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Development of pulsatile multiparticulate drug delivery system coated with aqueous dispersion Aquacoat® ECD

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Abstract

The objective of this study was to develop and evaluate a pulsatile multiparticulate drug delivery system (DDS), coated with aqueous dispersion Aquacoat® ECD. A rupturable pulsatile drug delivery system consists of (i) a drug core; (ii) a swelling layer, comprising a superdisintegrant and a binder; and (iii) an insoluble, water-permeable polymeric coating. Upon water ingress, the swellable layer expands, resulting in the rupturing of outer membrane with subsequent rapid drug release.

Regarding the cores, the lag time was shorter, when 10% (w/w) theophylline was layered on sugar cores compared with cores consisting of 100% theophylline. Regarding swelling layer, the release after lag time was fast and complete, when cross-linked carboxymethyl cellulose (AcDiSol®) was used as a swelling agent.

In contrast, a sustained release was achieved after the lag time, when low-substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate (Explotab®) were used as swelling agents. The optimal level of AcDiSol® to achieve a fast and complete release after the lag time was 26% (w/w) (based on the weight of the coated pellets) for poorly soluble theophylline and 48% (w/w) for highly soluble propranolol HCl. The lag time can be controlled by the coating level of an outer membrane and increased with increasing coating level of the outer membrane. Outer membrane, formed using aqueous dispersion Aquacoat® ECD was brittle and ruptured sufficiently to ensure fast drug release, compared to ethylcellulose membrane formed using organic solution. The addition of talc led to increase brittleness of membrane and was very advantageous because of (i) reduced sensitivity of lag time on variations in the coating level and (ii) fast and complete drug release. Drug release starts only after rupturing of outer membrane, which was illustrated by microscopical observation of pellet during release.

Keywords: Pulsatile release; Rupturing system; Superdisintegrant; AcDiSol®; Aqueous coating; Aquacoat® ECD

1. Introduction

In recent years there is a continuous interest in the development of controlled drug release systems, to achieve the optimal therapeutic effect of drugs. The typical oral controlled-release systems show a pattern of drug release, in which the drug concentration is maintained in the therapeutic window for a period of time, thereby ensuring sustained therapeutic action. For several diseases (e.g. bronchial asthma, hypertension, rheumatic disease and myocardial infraction) as well for control of body functions (blood pressure, levels of many hormones e.g. aldosterone, rennin, and cortisol) influenced by circadian rhythms, delayed or pulsatile drug release could be an optimal approach (Bussemer et al., 2001; Bussemer and Bodmeier, 2001; Ritschel and Forusz, 1994; Lemmer, 1999). Pulsatile release is also useful for the targeting of the drug irritating the stomach or degradable therein, as well for drugs developing biological tolerance or with an extensive first-pass metabolism e.g. β-blocker (Bussemer et al., 2001; Bussemer and Bodmeier, 2001; Ritschel and Forusz, 1994; Lemmer, 1999).

Pulsatile drug delivery systems (DDS) are characterized by a rapid drug release after a predetermined lag time and can be classified as single unit (e.g. tablet or capsule) or multiparticulate (e.g. pellets) systems (Bussemer et al., 2001; Bussemer and Bodmeier, 2001).

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Most of the pulsatile drug delivery systems contain a drug reservoir, surrounded by a barrier, which erodes/dissolves (Gazzaniga et al., 1995; Wilding et al., 1994; Pozzi et al., 1994) or ruptures (Bussemer et al., 2003a; Bussemer and Bodmeier, 2003; Sungthongjeen et al., 2004). Often the challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time (Gazzaniga et al., 1995; Wilding et al., 1994). Depending on drug solubility Chronotopic® (Gazzaniga et al., 1995) or Time Clock® (Wilding et al., 1994; Pozzi et al., 1994) systems, consisting of a drug containing core and a hydrophilic (HPMC) or lipophilic (carnauba or beewax) layer correspondingly, have been described. The Chronotopic® system works for poorly water soluble drugs, because highly water soluble drugs could diffuse through the swollen HPMC layer prior to complete erosion. High viscosity types of HPMC, e.g. Methocel® K4M, retarded the drug release in vivo, because the gel layer was mechanically too strong and withstood extensive erosion even after complete hydration. Time Clock® system is more suitable for the highly hydrophilic drugs, because of hindered diffusion through carnauba wax or beewax containing coating (Pozzi et al., 1994). The lag time in both systems was controlled by coatings thickness and was independent of the environmental pH.

In the rupturable multiparticulate pulstile DDS drug containing inner core is layered by a swellable layer and water insoluble polymer membrane as a top layer. Upon water ingress, the swellable layer expanded resulting in film rupturing with subsequent rapid drug release. In case of hard/soft gelatin capsules the lag time and completeness of release was independent of capsules content (Bussemer et al., 2003a; Bussemer and Bodmeier, 2003) and influenced remarkable by core composition in case of tablets (Sungthongjeen et al., 2004). Properties of swelling layer as well composition and thickness of the outer membrane are reported as major factors, affecting the rupturing and release parameters (Bussemer et al., 2003b, 2003c).

Multiparticulate systems (e.g. pellets) offer various advantages over single unit. These include no risk of dose dumping, flexibility of blending units with different release patterns, as well short and reproducible gastric residence time (Ghebre-Sellassie, 1994; Bechgaard, 1978).

As a rupturable multiparticulate pulsatile DDS a "time controlled explosion system (TES)" has been presented. The drug is layered on an inner core, followed by a swellable layer and water insoluble polymer membrane as a top layer (Ueda et al., 1994a, 1994b).

Irrespective on several advantages of aqueous coating over organic (lower raw material costs, environmentally friendly, etc.) for the rupturable pulsatile delivery systems so far only organic coatings are described (Bussemer et al., 2003a; Bussemer and Bodmeier, 2003; Sungthongjeen et al., 2004; Ueda et al., 1994a, 1994b).

The objectives of the present study were to develop and evaluate a multiparticulate pulsatile drug delivery system consisting of a drug core, layered with a swelling layer and coated with an insoluble polymeric membrane, using aqueous dispersion Aquacoat® ECD.

2. Materials and methods

2.1. Materials

Sugar pellets—Suglets®: NP 425–500 μm (NP Pharma S.A., c/o Gustav Parmentier, Frankfurt, Germany); propranolol HCl and theophylline anhydrous (BASF AG, Ludwigshafen, Germany); hydroxypropyl methylcellulose, HPMC (Methocel® E5, Colorcon, Dartford, England), aqueous dispersion of ethylcellulose, Aquacoat® ECD and croscarmellose sodium, AcDiSol® (FMC Newark, DE, USA); low-substituted hydroxypropyl cellulose, L-HPC 11 (Shin-Etsu Chemical, Tokyo, Japan); sodium starch glycolate, Explotab® (Penwest Pharmaceuticals, Patterson, NY, USA); polyethylene glycol, Lutrol®E 4000 (BASF AG, Ludwigshafen, Germany); ethylcellulose, Ethocel® Standard 10, Ethocel® Standard 100 (Dow Chemical Company, Midland, MI, USA); hydroxypropylcellulose, Klucel® MF (Hercules Inc., Wilmington, DE, USA); triethyl citrate, TEC and dibutyl sebacate, DBS (Morflex, Greensboro, NC, USA); talc (Luzenac Deutschland GmbH). All other ingredients were of analytical grade and were used as received.

2.2. Preparation of pulsatile multiparticulate DDS

2.2.1. Drug layering

Propranolol HCl or theophylline were layered on sugar pellets using 15% (w/v) solution or suspension, respectively, in ethanol/water (60:40 w/w) mixture containing 1.5% (w/v) HPMC (Methocel® E5) in a fluidized bed coater (Glatt GPCG-1, Glatt GmbH, Binzen, Germany) to achieve a 10% (w/w) drug content. The layering conditions were: batch size 800 g, inlet temperature 30 °C, product temperature 26 °C, air flow 130 m^3/h, nozzle diameter 1.2 mm, spray pressure 1.2 bar, spray rate 8.5 g/min, final drying at 40 °C for 15 min.

2.2.2. Layering of swelling layer

Drug containing pellets were layered with a 5% (w/w) suspension of AcDiSol®, Explotab®, or L-HPC in a 2% (w/w) Klucel® MF solution in 96% (v/v) ethanol using a fluidized bed coater (Strea 1, Aeromatic-Fielder AG, Bubendorf, Switzerland) to achieve required weight gain. The process conditions were: batch size, 600 g; pre-warming of the cores at 40 °C for 10 min; spray nozzle diameter, 1.2 mm; atomizing air pressure, 2.0 bar; air flow rate, 80 m^3/h; inlet air temperature, 33 °C; product temperature, 22 °C; spray rate, 15 g/min; post-drying at 40 °C for 10 min.

2.2.3. Coating with ethylcellulose

The pellets layered with the swelling layer were then coated with an aqueous ethylcellulose dispersion (Aquacoat® ECD), diluted with water to a 15% (w/w) solids content and plasticized with 25% (w/w) TEC or DBS by stirring for 30 min (TEC) or 24 h (DBS). Optionally 10% talc was added. Plasticizers and talc amounts are based on total solids content of the dispersion. Coating was performed in a fluidized bed coater (Strea 1, Aeromatic-Fielder AG, Bubendorf, Switzerland) to achieve required weight gain under following conditions: batch size,

600 g; inlet temperature, 60 °C; outlet temperature, 36 °C; air flow 100 m^3/h; nozzle diameter, 1.2 mm; spray pressure, 2 bar; spray rate, 6 g/min; final drying, 40 °C for 15 min. The coated pellets were cured in an oven at 60 °C for 24 h.

Alternatively, pellets were coated with a 3.5% (w/v) ethylcellulose solution in 96% (v/v) ethanol, plasticized with 5% DBS (w/w) (based on the weight of the polymer) under the conditions described above, except inlet/outlet temperature was 28/22 °C.

2.3. Drug release

Approximately 250 mg of pellets were processed in a USP paddle apparatus (Vankel VK 300, Vankel Industries, Edison, NJ, USA) (900 ml 0.1N HCl, 37 °C, 100 rpm, $n = 3$). Three milliliters samples were withdrawn at predetermined time points and analyzed by UV at $\lambda = 270$ and $\lambda = 290$ nm for theophylline and propranolol HCl, respectively (Shimadzu UV-2101PC UV–vis Scanning spectrophotometer; Shimadzu Europe, Duisburg, Germany). The lag time was determined by extrapolation of the upward part of release profile to the time axis. $t_{75\%}$ = time to release 75% of drug minus lag time.

Optionally, pellets were observed under a light microscope during the dissolution at predetermined time points (Axioscope, Carl Zeiss Jena GmbH, Jena, Germany).

2.4. Mechanical properties of polymer films

2.4.1. Preparation of polymer films

An aqueous ethylcellulose dispersion (Aquacoat® ECD) was diluted with water to a 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 and optionally 10% (w/w) (based on total solids content of the dispersion) talc was added. Ethocel® 10 or Ethocel® 100 were 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). The resulting solutions/dispersions were cast onto a Teflon plates, 14 cm × 14 cm, dried for 24 h at room temperature (ethanolic solutions) or at 60 °C (aqueous dispersions) and carefully removed by hand and equilibrate at ambient conditions at least for 24 h. The film thickness was measured at five points with a thickness gauge Minitest 600 (Erichsen, Hemer, Germany).

2.4.2. Mechanical properties test

Films (9.0 cm × 6.5 cm) were fixed in a self-designed Teflon holder with 18 holes (diameter 10 mm). The mechanical properties of the films were measured with a puncture test using a Texture analyzer (TA.XT. plus texture analyzer, Stable Micro Systems Ltd., UK) ($n = 6$). A metal probe with a hemispherical end (diameter 5 mm, length 15 cm) was driven through the dry film at a speed of 5 mm/min. Force (N) versus displacement (mm) curves were recorded with a 5 kg load cell, $n = 6$. Then holder with the fixed film was immersed into 0.1N HCl at 37 °C for 1 h and puncture tests were performed as described above on the wet film, $n = 6$. The following parameters were calculated:

- Puncture strength:

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

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 ($A_{CS} = 2r\delta$, where r is the radius of the hole, δ is the thickness of the film).

- Elongation at film break:

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

where r is the radius of the hole and D is the displacement of the punch.

3. Results and discussion

A rupturing pulsatile drug delivery system consists of (i) a drug containing core; (ii) a swelling layer, comprising a superdisintegrant; and (iii) an insoluble, water-permeable polymeric coating. Upon water ingress, the swellable layer expands, resulting in the rupturing of outer membrane with subsequent rapid drug release. As a drug cores sugar spheres layered with highly water soluble (220–253 mg/ml) propranolol HCl (Bodmeier and Chen, 1989) and poorly water soluble (12–15 mg/ml) theophylline (Bodmeier and Chen, 1989) were used.

3.1. Swelling layer

First, cores containing poorly water soluble theophylline (10%, w/w) were layered with sodium starch glycolate (Explotab®), low-substituted hydroxypropyl cellulose (L-HPC) and croscarmellose sodium (AcDiSol®) and top-coated with different coating level of aqueous dispersion of ethylcellulose (Aquacoat® ECD). The rupturing of the outer membrane was poor resulting in slow release, when Explotab® or L-HPC was used as a swelling agent (Fig. 1A and B). In contrast, desired pulsatile release profile with a clear lag time, followed by rapid and complete release was obtained with AcDiSol® for all investigated coating levels (Fig. 1C). This is because higher swelling energy of AcDiSol® compared to Explotab® and L-HPC (Bussemer et al., 2003b). The lag time was slightly increased and the following drug release was remarkably faster by increasing AcDiSol® amount from 5 to 26% (w/w) (Fig. 2). It is because higher amount of AcDiSol® absorb more water until pressure, sufficient for rupturing is reached. However, both the lag time and the following release were unchanged by further increase of AcDiSol® level up to 58% (w/w) (Fig. 3).

In contrast, release of the water soluble propranolol HCl from the pellets layered with AcDiSol® 26% (w/w) as swelling agent was sustained (Fig. 4), because of not sufficient rupturing of outer membrane. In this case swelling of AcDiSol® was reduced due to competition of its carboxylic groups with highly soluble drug for free water (Bussemer et al., 2003b). In addition, dissolved drug layer and probably sugar core have low mechanical

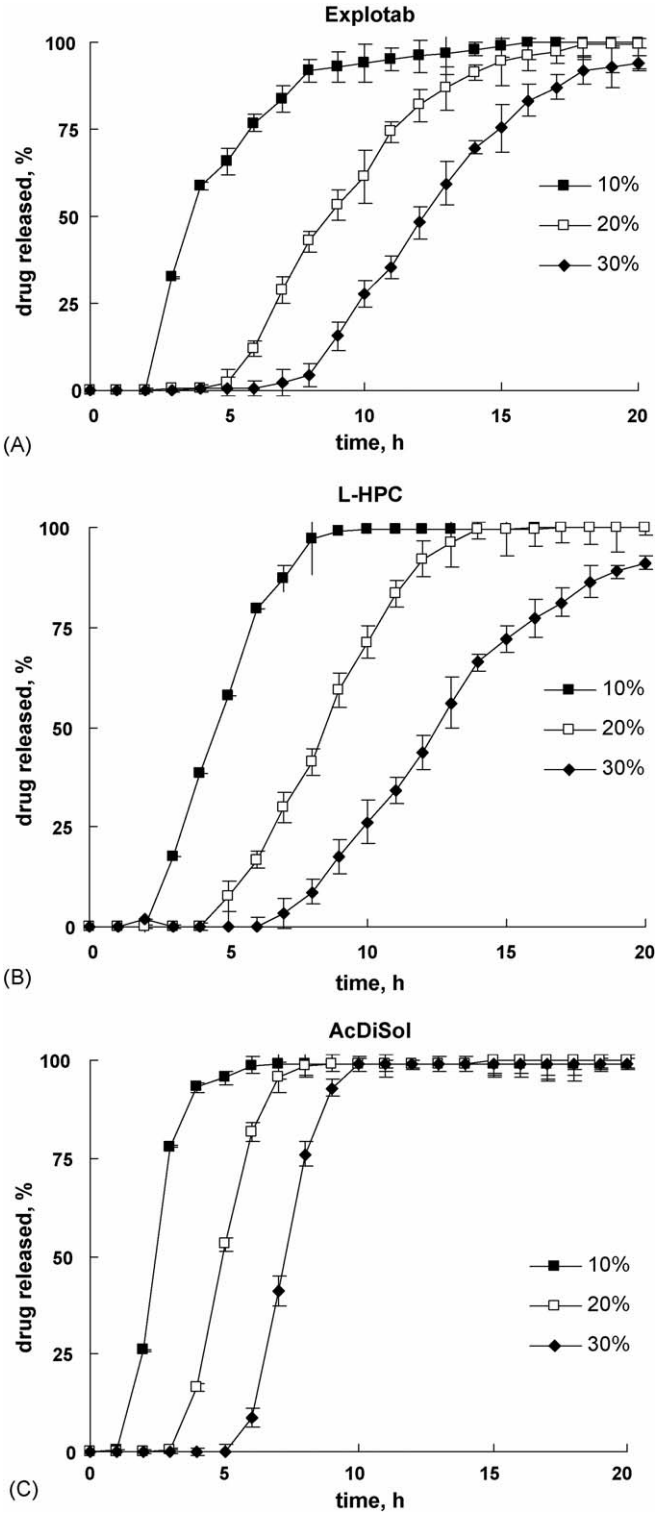

Fig. 1. Drug release from theophylline layered (10%, w/w) sugar cores layered with 26% (w/w): (A) Explotab®, (B) L-HPC or (C) AcDiSol®, coated with 10, 20 and 30% (w/w) Aquacoat® ECD, 25% (w/w) TEC, 10% (w/w) talc.

resistance and swelling pressure towards the outer membrane is again diminished.

A clear lag time, rupturing of membrane and complete release was achieved by increasing the coating level of AcDiSol® from 26 to 48% (w/w) (Fig. 5). Therefore, to achieve typical pulsatile

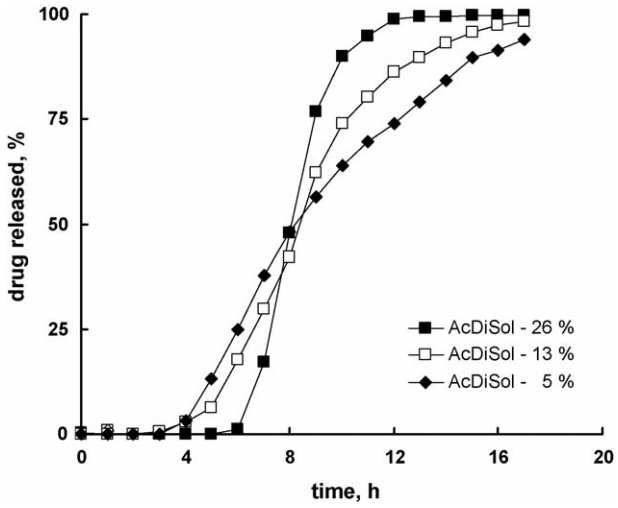

Fig. 2. Effect of AcDiSol® amount on theophylline release from pellets layered with different amount of AcDiSol® and coated with 30% (w/w) Aquacoat® ECD, 25% (w/w) TEC, 10% (w/w) talc.

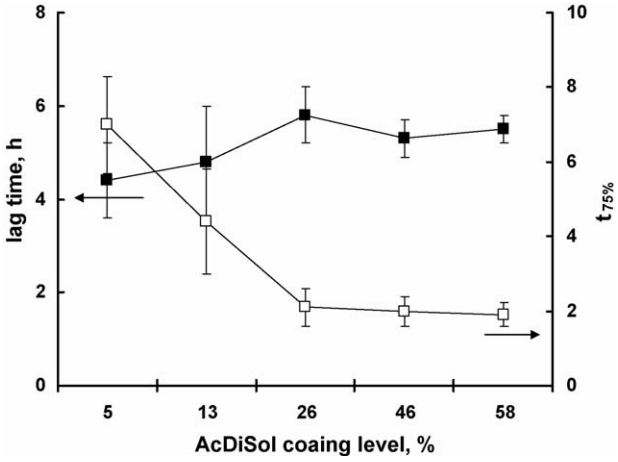

Fig. 3. Effect of AcDiSol® amount on lag time and $t_{75\%}$ of pellets coated with 30% (w/w) Aquacoat® ECD, 25% (w/w) TEC, 10% (w/w) talc.

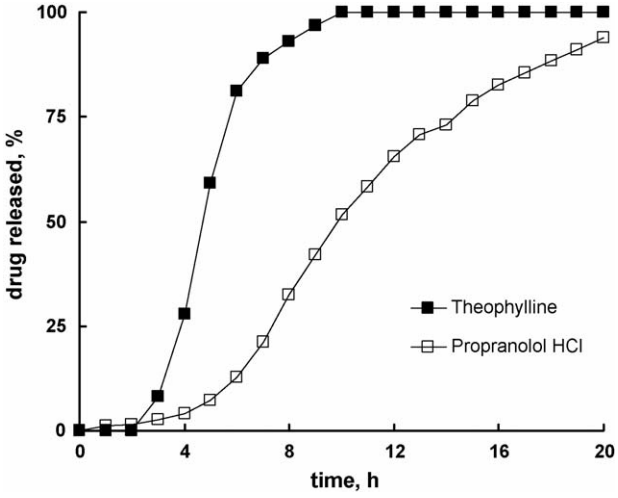

Fig. 4. Theophylline and propranolol HCl release from pellets layered with 26% (w/w) AcDiSol® and coated with 20% (w/w) Aquacoat® ECD, 25% TEC, 10% (w/w) talc.

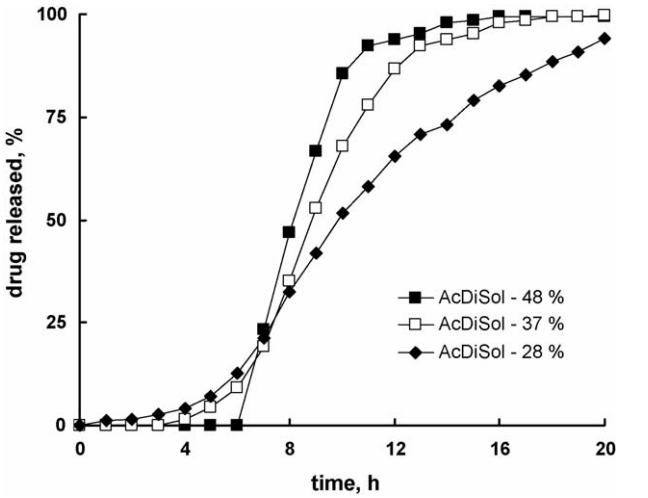

Fig. 5. Effect of AcDiSol® amount on propranolol HCl release from pellets coated with 30% (w/w) Aquacoat® ECD, 25% (w/w) TEC, 10% (w/w) talc.

release profile generally higher level of swelling agent could be recommended for highly water soluble drugs, compared with poorly soluble.

3.2. Outer membrane

Besides the water permeability, the mechanical properties of the outer membrane are very important for the performance of the pulsatile system. In general, mechanically weak and non-flexible films are suitable, while highly flexible films expand and often do not rupture during release test (Bussemer et al., 2003c).

3.2.1. Composition of outer membrane

Aquacoat® ECD was selected to form the outer membrane, because of the brittleness of the membrane prepared therefrom (Paeratakul and Bodmeier, 1994), which is advantageous for completeness of the rupturing. From another hand, plasticizers, usually added to ensure the film formation, improve flexibility of the films. Therefore plasticizer content should be carefully selected.

Immediate release was achieved for all coating levels with low amount of TEC (10%, w/w), because of not sufficient film formation (Fig. 6A). On the contrary, high amount of TEC (35%, w/w) results in flexible, not rupturable (under given conditions) films and therefore very slow release at coating levels over 20% (w/w) (Fig. 6C). As an optimal plasticizer amount for investigated system seems to be 25% (w/w) of TEC, because of sufficient film formation (ensure integrity of the dosage form during the lag time) and with suitable mechanical properties (brittleness) to achieve complete rupturing. Drug release was typically pulsatile and lag time can be controlled by coating level (Fig. 6B).

The lag time was shorter and the release was slightly quicker (lower $t_{75\%}$) using a water soluble plasticizer TEC, compared to water insoluble DBS (Table 1). This is because of complete leaching of TEC from Aquacoat® ECD films in the dissolution medium, which affects the permeability and the

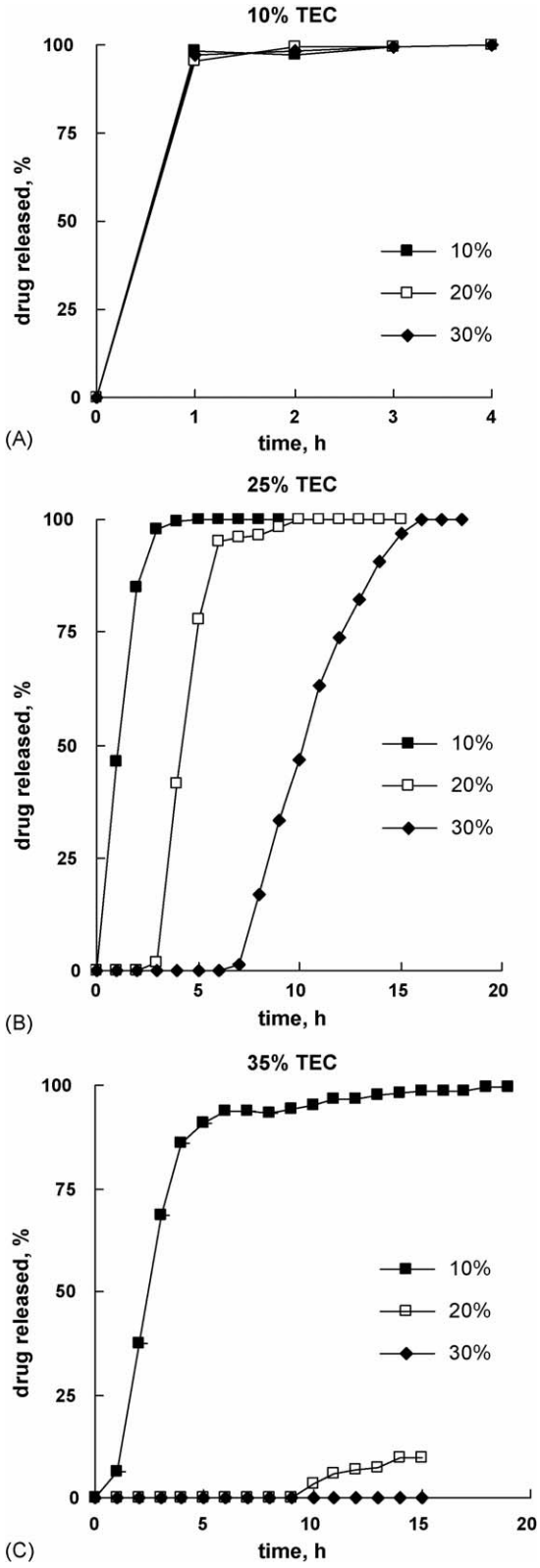

Fig. 6. Theophylline release from pellets layered with 26% (w/w) AcDiSol® and coated with different coating level of Aquacoat® ECD with addition of (A) 10%, (B) 25% and (C) 35% (w/w) TEC.

Table 1
Lag time and $t_{75\%}$ during theophylline release from pellets layered with 26% (w/w) AcDiSol® and coated with Aquacoat® ECD, with/without talc, plasticized with 25% (w/w) TEC or DBS

Coating level (%, w/w)	10% (w/w) talc				No talc	
	TEC		DBS		TEC	
	Lag time (h)	$t_{75\%}$ (h)	Lag time (h)	$t_{75\%}$ (h)	Lag time (h)	$t_{75\%}$ (h)
10	1.4 (0.6)	1.6 (0.9)	2.2 (0.5)	1.9 (0.9)	2.1 (0.7)	1.8 (0.8)
20	3.8 (1.2)	1.9 (0.7)	5.1 (0.9)	2.0 (0.8)	4.4 (1.0)	2.9 (0.9)
30	6.1 (0.5)	2.1 (0.5)	7.1 (1.6)	2.8 (1.2)	7.0 (1.8)	4.2 (1.5)

m.v. (S.D.), $n = 3$.

mechanical properties of the polymeric coating during dissolution (Paeratakul and Bodmeier, 1992).

The outer membrane became more brittle by addition of 10% (w/w) of talc (based on the total solid content of dispersion), indicated by reduced puncture strength and elongation (Table 2). Therefore lag time of the pellets, coated with Aquacoat® ECD by addition of the talc, decreased and the following release was faster (Table 1). Addition of the talc is very advantageous because lag time is less sensitive to variations in the coating level and completeness of rupturing.

3.2.2. *Effect of the coating system (aqueous versus organic)*

A higher coating level (20% versus 10%, w/w) was needed by coating with Aquacoat® ECD (25%, w/w TEC) compared to coating with ethanolic Ethocel® 10 solution (plasticized with 5% DBS) to achieve comparable drug release profiles (Fig. 7). This could be explained by higher brittleness (low puncture strength and elongation) of films prepared from aqueous dispersion Aquacoat® ECD compared to films prepared from ethanolic solution of ethylcellulose (Table 2).

The importance of the brittleness of outer membrane could be underlined by comparison of different molecular weights of ethylcellulose for outer membrane formation. Drug release decreased after lag time remarkably by increasing of coating level of Ethocel® 10, resulted in mechanically stronger outer membrane (Fig. 8A). Drug release was extremely slow in case of coating with higher molecular weight ethylcellulose—Ethocel® 100 (Fig. 8B), due to increased puncture strength and especially elongation of the films in dry and wet state, compared to Ethocel® 10 films (Table 2).

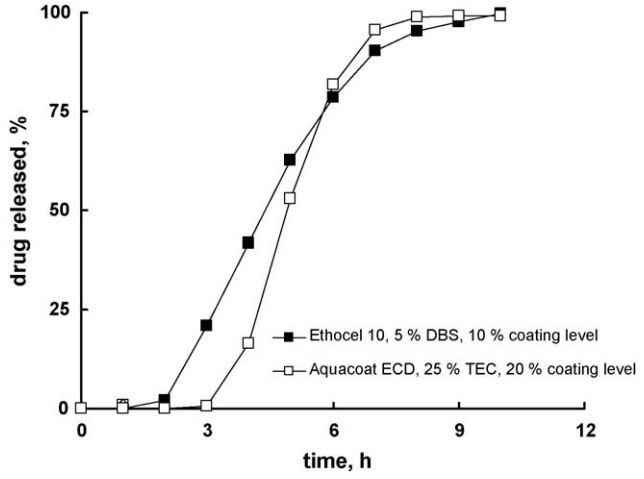

Fig. 7. Theophylline release from pellets layered with 26% (w/w) AcDiSol® and coated with Ethocel®, 5% (w/w) DBS—coating level 10% (w/w) or with Aquacoat® ECD, 25% (w/w) TEC, 10% (w/w) talc—coating level 20% (w/w).

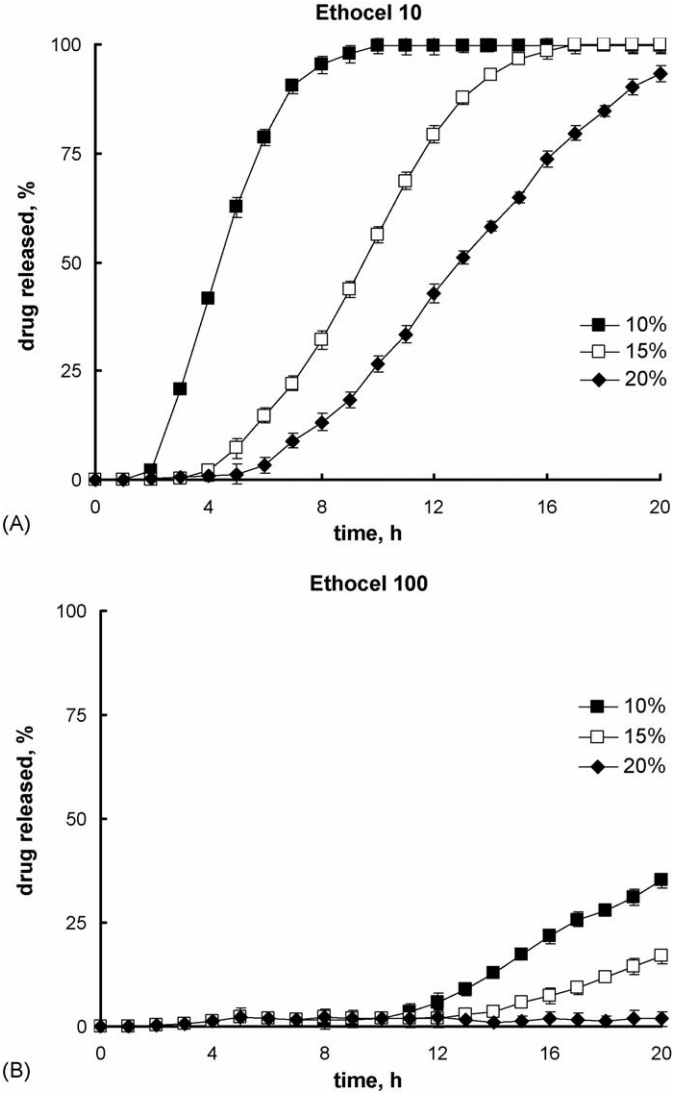

Fig. 8. Drug release from theophylline pellets layered with 26% (w/w) AcDiSol® and coated with different coating level of Ethocel® 10 or Ethocel® 100, both plasticized with 5% DBS.

Table 2
Mechanical properties of ethylcellulose films in the dry and wet state (1 h incubation in 0.1N HCl, 37 °C)

Film formulation	Solvent system	Films thickness (μm)	Puncture strength (MPa)		Elongation at break (%)	
			Dry state	Wet state	Dry state	Wet state
Ethocel 10, 5% DBS	Organic	112 (04)	16.2 (5.7)	7.7 (0.9)	7.1 (1.6)	5.8 (1.1)
Ethocel 100, 5% DBS	Organic	115 (18)	38.2 (3.2)	28.7 (0.9)	32.6 (6.4)	49.5 (12.7)
Aquacoat® ECD, 25% TEC	Aqueous	216 (28)	3.7 (2.3)	0.8 (0.5)	0.7 (0.2)	0.7 (0.5)
Aquacoat® ECD, 25% TEC, 10% talc	Aqueous	226 (14)	1.2 (2.3)	0.4 (0.8)	0.2 (0.1)	0.4 (0.5)

m.v. (S.D.), $n = 6$.

3.3. Microscopical observation during release

Very clear correlation between rupturing time and drug release onset was seen, by microscopical observation of the individual pellets during the release. Drug release onset and first cracks on the surface of the outer membrane were observed after 2 h (Fig. 9). This stage corresponds to the pressure exerted by the swelling layer exceeds the mechanical resistance of the membrane at the end of the lag time. Progressing water flux into the swelling layer caused a further expansion—the crack spread over the pellet surface after 2.5 h and enlarge after 3 h (Fig. 9b) and drug release was completed within 2 h after lag time (Fig. 9A).

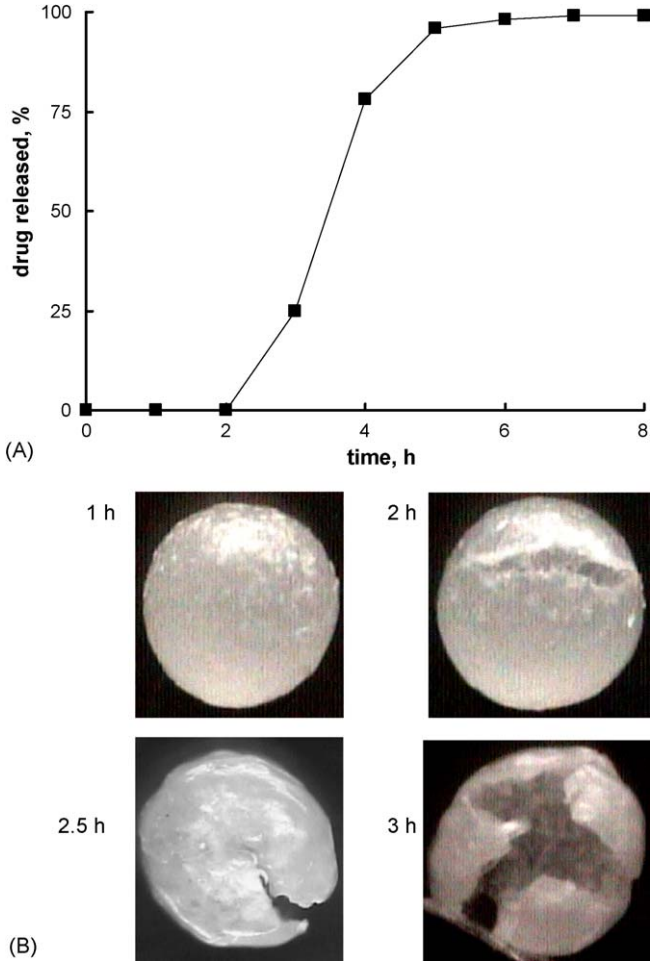

Fig. 9. Theophylline single pellet layered with 26% (w/w) AcDiSol® and coated with 20% (w/w) Aquacoat® ECD, 25% TEC, 10% talc—(A) drug release and (B) microscopic pictures.

4. Conclusion

To achieve pulsatile drug release profile as swelling agent AcDiSol® with minimum layering amount 26% (w/w) was needed for poorly soluble theophylline and 48% (w/w) for highly soluble propranolol HCl. Outer membrane, formed using aqueous dispersion Aquacoat® ECD was brittle and ruptured sufficiently for complete drug release, compared to membrane formed by ethylcellulose from ethanolic solution. The lag time was controlled by coating level. Using water soluble plasticizer (TEC) resulted in slightly shorter lag time and faster release, compared with water insoluble plasticizer (DBS) due to its leaching. Addition of the talc is very advantageous due to reduced sensitivity of lag time to the variations in the coating level and completeness of rupturing. Drug release mechanism controlled by rupturing of outer membrane was confirmed by microscopical observation of pellet behavior during release.

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