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Research paper

pH-independent pulsatile drug delivery system based on hard gelatin capsules and coated with aqueous dispersion Aquacoat® ECD

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Abstract

The objective of this study was to develop a rupturable, capsule-based pulsatile drug delivery system with pH-independent properties prepared using aqueous coating. The drug release is induced by rupturing of the top-coating, resulting by expanding of swellable layer upon water penetration through the top-coating.

Croscarmellose sodium (AcDiSol®) is a preferable superdisintegrant compared to low substituted hydroxypropylcellulose (L-HPC) and sodium starch glycolate (Explotab®), because of controlled lag time, followed by a quick and complete drug release. However, due to its anionic character, AcDiSol® showed pH-dependent swelling characteristics (pH 7.4 >0.1 N HCl) resulting in a pH-dependent lag time. The pH dependency could be eliminated by the addition of fumaric acid to the swelling layer, which allowed to keep an acidic micro-environment.

Formation of the rupturable top-coating was successfully performed using an aqueous dispersion of ethylcellulose (Aquacoat® ECD), whereby sufficient drying during the coating was needed to avoid swelling of the AcDiSol® layer. A higher coating level was required, when aqueous dispersion was used, compared to organic coatings. However, an advantageous aspect of the aqueous coating was the lower sensitivity of the lag time to a deviation in the coating level.

Keywords: pH independent; Pulsatile drug release; Superdisintegrants; AcDiSol®; Ethylcellulose; Aquacoat® ECD; Hard gelatin capsule

1. Introduction

Pulsatile drug delivery systems release active ingredient completely and rapidly after a defined lag time [1]. Such systems are advantageous for (i) drugs with an extensive first pass metabolism and developed biological tolerance, (ii) the targeting of locally absorbed or acting drugs to a specific site in the intestinal tract (e.g. colon), (iii) the adaptation of the therapy to chronopharmacological needs [1,2].

Pulsatile drug delivery systems are usually of reservoir type, whereby a drug reservoir is surrounded by a diffusional barrier. This barrier erodes, dissolves or ruptures after a specified lag time, followed by a rapid drug release [1]. An erosion system – Chronotopic® consists of a drug containing core and a HPMC layer, optionally coated with an outer enteric coating [3–5]. The lag time prior to drug release is controlled by thickness and viscosity grade of the HPMC layer. A typical problem of eroding or dissolving systems is the retardation of drug release after the lag time [5].

The release performance of capsular-shaped systems from the principal is independent of the capsules content [6–10]. Such systems can be designed as insoluble capsule body and a swellable (e.g. Pulsincap® [6,7]) or degradable plug [8]. Rupturable systems were designed as drug containing reservoir, covered with swellable layer and coated with a water-insoluble polymer membrane. Upon water ingress, the swellable layer expands resulting in film rupturing with subsequent rapid drug release. Such drug delivery systems can be based on hard or soft gelatin capsules [9,10],

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tablets [11] or multiparticulates [12,13]. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time, which can be controlled by coating level of the outer membrane [9–13].

Superdisintegrants are substances with a high swelling potential and can be used to form the swelling layer of rupturable systems. Cross-linked sodium carboxymethylcellulose (AcDiSol®) has a higher swelling energy and therefore is preferable for this purpose, compared with sodium starch glycolate (Explotab®), low substituted hydroxypropylcellulose (L-HPC), cross-linked polyvinyl pyrrolidone (Kollidon® CL) or hydroxypropylmethylcellulose (Methocel® K4M) [14]. However, in case of cross-linked sodium carboxymethylcellulose (AcDiSol®), swelling and drug release from rupturable pulsatile drug delivery systems is pH dependent [14]. This can be attributed to the presence of carboxylic groups in AcDiSol®, which are unionized in an acidic environment, thus resulting in a lower water uptake and swelling [15].

To overcome the problem of pH-dependent solubility of weakly basic drugs following approaches are described in the literature: admixing of pH adjusters, i.e. organic acids of sufficient acidic strength (low pK_a-values) i.e. fumaric, succinic, adipic, tartaric, citric acid [16–18], alkali substances e.g. magnesium oxide [19] or a mixture of them i.e. disodium hydrogen orthophosphate and citric acid [20] to the drug formulation in order to control micro pH inside of dosage form.

Another aspect of coated drug delivery systems is the coating system (organic or aqueous). Aqueous systems for coating have several advantages over the organic polymer solution systems, such as the lower raw material costs, avoidance of capital cost for solvent recovery and explosion proof equipment, with a safer working environment in development and production, environmentally friendly, faster processing time, while still providing reliable coating performance, and faster development and scale up process [21]. However, for the rupturable pulsatile delivery systems so far only organic coatings have been described [9–13]. The aim of this study was the development and evaluation of a time-controlled pH-independent pulsatile drug delivery system by adjusting the micro-environmental pH inside the swelling layer and the investigation of aqueous coating for formation of outer membrane.

2. Materials and methods

2.1. Materials

Croscarmellose sodium, AcDiSol® and aqueous dispersion of ethylcellulose (Aquacoat® ECD, FMC, Newark, DE, USA); low substituted hydroxypropylcellulose (L-HPC, Shin-Etsu Chemical, Tokyo, Japan); sodium starch glycolate (Explotab®, Penwest Pharmaceuticals, Patterson, NY, USA); polyvinyl pyrrolidone (Kollidon® 90F, BASF, Ludwigshafen, Germany); ethylcellulose (EC, Ethocel® Standard 10 cP, Dow Chemical Company, Midland, MI, USA); hard gelatin capsules (size #0, containing 340 mg acetaminophen, 134 mg lactose monohydrate, 45 mg microcrystalline cellulose, 0.90 mg magnesium stearate, 0.54 mg colloidal hydrophobic silica) (Capsugel, Bornem, Belgium); triethyl citrate, TEC; dibutyl sebacate, DBS (Morflex, Greensboro, NC, USA); fumaric acid (Bartek Ingredients Inc., Stoney Creek, Ont., Canada); citric acid monohydrate and disodium hydrogen phosphate heptahydrate (Merck KGaA, Darmstadt, Germany). All other reagents were of analytical grade and were used as received.

2.2. Preparation of pulsatile hard gelatin capsules

2.2.1. Layering of swelling layer

Hard gelatin capsules were layered to achieve 45.1 mg/cm^2 weight gain in a pan coater (Glatt GC-300, Glatt GmbH, Pratteln, Switzerland), using coating dispersions according to Table 1. The process conditions were: batch size, 1 l capsules (370 g); spray nozzle diameter, 1.2 mm; atomizing air pressure, 0.9 bar; air flow rate, 110 m^3/h; inlet air temperature, 36 °C; product temperature, 24 °C; spray rate, 15 g/min; pan rotation, 30 rpm; post-drying at 35 °C for 10 min.

2.2.2. Ethylcellulose top-coating

The capsules layered with the swelling layer were then coated with a 3.5% w/v ethylcellulose solution in 96% v/v ethanol plasticized with 5% w/w DBS (based on polymer content) in the GC-300 drum coater under the conditions described above, except that the inlet and product temperatures were 35 °C and 22 °C, correspondingly.

Alternatively, the capsules were coated with an aqueous ethylcellulose dispersion (Aquacoat® ECD), diluted with water to 15% w/w solids content and plasticized with 25% w/w TEC (based on total solids content of the dispersion) and stirred for 30 min. The coating was performed in pan coated Glatt GC-300 under following conditions: batch size, 1 l; nozzle diameter, 1.2 mm; atomizing air pressure, 0.9 bar; air flow, 130 m^3/h pre-warming of capsules at 40 °C for 10 min; inlet temperature, 60 °C; product temperature, 40 °C; spray rate, 7 g/min; pan speed, 30 rpm; final drying at 40 °C for 15 min. Coated capsules were cured in oven at 60 °C for 24 h.

Table 1
Formulations (weight parts) of AcDiSol® layering dispersions

Ingredients	Fumaric acid, % (based on AcDiSol® amount)		
	0	10	50
AcDiSol®	12.0	12.0	12.0
Kollidon 90 F	3.5	3.5	3.5
Fumaric acid	0.0	1.2	6.0
Ethanol (96% v/v)	84.5	84.5	84.5

2.3. Determination of drug release and lag time

Drug release and lag time were determined in a USP paddle apparatus (Vankel VK 300, Vankel Industries, Edison, NJ, USA) (0.1 N HCL or USP phosphate buffer, pH 7.4, 37 °C, 50 rpm, $n = 5$). Three milliliter samples were withdrawn at predetermined time points and analyzed after appropriate dilution by UV at $\lambda = 240$ nm (Shimadzu UV-2101PC UV-Vis Scanning spectrophotometer; Shimadzu Europe, Duisburg, Germany). The time point at which the top-coating ruptured (visual observation) was considered as lag time.

2.4. Swelling volume

Ten milliliter of 0.1 N HCl or phosphate buffer, pH 7.4, was added to scaled tubes (Duran, Giessen, Germany), prefilled with 1 ml (bulk volume) superdisintegrant powder without/with (10, 20, 30, 40, 50, 75, 100, 200% w/w) fumaric acid or $Na_2HPO_4{\cdot}7H_2O$ (based on AcDiSol). The volume of the swollen powder (height in the scaled tubes) was measured after 30 min and expressed as a percentage relative to the initial bulk volume of the superdisintegrant. At the same time, the pH of this suspension was measured by using pH meter (CG 711, Schott, Mainz, Germany). Citric acid/Na_2HPO_4 buffers with pH values ranging from 1.2 to 7.4 and an osmolality of 0.41 osmol/kg (adjusted with NaCl) were used to investigate the pH-dependent swelling of AcDiSol®.

2.5. Swelling energy

2.5.1. Casting of swelling discs

Three gram suspensions used for layering of swelling agent (see Section 2.2) 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 desiccator until further testing.

2.5.2. Swelling experiments

Swelling experiments were performed with a self-built swelling device ($n = 3$) [14]. The superdisintegrant disc/powder was placed inside a Plexiglas cylinder on a glass filter (porosity #1). A tightly fitting punch (100 g) was placed on top of the sample. Medium (purified water, 0.1 N HCl or phosphate buffer, pH 7.4) was added to a vessel filled with the medium to the level of the glass filter. The displacement of the punch was measured with a caliper gauge over time.

The swelling energy was calculated as follows: $E = F_{\text{weight}} \cdot d$, where E is the swelling energy (mJ), F_{weight} is the predetermined weight force of the punch (N), and d is the displacement of the punch (mm).

The normalized energy was calculated as: $E_{\text{norm}} = E/$(amount of swelling agent, g).

To investigate the effect of humidity on the swelling energy, AcDiSol® powder was stored for 24 h at 40 °C/75% r.h., 25 °C/60% r.h., or 40 °C-desiccator, followed by measurements of swelling energy and water uptake/weight loss (determined gravimetrically).

2.6. Mechanical properties of polymer films

2.6.1. Preparation of polymer films

Ethocel® 10 cP was dissolved in 96% v/v ethanol at a concentration of 10% w/w and plasticized with 5% w/w DBS (based on the weight of the polymer). An aqueous ethylcellulose dispersion (Aquacoat® ECD) was diluted with water to 15% w/w solids content and plasticized with 25% w/w TEC (based on total solids content of the dispersion) by stirring for 30 min. The resulting solutions/dispersions were cast onto a Teflon plate, 14×14 cm^2, dried for 24 h at room temperature (solution) or at 60 °C (dispersion) and resulting films were carefully removed. The film thickness was measured at five points with a thickness gauge Minitest 600 (Erichsen, Hemer, Germany).

2.6.2. Mechanical properties

Polymer films (6.5×6.7 cm^2) were fixed in a self-designed Teflon holder [14,23] with several holes (diameter 10 mm). Films were fixed using the holder and optionally immersed into 0.1 N HCl at 37 °C for 2 h (wet films). The mechanical properties of the dry and wet films were measured with a puncture test using a Texture analyzer (TA. XT. Plus Texture Analyzer, 50 kg load cell, Stable Micro Systems Ltd, UK) ($n = 3$). A metal probe with a hemispherical end (diameter 5 mm, length 15 cm) was driven at a speed of 5 mm/min until the film ruptured force–displacement curves were recorded and following parameters were calculated:

$$\text{puncture strength} = \frac{F_{\max}}{A_{\text{CS}}},$$

where $F_{\max}$ is the maximum applied force at film break, A_{CS} is the cross-sectional area of the edge of the film located in the path of the cylindrical hole of the film holder, with $A_{\text{CS}} = 2r \cdot \delta$, where r is the radius of the hole in the holder and δ is the thickness of the film.

Elongation at break was calculated as follows:

$$\%\ \text{elongation} = \frac{\Delta l}{r} \cdot 100 = \frac{\sqrt{r^2 + D^2} - r}{r} \cdot 100,$$

where Δl is the linear expansion of the film, r is the radius of the hole in the holder and D is the displacement of the punch.

3. Results and discussion

The pulsatile hard gelatin capsule system consists of (i) a drug containing hard gelatin capsule (ii) a swelling layer (superdisintegrant and binder), and (iii) a water-insoluble, but -permeable, ethylcellulose coating. Upon ingress of release medium, the swelling layer expands resulting in film rupturing with subsequent rapid drug release.

When Explotab® and L-HPC were used as superdisintegrants to form a swelling layer, high variations in lag time,

slow and not complete drug release after the lag time were observed (Fig. 1A and B). In contrast, a typical pulsatile release profile (no drug release during the lag time followed by a rapid and complete release) was obtained using AcDiSol® (Fig. 1C). The better performance of rupturable system based on AcDiSol® compared to Explotab® and L-HPC has been described [14]. The explanation was higher swelling energy of AcDiSol® (approx. 3-fold and over 10-fold) compared to L-HPC and Explotab® [14].

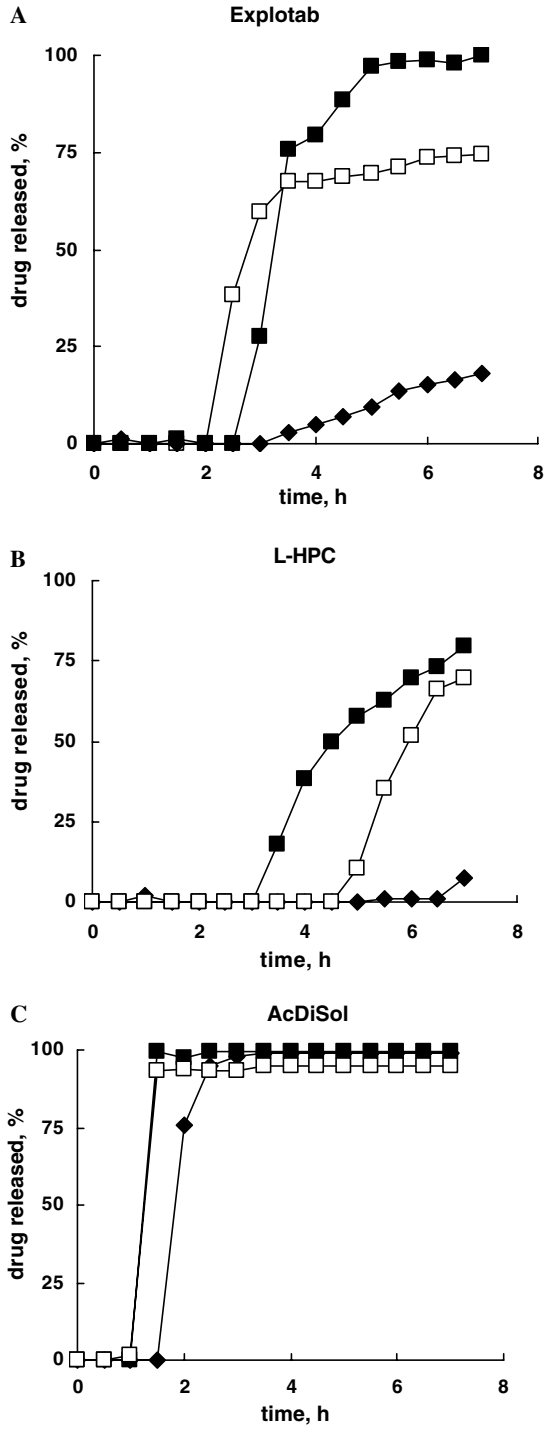

Fig. 1. Acetaminophen release from capsules layered with 45.1 mg/cm^2 of (A) Explotab®, (B) L-HPC and (C) AcDiSol® and coated with (4.5 mg/cm^2) ethylcellulose (5% w/w DBS) ($n = 3$, release of individual capsules shown).

However, the lag time of the rupturable capsules based on AcDiSol® as a swelling agent was strongly dependent on the pH of the release medium. Lag times were longer in 0.1 N HCl than in phosphate buffer, pH 7.4, for all investigated coating levels of the outer membrane (Fig. 2). The swelling volume of AcDiSol® was nearly constant (approx. 750%) in the pH-range 1.2–5.4, but increased continuously (up to 1000%) in the pH-range 5.4–7.4 (Fig. 3). Correspondingly the swelling energy of AcDiSol® was higher in phosphate buffer, pH 7.4, and lower in 0.1 N HCl (Fig. 4). This could be attributed to the presence of carboxylic groups in AcDiSol®, which were unionized in an acidic environment, thus resulting in a lower water uptake and swelling [15].

In order to maintain a pH-independent swelling, an acidic micro-environment can be created, by addition of organic acids, in analogue to matrix tablets with weakly basic drugs [16–18]. For this purpose substances with high acidic strength (low pK_a-value) and relatively low solubility in 0.1 N HCl are suitable e.g. fumaric acid (p$K_{a1} = 3.03$,

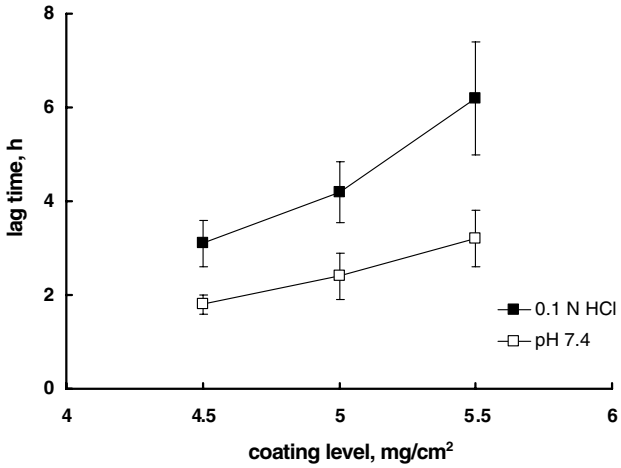

Fig. 2. Lag time of pulsatile hard gelatin capsules. Swelling layer: AcDiSol® 45.1 mg/cm^2, rupturable membrane: ethylcellulose–5% DBS, in 0.1 N HCl and phosphate buffer, pH 7.4, 37 °C.

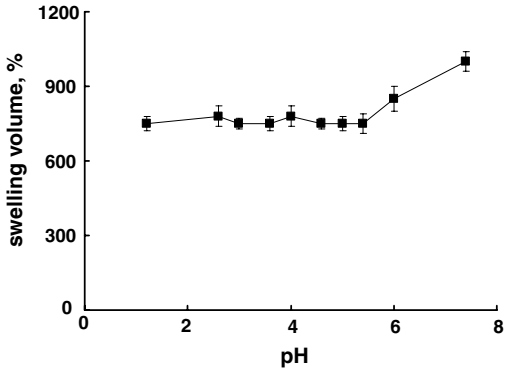

Fig. 3. Swelling volume of AcDiSol® as a function of medium pH.

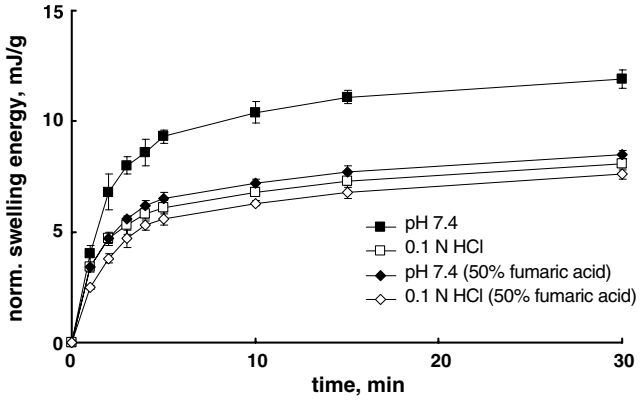

Fig. 4. Normalized swelling energy of discs containing (AcDiSol®: Kollidon® 90, 3:1 and optionally 50% w/w fumaric acid); punch weight: 100 g, medium: 0.1 N HCl and phosphate buffer, pH 7.4.

$pK_{a2} = 4.54$ and a solubility of 7.97 mg/ml). An addition of fumaric acid up to 100% (based on AcDiSol®) did not influence pH (approx. 3.2) and swelling volume (approx. 600%) in 0.1 N HCl (Fig. 5). In phosphate buffer pH dropped to 4.2 and 3.5 by addition of 10 and 20% w/w fumaric acid correspondingly (Fig. 5A), which was sufficient to reduce the swelling from approx. 830% to the level, observed in 0.1 N HCl (Fig. 5B). By further addition of fumaric acid (20–100%) pH and swelling were nearly constant (Fig. 5A and B). Similar, the normalized swelling energy in 0.1 N HCl decreased only slightly by addition to AcDiSol® 50% fumaric acid (Fig. 4), due to increased distance between superdisintegrant particles, "diluted" by fumaric acid. However, in phosphate buffer, pH 7.4, the swelling energy of AcDiSol® decreased remarkably, when 50% fumaric acid were added and reached nearly the level of swelling in 0.1 N HCl (Fig. 4).

An approaching of AcDiSol® swelling in 0.1 N HCl and, pH 7.4, also could be achieved by buffering with basic substances, such as Na_2HPO_4 (pH 9.1, for a 1% w/v aqueous solution, $pK_{a1} = 2.15$, $pK_{a2} = 7.20$ [22]). In this case pH and swelling in 0.1 N HCl increased to the level in phosphate buffer, pH 7.4, however a very high amount Na_2HPO_4 (at least 75% w/w based on the amount of AcDiSol®) is required (Fig. 6). Therefore this approach was not followed further.

Lag times of capsules were prolonged, with increasing amount of fumaric acid in 0.1 N HCl and, pH 7.4 (Table 2), because of a reduced portion of AcDiSol®, responsible for swelling. Nevertheless, the lag times in both media nearly approached each other, when 50% w/w fumaric acid were added to swelling layer (Table 2).

General advantages of aqueous vs. organic coating have been mentioned in the introduction. Besides the water permeability, mechanical properties of the top-coating are

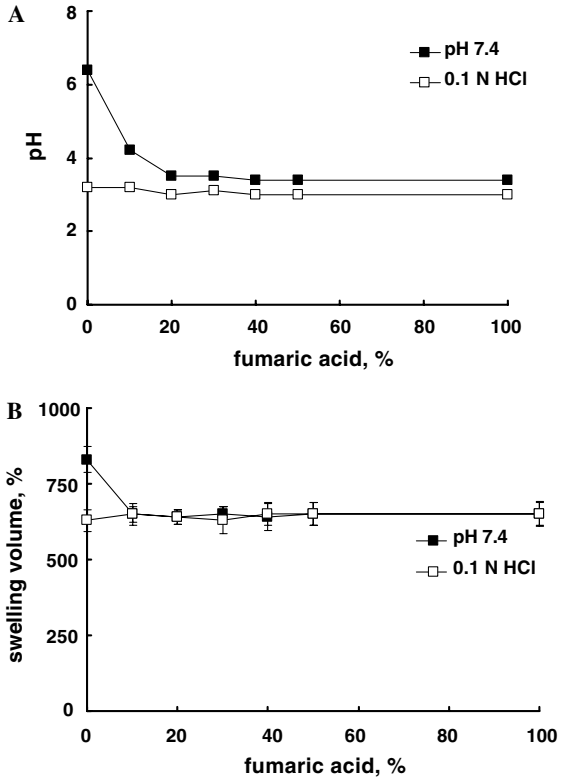

Fig. 5. Effect of fumaric acid addition on (A) pH and (B) swelling volume of AcDiSol® in 0.1 N HCl and phosphate buffer, pH 7.4.

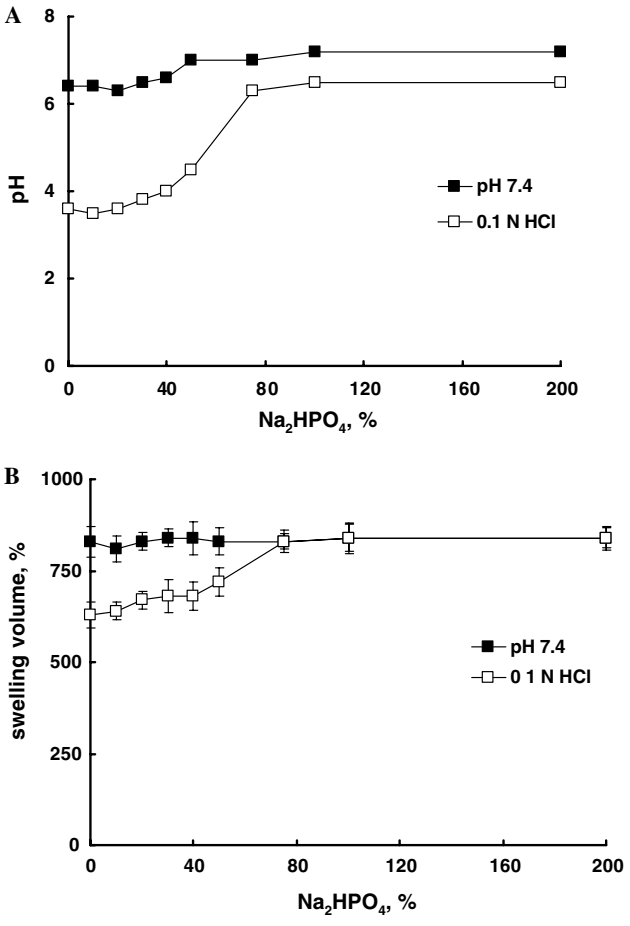

Fig. 6. Effect of Na_2HPO_4 addition on (A) pH and (B) swelling volume of AcDiSol® in 0.1 N HCl and phosphate buffer, pH 7.4.

Table 2
Lag times of hard gelatin capsules, layered with AcDiSol®: Kollidon 90 F (without or with fumaric acid) as swelling layer and coated with ethylcellulose-5% DBS, in different media (0.1 N HCl and phosphate buffer, pH 7.4)

Coating level, mg/cm^2	Lag time, h (s.d.)					
	0% fumaric acid		10% fumaric acid		50% fumaric acid	
	pH 1.2	pH 7.4	pH 1.2	pH 7.4	pH 1.2	pH 7.4
4.4	2.9 (0.6)	1.4 (0.3)	3.4 (0.3)	2.6 (0.4)	4.7 (0.9)	5.3 (1.3)
5.0	3.5 (0.5)	2.3 (0.8)	4.6 (0.7)	4.1 (0.7)	6.6 (1.0)	6.9 (1.3)
6.8	6.8 (0.9)	3.0 (0.4)	6.7 (1.0)	7.4 (0.8)	8.4 (1.4)	9.3 (0.9)

very important for the rupturable pulsatile system. In general, mechanically weak and nonflexible films are suitable, while highly flexible films expand and often do not rupture during release studies [23]. Irrespective of the higher amount of plasticizer used in case of the aqueous coating (necessary to ensure coalescence of the polymeric particles and film formation), dry and wet films were mechanically weaker (lower puncture strength and elongation), compared to films prepared from organic solutions (Table 3).

However, for the rupturable pulsatile delivery systems so far only organic coatings have been described, probably due to assumed unwanted pre-swelling of the superdisintegrant during aqueous coating.

In fact, the swelling energy of AcDiSol® powder stored for 24 h at elevated humidity (40 °C-75% r.h. or 25 °C-60% r.h.) decreased dramatically compared to AcDiSol® stored at 40 °C in a desiccator (Fig. 7), because of high water uptake (approx. 20% w/w). When pre-swollen powder (40 °C-75% r.h., 24 h) was dried in a dessiccator at 40 °C up to a loss on drying 2% w/w, the swelling energy was recovered (Fig. 7). Therefore, AcDiSol®-layered capsules could be coated with aqueous ethylcellulose dispersion, when optimal spraying/drying equilibrium was ensured. In our experiments (coating conditions described in Section 2) the water uptake of AcDiSol®-layered capsules during the coating process was approx. 1% w/w.

Dosage forms coated with aqueous polymeric dispersions (e.g. Aquacoat ECD) are often treated at elevated temperature (curing) to complete film formation and to obtain stable release profiles [24]. Curing (60 °C, 24 h) of capsules in this study was also necessary, otherwise the top-coating rapidly ruptured in the release medium and release was immediate (data not shown).

When comparing aqueous vs. organic coating systems within this study it was found that pulsatile capsules

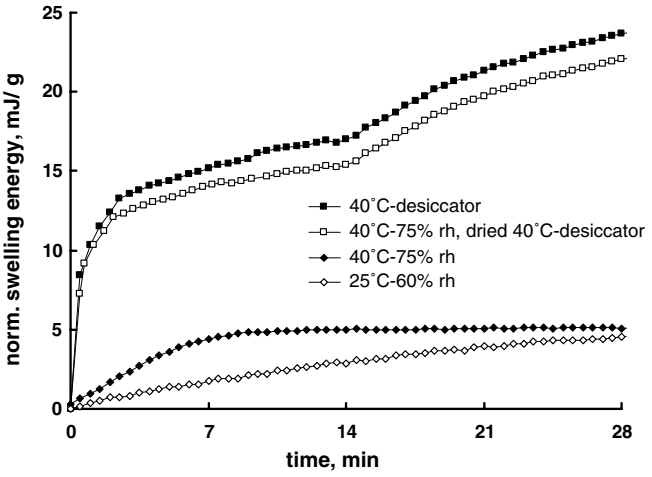

Fig. 7. Normalized swelling energy of AcDiSol® powder stored under different conditions (40 °C-75% r.h., 25 °C-60% r.h., and 40 °C-desiccator, and 40 °C-75% r.h. and dried again at 40 °C-desiccator), medium: purified water, 37 °C.

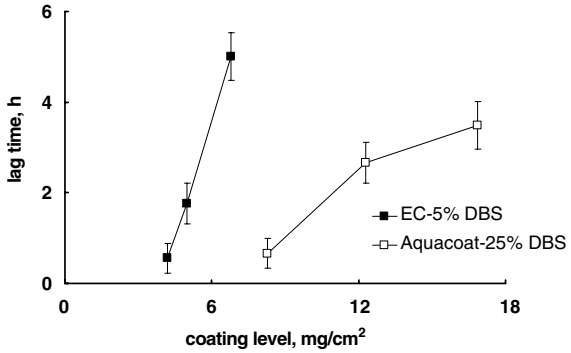

Fig. 8. Lag time of pulsatile hard gelatin capsules, swelling layer: AcDiSol® 45.1 mg/cm^2, rupturable membrane: Ethocel 10 cP, 5% DBS and Aquacoat® ECD, 25% DBS, in 0.1 N HCl.

Table 3
Mechanical properties of Ethocel® 10 cP films (plasticized with 5% w/w DBS) and Aquacoat® ECD (plasticized with 25% w/w TEC) in the dry and wet state (60 min incubation in 0.1 N HCl, 37 °C), $n = 3$

Polymer	Puncture strength, Mpa (m.v. ±s.d.)		Elongation at break, % (m.v. ±s.d.)	
	Dry	Wet	Dry	Wet
Ethocel 10 cP, 5% DBS	16.2 (5.7)	7.73 (0.9)	7.1 (1.6)	5.8 (1.1)
Aquacoat® ECD, 25% TEC	03.7 (2.3)	0.76 (0.5)	0.7 (0.2)	0.7 (0.5)

prepared using the aqueous coating required a higher coating level compared to the organic coating in order to achieve the same lag time (Fig. 8), because of mechanically weaker films (Table 3). On the other hand, the profile of the rupture time vs. coating level became flatter when coating with aqueous dispersions (Fig. 8). This could be very advantageous, because a deviation in coating level would result in only relatively small changes in lag time and

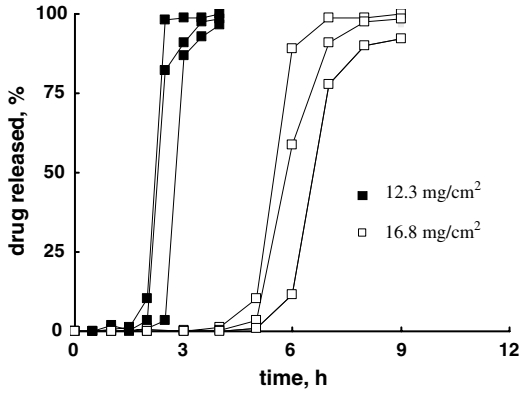

Fig. 9. Acetaminophen release in 0.1 N HCl from pulsatile hard gelatin capsules layered with 45.1 mg/cm^2 AcDiSol® as a function of Aquacoat® ECD (25% w/w DBS) coating level ($n = 3$, release of individual capsules is shown).

consequently reproducible drug release profiles, with rapid and complete drug release (Fig. 9).

4. Conclusion

The pH-independent swelling of AcDiSol® and thus pH-independent lag times of rupturable pulsatile capsule system could be achieved by adding fumaric acid to the swelling layer allowing control over the micro-environmental pH. Aqueous coating could be successfully applied, since during coating spraying/drying equilibrium was adjusted to ensure low water uptake (<2%). In case of aqueous coating the lag time was less sensitive to deviations in the coating level.

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