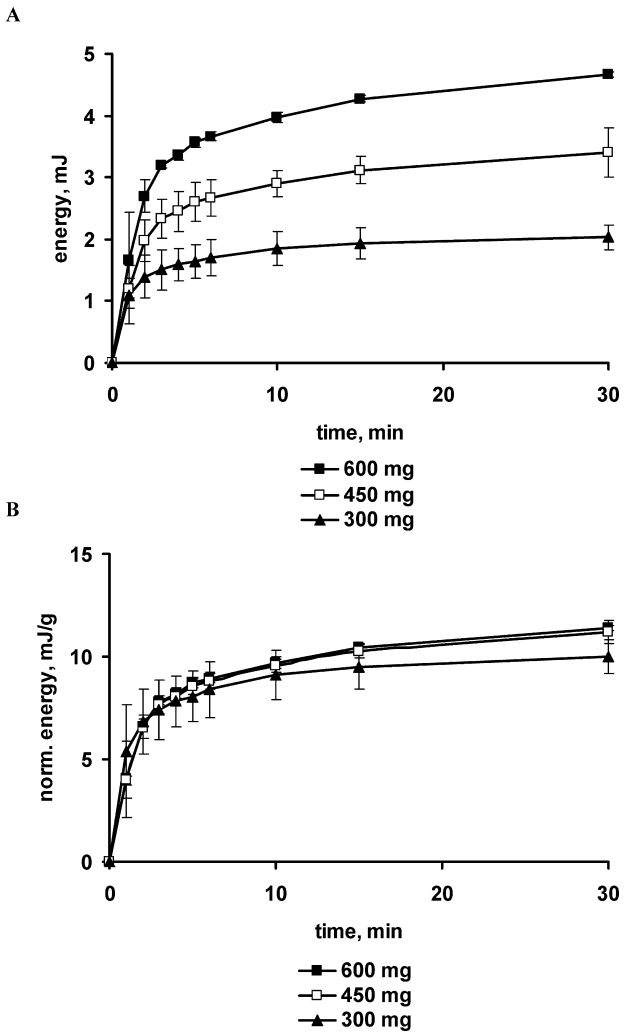

Fig. 5. Effect of disintegrant disc weight (Ac-Di-Sol®:Kollidon® 30, 3:1 w/w) on (A) the swelling energy and (B) the normalized swelling energy; punch weight: 100 g; medium: purified water, 37 °C.

punch moved significantly. Ac-Di-Sol® showed the highest degree of swelling under load and was, therefore, selected for the use in the swelling layer of the pulsatile DDS and was further investigated. These results are in good agreement with results from other studies, where Ac-Di-Sol® had a superior effectiveness as a disintegrant when compared with other materials [24,25].

3.3. Effect of the amount of the swellable polymer

As expected, the absolute swelling energy increased with a higher amount of disc weight (Fig. 5A). When the swelling energy was normalized to the amount of superdisintegrant present in the sample disc, the curves were almost identical (Fig. 5B). Thus, the exerted absolute swelling energy could be controlled by the amount of the swellable substance. A pulsatile DDS with a thicker swelling layer would develop the critical swelling energy, which is necessary to break the

outer coating film faster. Therefore, the lag time of the pulsatile DDS should be shortened.

3.4. Simulated rupture test

The effect of the amount of the swelling layer on the time until film rupture (lag time) was determined in a simulated rupture test. The data (not shown) show a dependence of the lag time on the amount of the swelling layer, which was expressed in mg/cm^2. Below a critical amount of 47 mg/cm^2 of the swellable polymer, the lag time was in excess of 24 h, but at an amount above 64 mg/cm^2, the lag time did not change significantly and was less than 1 h.

3.5. Effect of superdisintegrant content within the swelling layer

The swelling layer consisted of the swellable polymer, Ac-Di-Sol®, and the binder PVP. The Ac-Di-Sol® particles would not adhere to the capsule surface without a binder. PVP was, therefore, responsible for the formation of the swelling layer from the Ac-Di-Sol® particles on the hard gelatin capsule shells. Increasing the amount of Ac-Di-Sol® and reducing the amount of PVP within the swelling layer reduced the lag time (Fig. 6). The differences disappeared only at relatively high superdisintegrant levels: there was no significant difference between an Ac-Di-Sol-content of 75% w/w and 85.7% w/w (corresponding to Ac-Di-Sol®-to-binder ratios of 3:1 or 6:1, respectively). The amount of Ac-Di-Sol® could not be increased further, because a certain amount of binder was needed to form the cast discs or the swelling layer, which otherwise became too brittle and could not form a mechanically stable layer.

3.6. Effect of binders

A binder was necessary to cast superdisintegrant-containing discs or coat the capsules, because the superdisintegrant was suspended and not dissolved in the medium and hence, cannot form a film by itself The superdisintegrant gave the major contribution to the swelling force, however, the binder could also influence the swelling behavior, either by a spatial separation of the swelling particles [26] or by a competition for free water after the binder was dissolved [27,28]. Both phenomena were reported to reduce the swelling capacity of superdisintegrants.

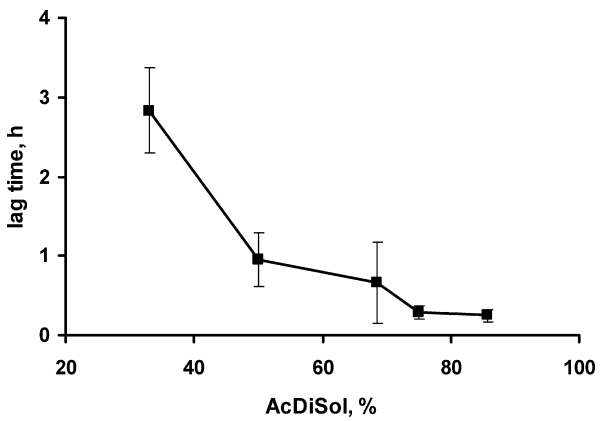

Fig. 6. Lag time obtained with a simulated rupture test as a function of the Ac-Di-Sol® content within the swelling layer; weight per area: 132.6 mg/cm^2, binder: Kollidon® 90. Polymer film: ethylcellulose:HPMC (55:45 w/w), 20% w/w TEC, 7.4 mg/cm^2. Medium: purified water, 37 °C.

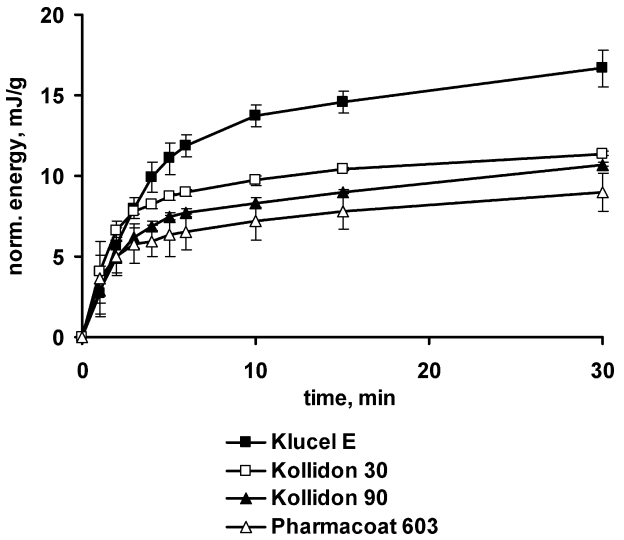

Fig. 7. Effect of different binders on the normalized swelling energy of discs containing Ac-Di-Sol®:different binders (3:1 w/w). Total disc weight: 600 mg; punch weight: 100 g; medium: purified water, 37 °C.

Klucel® E, Kollidon® 30, Kollidon® 90, and Pharmacoat® 603 were evaluated as potential binders (Fig. 7). The combination of Ac-Di-Sol® with Klucel® E gave the highest swelling energy, followed by Kollidon® 30. The energy development of Kollidon®-90-containing samples was slightly delayed and lower during the first minutes, but approached the Kollidon®-30-values after 30 mm. Pharmacoat® 603 had the lowest values. Klucel® E, Kollidon® 30, and 90 led to short lag times and a complete rupture of the outer coating in the simulated rupture test (Fig. 8). Pharmacoat® 603 (low molecular weight HPMC) showed a long delay before rupture and an incomplete coating rupturing, which can be explained by a higher retardation of the water penetration into the swelling layer by the HPMC, building a highly viscous gel. These data are in accordance with the swelling energy data. From a practical point of view, the viscosity of an ethanolic Klucel® E solution was too high for the use in the spray coating process. Kollidon® 30 and Kollidon® 90 solutions were less viscous and were, therefore, used for further investigations.

3.7. Effect of the medium on the swelling behavior

Since an orally administered DDS comes into contact with gastro-intestinal fluids of different pH and ionic

strength, it was also important to investigate the swelling behavior of Ac-Di-Sol® in different media (Fig. 9). The highest swelling energy was developed in purified water and phosphate buffer pH 7.4. The energy was lower in 0.1 N HCl. This could be attributed to the presence of carboxylic groups in Ac-Di-Sol®, which is a cross-linked carboxymethylcellulose sodium. In an acidic environment, the carboxylic groups were unionized, thus resulting in a lower water uptake and swelling ([16]). As expected, a higher ionic concentration in 0.9% NaCl reduced the swelling energy because of a competition of the ions for free water. However, the swelling energy of Ac-Di-Sol® even at low pH or in 0.9% NaCl was still superior to the other tested superdisintegrants.

In order to confirm these observations, the swelling samples were also investigated in the simulated rupture test in different media (Fig. 10). The lag times corresponded well to swelling energy data (Fig. 8). The lag times in purified water and buffer pH 7.4 (USP 25) were shortest and similar. The time to rupture was prolongated in 0.9% NaCl solution as well as in 0.1 N HCl. This can be explained by the lower swelling energy and the slower rate of energy development, resulting in a later rupture of the outer polymer coating.

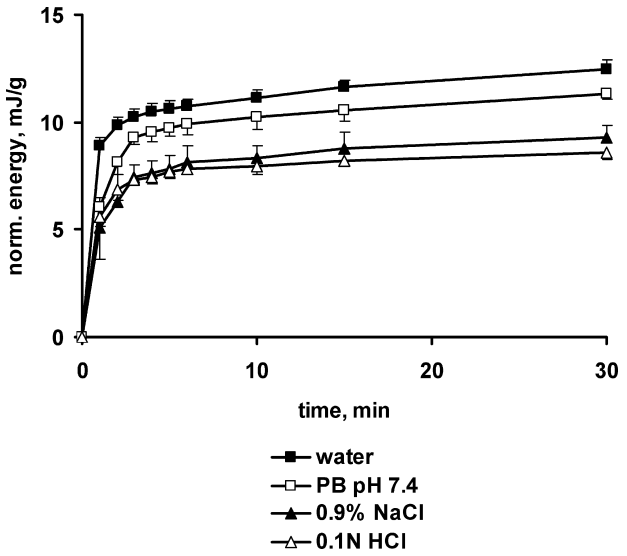

Fig. 9. Normalized swelling energy of discs containing Ac-Di-Sol® (85.7% w/w) and Kollidon® 90 (14.3% w/w) in different media (37 °C); total disc weight: 600 mg; punch weight: 100 g. PB, phosphate buffer (USP 25).

3.8. Swelling force measurements

The swelling force of cast discs initially increased as a function of time and then reached a plateau after approximately 18 mm (Fig. 11A). The development of swelling forces of superdisintegrants during water penetration was examined by [29], where a mathematical model was derived to describe the time-dependency of the swelling force. [16] tested polymeric discs, which were thin non-porous continuous films of low hydrophilicity.

In Eq. (5), the swelling force F was normalized to the maximum determined force F_{inf}:

$$\frac{F}{F_{inf}} = 1 - e^{-kt^n} \quad (5)$$

where t is the time, k and n are constant parameters describing the rate and molecular mechanism of force development. With an exponent $n > 1$, the macromolecular relaxations controlled the swelling force development, and with a value $n < 1$, water diffusion was the controlling factor.

In order to prove whether results obtained for cast discs fit to Eq. (5), the data from Fig. 11A were normalized to F_{inf} (Fig. 11B) and Eq. (5) was linearized:

$$\ln\left[-\ln\left(1 - \frac{F}{F_{inf}}\right)\right] = \ln k + n \ln t \quad (6)$$

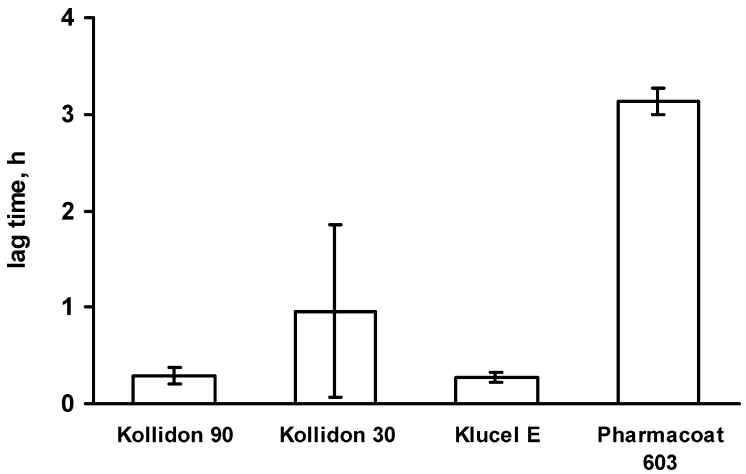

Fig. 8. Lag time in a simulated rupture test as a function of binder. Swelling layer: Ac-Di-Sol®:different binders (3:1 w/w), weight per area of the swelling layer: 132.6 mg/cm^2. Polymer film: ethylcellulose:HPMC (55:45 w/w), 20% w/w TEC, 7.4 mg/cm^2. Medium: purified water, 37 °C.

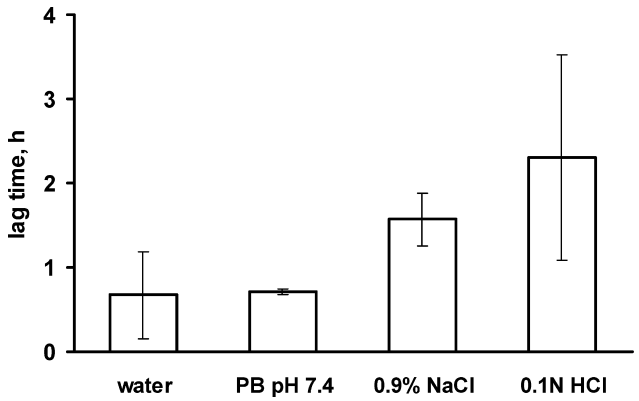

Fig. 10. Lag time obtained with a simulated rupture test in different media (37 °C). Swelling layer: Ac-Di-Sol® (68.5% w/w); binder: Kollidon® 90 (31.5% w/w). Polymer film: ethylcellulose:HPMC (55:45 w/w), 20%w/w TEC, 7.4 mg/cm^2.

The data for the swelling force of superdisintegrant-containing discs measured in water gave a straight line according to Eq. (6) with $r^2 = 0.9797$ (Fig. 12A). The n-value represented as the slope of the linearized plot was 0.82. This n-value below 1 indicated a diffusion-controlled swelling force development predominantly controlled by the penetration rate of the medium (e.g. water) into the disc containing the superdisintegrant.

The achievement of a critical swelling force, which is able to rupture the outer polymer coating in a rupturable pulsatile DDS, can, therefore, be controlled by an outer polymer coating, whereby the lag time of a such a pulsatile system can be controlled by varying the permeability of the coating.

In 0.1 N HCl, the resulting n-value was 0.62 and, therefore, lower compared with the n value obtained in water (Fig. 12B). With a lower n value, the system was more dependent on the media-diffusion because more carboxylic groups of Ac-Di-Sol® (croscarmellose) were unionized, which limited the diffusion of the medium. The limiting step (here, diffusion or penetration of the medium into the disc) played a bigger role with 0.1 N HCl than with water.

3.9. Lag time of pulsatile DDS

The lag time of the multiplayer pulsatile capsule shaped DDS was investigated and could be mainly controlled by the coating level (EC:HPMC, 55:45 w/w) of the outer polymer coating (Fig. 13). The lag time increased with higher coating levels because of the increased mechanical strength of the coating and the reduced medium permeation rate at higher coating thickness. The lag time also depended on the thickness of swelling layer. At low polymer coating levels, the lag time was not affected by the amount of swelling layer, but for higher polymer coating levels, a slight decrease in lag time could be observed with increasing amount of swelling layer. The fact that the lag time did not change much with the amount of the swelling layer can be explained by a sufficient development of swelling energy to break the film. The critical amount of swelling layer, above which a sufficient energy was developed, was apparently lower in the DDS than in the simulated rupture tests due to differences in the film formation process (casting method in the simulation, spraying in case of DDS), leading to stronger films in the case of casting.

4. Conclusions

The suitability of highly swellable polymers (superdisintegrants) as a swelling layer in a rupturable pulsatile DDS was demonstrated. The swelling was characterized as a time-dependent process with progressively increasing swelling energy and swelling force using a special device with a moveable punch or a fixed punch, respectively. Differences in the swelling performance became discernible with these methods: Ac-Di-Sol® had the highest degree of swelling under load, followed by L-HPC, while Explotab®, Kollidon® CL, and Methocel® K100M developed insufficient swelling. Therefore, Ac-Di-Sol® was identified as the best choice for a rupturing release system. The swelling force of Ac-Di-Sol® depended on the pH and the ionic

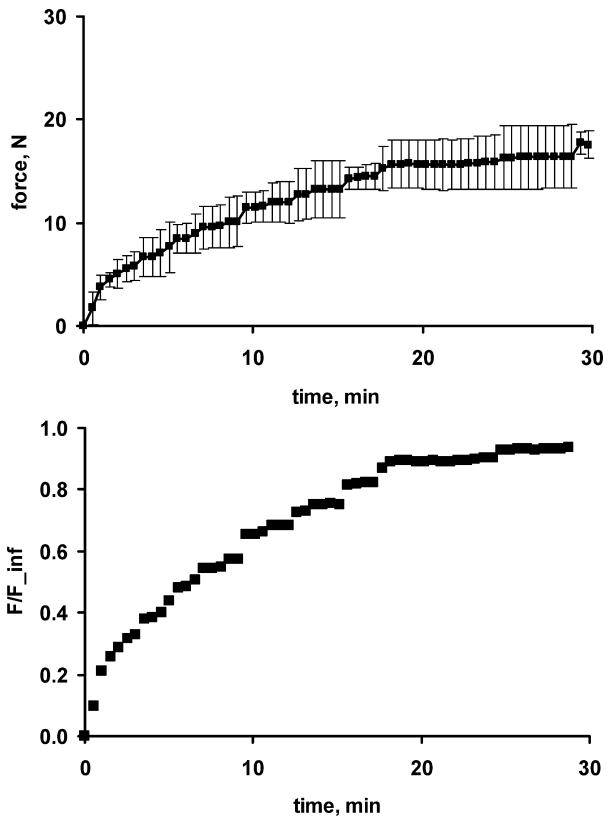

Fig. 11. (A) Swelling force of discs containing Ac-Di-Sol® (85.7% w/w) and Kollidon® 90 (14.3% w/w); disc weight and thickness: 700 mg and 2.4 mm. (B) Swelling force F, normalized to the maximum force F_{inf}. Medium: purified water, 37 °C.

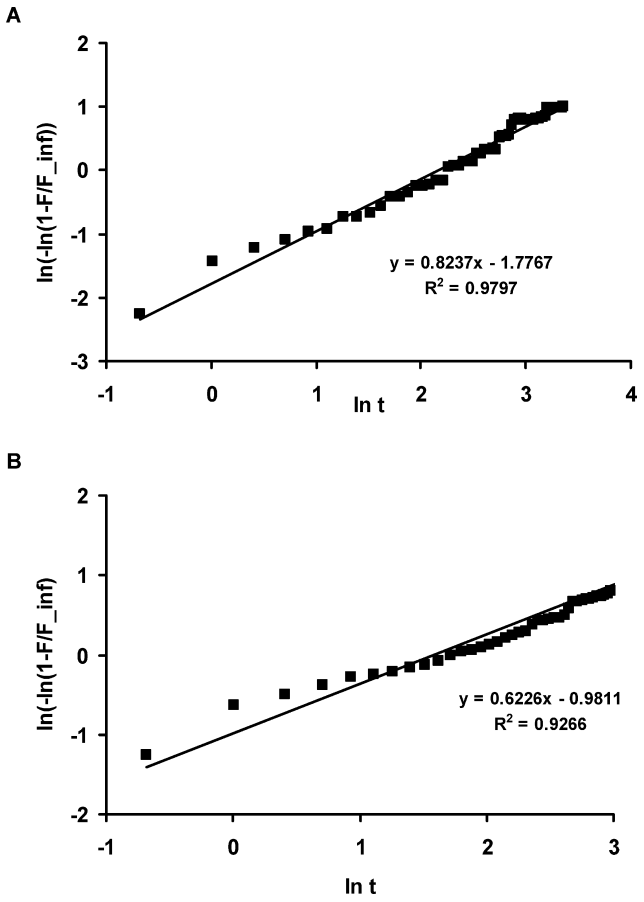

Fig. 12. Linearization of the normalized swelling force data, according to Eq. (6). Medium: (A) purified water and (B) 0.1 N HCl, at 37 °C. Squares: experimental data points; solid line: linear regression of the experimental data.

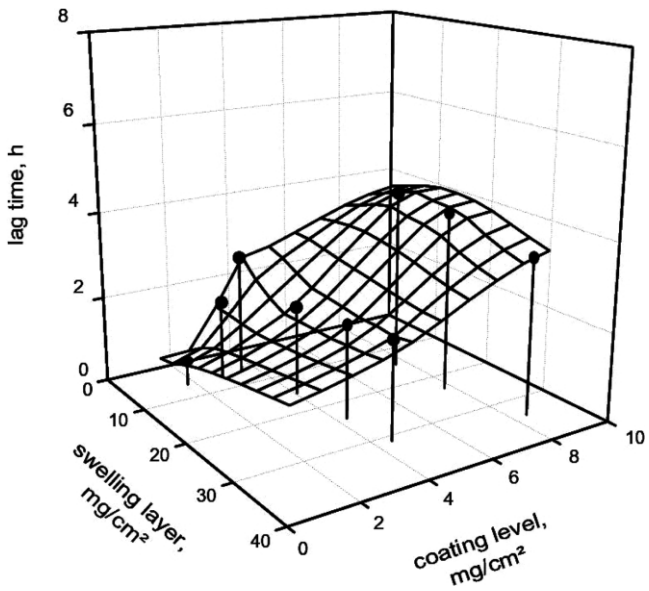

Fig. 13. Lag time of rupturable pulsatile DDS with a swelling layer containing Ac-Di-Sol® (68.5% w/w) and Kollidon® 90 (31.5% w/w). Coating: ethylcellulose:HPMC (55:45 w/w), 20% w/w TEC.

strength of the medium. Due to the presence of carboxylic groups in Ac-Di-Sol®, the swelling was lower in an acidic environment and at higher ionic strength of the medium, but was still significantly higher than the swelling of the other materials tested. Simultaneously measured medium uptake revealed a constant ratio of swelling energy to medium uptake, indicating that the medium uptake was the driving force for the exertion of energy. Evaluation of swelling force experiments according to an exponential model elucidated the mechanism of the swelling as a diffusion-controlled process, primarily controlled by the medium penetration rate. The swelling of the embedded super-disintegrants could be controlled by the medium influx through the use of an outer penetration-controlling insoluble polymer coating, which required a certain mechanical strength to resist the developing swelling pressure and to rupture after the desired lag time.

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