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Floating or pulsatile drug delivery systems based on coated effervescent cores

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Abstract

The objective of this study was to develop and evaluate floating and pulsatile drug delivery systems based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating. Preliminary studies identified important core and coating properties for the two systems. The mechanical properties (puncture strength and elongation) of acrylic (Eudragit® RS, RL or NE) and cellulosic (cellulose acetate, ethyl cellulose) polymers, which primarily determined the type of delivery system, were characterized with a puncture test in the dry and wet state. For the floating system, a polymer coating with a high elongation value and high water- and low CO_2 permeabilities was selected (Eudragit® RL/acetyltributyl citrate 20%, w/w) in order to initiate the effervescent reaction and the floating process rapidly, while for the pulsatile DDS, a weak, semipermeable film, which ruptured after a certain lag time was best (ethyl cellulose/dibutyl sebacate 20%, w/w). With the floating system, the polymeric coating did not retard the drug release. A polymer (cellulose acetate or hydroxypropylmethylcellulose) was added to the core to control the drug release. The time to flotation could be controlled by the composition (type of filler, concentration of effervescent agents) and hardness of the tablet core and the composition (type of polymer and plasticizer) and thickness of the coating. For the pulsatile system, a quick releasing core was formulated in order to obtain a rapid drug release after the rupture of the polymer coating. The lag time prior to the rapid drug release phase increased with increasing core hardness and coating level.

Keywords: Coating; Controlled drug release; Effervescence; Floating drug delivery systems; Oral drug delivery; Polymeric films; Pulsatile drug release

1. Introduction

Recent studies in the area of oral controlled drug delivery include novel approaches, which prolong the gastrointestinal residence time (Deshpande et al., 1996) and delivery systems, which release the drug in a pulsatile fashion (Gurny et al., 1993).

The gastrointestinal residence time determines the time period available for drug release from oral controlled release delivery systems within the gastrointestinal tract. Approaches to increase the

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gastrointestinal residence time include: (1) bioadhesive delivery systems, which adhere to mucosal surfaces (Gurny and Junginger, 1990); (2) delivery systems, which increase in size to retard the passage through the pylorus (Asmussen et al., 1995; Becher, 1995; Curatolo and Lo, 1995); and (3) density-controlled delivery systems, which either float or sink in gastric fluids (Moes, 1993; Wong et al., 1993). Floating has been achieved with the preparation of low-density dry solid systems (e.g. inclusion of sponges, highly porous systems) (Müller, 1989; Nakamichi et al., 1996) or with systems, which decrease in density upon contact with gastric fluids based on the expansion of swelling agents (Bolton et al., 1989; Aguadisch et al., 1991) or CO_2 generation (Ichikawa et al., 1987; Sinnreich, 1989).

Pulsatile drug delivery systems are characterized by two release phases, a first phase with no or little drug being released, followed by a second phase, during which the drug is released completely within a short period of time after the lag-time (Gurny et al., 1993). The release can be either time- or site-controlled. The release from the first group is essentially determined by the system, while the release from the second group is primarily controlled by the biological environment in the gastrointestinal tract (e.g. pH or enzymes). Most pulsatile delivery systems are reservoir devices covered with a barrier coating, which dissolves (Poli et al., 1993), erodes (Pozzi and Furlani, 1992; Phuapradit et al., 1995) or ruptures (Ueda et al., 1994) after a certain time period, followed by rapid drug release from the reservoir (Minoru et al., 1995). Several single-unit pulsatile dosage forms with a capsular design have been developed, releasing the drug in a pulsatile fashion either after ejection or erosion of a plug or a capsule half (McNeil et al., 1990; Wong et al., 1995; Bodmeier and Krögel, 1997; Krögel and Bodmeier, 1998).

Reservoir-type delivery systems based on the expansion of the core have been evaluated for both floating delivery systems having a lower density than gastrointestinal fluids, and for pulsatile systems in which the core expansion causes rupturing of the coating to allow rapid drug release (Schultz and Kleinebudde, 1997). The objective of this work was to develop floating and pulsatile systems, whereby the expansion was based on an effervescent core (Krögel and Bodmeier, 1996, Krögel and Bodmeier, 1997). Ideally, the expansion of the core could result in (1) a floating dosage form with a prolonged residence time and extended drug release or in (2) a pulsatile dosage form, in which the drug is released rapidly in a time-controlled fashion after rupturing of the coating. In order to achieve these goals, the properties of the effervescent core and the coating were investigated and optimized.

2. Materials and methods

The following chemicals were obtained from commercial suppliers and used as received: chlorpheniramine maleate (CPM; Dolorgiet, Germany), granulated lactose (Tablettose® 80, Meggle, Wasserburg, Germany), microcrystalline cellulose (Avicel® PH102, FMC/Lehmann & Voss, Hamburg, Germany), dibasic calcium phosphate (Emcompress®, Mendell, Patterson, USA), hydroxypropyl methylcellulose (HPMC; Methocel® K4M, Colorcon, Orpington, UK), polyethylene glycol (PEG 1500 and 4000; BASF, Ludwigshafen, Germany), cellulose acetate (CA-398-10, Eastman Fine Chemicals, Kingsport, TN, USA), Eudragit® RS 100 or Eudragit® RL 100 (poly(ethylacrylate-methylmethacrylate-trimethylammoniumethyl-methacrylate chloride)), Eudragit® NE 30 D (aqueous dispersion of poly(ethylacrylate-methylmethacrylate); Röhm, Darmstadt, Germany), ethyl cellulose (Ethocel® 7, Dow Chemical, Midland, USA), acetyltributyl citrate (ATBC), triethyl citrate (TEC) (Morflex, Greensboro, USA), dibutyl sebacate (DBS; Henkel, Düsseldorf, Germany), anhydrous citric acid, sodium bicarbonate ($NaHCO_3$; Merck, Darmstadt, Germany), ethanol, acetone, isopropyl alcohol (Sigma–Aldrich, Deisenhofen, Germany).

The components (passed through a 315-μm sieve) were weighed and mixed in a Turbula®-blender (W.A. Bachhofen Maschinenfabrik, Basel, Switzerland) for 15 min. The tablets (diameter, 9 mm; convex-shaped; weight, 250–350

mg; hardness, 30, 50, 60 and 100 N) were compressed with a single punch press (EK0, Korsch, Berlin, Germany). Paraffin was used as an outer lubricant to avoid sticking of the tablets to the punches. The core of the one-layer floating system contained 50 mg CPM, lactose, effervescent agents and PEG 4000 in varying concentrations.

Two-layer floating tablets were prepared by compressing the first layer, followed by hand-filling of the second layer onto the pre-compressed first layer and compression into the final tablet. The first layer (200 mg) of the two-layer tablets consisted of 50 mg chlorpheniramine maleate, either cellulose acetate or HPMC (10, 30 or 50% (w/w) based on the weight of the layer) as retarding agent, and PEG 4000 q.s. to 200 mg and the second layer (100 mg) consisted of effervescent agents and PEG 4000 (4%, w/w, based on the weight of the layer).

The standard formulations for the pulsatile tablets were 50 mg chlorpheniramine maleate, 30 or 50% (w/w) effervescent agents ($NaHCO_3$:citric acid, 1:0.76), PEG 4000 (4%, w/w, based on the total core weight) and either lactose or microcrystalline cellulose as filler. For comparison, a batch without effervescent agents was prepared.

For preliminary coating and screening studies, the cores were dip-coated with organic polymer solutions (15%, w/v). The tablet cores were completely dipped into the polymeric solution and were dried after each dipping step (three to four steps) with a hair-dryer. Eudragit® RS 100 and RL 100 were dissolved in isopropanol, cellulose acetate in acetone, ethyl cellulose in ethanol, and Eudragit NE 30 D was lyophilised and then dissolved in acetone. Alternatively, the cores (drug-containing cores plus placebos with a total weight of 20 g) were spray-coated in a self-built pan device (consisting of a rotary evaporator and a cut round glass flask, which was used as the pan) with the organic polymer solution (Eudragit® RS and RL 15%, w/w, and 20%, w/w, plasticizer based on the polymer) using an automatic spray gun (Walther, Wuppertal, Germany; 1.2-mm nozzle; atomising air pressure, 1.2 bar; temperature, 25–30°C; heated with an IR lamp). The coating level in percent (w/w) was determined from the weight gain of ten placebo tablets, which were coated at the same time.

The cores for the pulsatile system were coated with an ethanolic ethyl cellulose (10%, w/v) solution, 20% (w/w) dibutyl sebacate based on the polymer weight) in a Glatt lab-coater (GC 300, Glatt Maschinen- und Apparatebau, Pratteln, Switzerland). The coating conditions were: air inlet temperature, 40–45°C; outlet temperature, 26–30°C; air flow, 110 m^3/h; pan speed, 10 rpm; nozzle diameter, 1.2 mm; atomising air pressure, 1.1 bar; spray rate, 40 g/min).

Polymer films were prepared by casting the organic polymer solution onto Teflon frames mounted on levelled glass plates (area of casting, 12.0×12.0 cm^2; standard formulation, polymer, 6 g; plasticizer, 1.2 g (20%, w/w, based on the polymer); solvent, 40 ml (ethanol for Eudragit® RS and RL and ethyl cellulose and acetone for cellulose acetate and lyophilised Eudragit® NE). The films were dried for 48 h at room temperature, then peeled from the Teflon plate and stored at room temperature at 52% RH for 48 h and cut into pieces of 4×4 cm^2. The exact film thickness (300–400 μm) was measured at five points with a thickness gauge Minitest 600 (Erichsen, Hemer, Germany). For the preparation of wet films, the dry films were put into bags (7×7 cm^2, made from a 40-mesh plastic screen with three sides sewn closed) to avoid sticking and folding of the films in the medium. The bags with the films were then placed in 0.1 N HCl and shaken in a horizontal shaker (GFL® 3033, Gesellschaft für Labortechnik, Burgwedel, Germany; 37°C, 70 rpm, 24 h).

The mechanical properties of the films in the dry and wet state were measured by a puncture test with an Instron® 4466 (Instron Wolpert, Ludwigshafen, Germany) using a Teflon probe (hemispherical end; diameter, 5 mm; length, 50 mm). The load at break and the maximum displacement of the film samples were measured, and then converted to puncture strength (MPa) and elongation at puncture (%). A detailed description of the puncture test has been published previously (Bodmeier and Paeratakul, 1993, 1994). The mechanical properties in the dry and wet state were determined with different polymers (Eudragit® RS100, RL100, lyophilized NE 30D, ethyl cellulose, cellulose acetate) and plasticizers (TEC, ATBC and DBS) ($n = 4$).

The time to flotation and the drug release were evaluated with a USP XXIII paddle dissolution apparatus (Vankel VK800, Vankel Industries, Edison, NJ, USA) (500 ml 0.1 N HCl, 37°C, 50 rpm, $n = 3$). The time to flotation and the lag time were both determined visually. The time to flotation was the time at which the dosage form started to float. The lag time was equated with the time at which CO_2 bubbles appeared from the coated dosage form or it was obtained from dissolution curves. Samples were withdrawn after predetermined time intervals, not replaced with medium, and the chlorpheniramine maleate concentration was measured after appropriate dilution with a spectrophotometer (Shimadzu UV-2101PC, Shimadzu Europa, Duisburg, Germany) at $\lambda = 261$ nm.

3. Results and discussion

For the development of floating or pulsatile systems based on coated effervescent cores, several preliminary studies were necessary to identify core and coating components resulting in the desired system properties.

Rapid expansion and formation of a low-density system within minutes after contact with gastric fluids were required to obtain a suitable floating dosage form. Citric acid and $NaHCO_3$ were used in the drug-containing core in the optimal stoichiometric ratio of 0.76:1 (Anderson et al., 1982). In contact with the dissolution medium, these two agents generate CO_2, which accumulates under the surrounding polymeric coating and results in its expansion.

First, properties of the core (type of filler, concentration of the effervescent agents and tablet hardness) were investigated. The influence of three commonly used fillers, microcrystalline cellulose, dibasic calcium phosphate and lactose, on the floating behaviour of the coated tablets was investigated. Drug-free cores with 20% (w/w) effervescent agents and 80% (w/w) filler were prepared and coated with Eudragit® RL 100, Eudragit® RS 100, cellulose acetate and ethyl cellulose. Tablets containing lactose floated earlier than tablets prepared with the inorganic filler dibasic calcium phosphate (data not shown). This could be explained by the different densities, lactose-containing tablets had the lowest density (1.0 g/cm^3 at a hardness of 30 N), whereas the dibasic calcium phosphate tablets had a much higher density (1.9 g/cm^3 at a hardness of 30 N). In addition, lactose has a higher water solubility and thus osmotic activity, resulting in a faster uptake of the medium into the core by diffusion through the coating. Microcrystalline cellulose, an insoluble filler with a high water uptake and disintegration capability, resulted in the rupturing of the coating and disintegration of the tablet. CO_2 did not accumulate under the coating and escaped through the ruptured films, floating was therefore not achieved. Based on these results, lactose was identified as the filler of choice and used for further investigations.

Increasing the concentration of effervescent agents in Eudragit® NE30D-coated cores from 20 to 50% (w/w) decreased the time to flotation from 3 min to less than 1 min because of a faster and higher CO_2 generation (data not shown). However, at high concentrations of the effervescent agents, the coating was less stable due to the increased inner pressure, and the risk of rupturing of the polymeric coating was higher. Besides the concentration of the effervescent agents, the hardness of the tablet core and the coating level also affected the time to flotation (Fig. 1). For example, increasing the hardness from 30 to 130 N

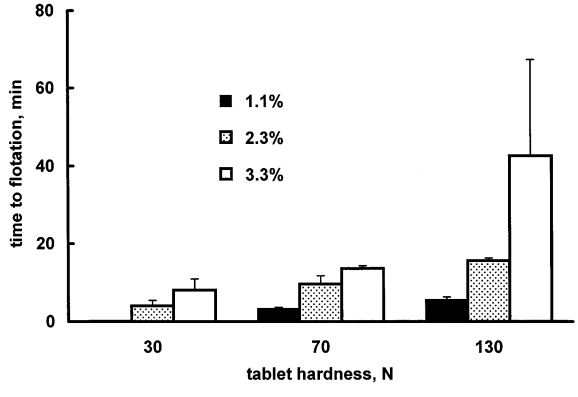

Fig. 1. Effect of tablet hardness and coating level on the time to flotation (coating, Eudragit® RS/ATBC 20%, w/w; core, 20%, w/w, effervescent agents).

Table 1
Mechanical properties of different polymer films (20%, w/w, plasticizer based on the polymer) in the dry and wet state; in parenthesis coefficient of variation in%; $n = 4$); film thickness approx. 350 μm

Polymer/plasticizer	Elongation at break (%)		Puncture strength (MPa)	
	Dry	Wet	Dry	Wet
Eudragit NE	152.76 (5.68)	196.44 (9.50)	3.94 (9.90)	2.23 (11.81)
Eudragit RL/TEC	35.11 (4.98)	11.61 (27.39)	2.35 (8.70)	0.74 (30.78)
Eudragit RL/ATBC	17.64 (5.12)	49.61 (14.39)	3.96 (3.67)	0.02 (68.41)
Eudragit RS/TEC	65.40 (5.07)	51.10 (4.84)	2.02 (11.40)	1.24 (4.71)
Eudragit RS/ATBC	40.95 (5.24)	77.30 (12.81)	3.20 (4.31)	1.26 (10.66)
Cellulose acetate	11.47 (31.02)	15.23 (64.47)	15.07 (27.35)	7.11 (24.31)
Ethyl cellulose/TEC	2.86 (9.30)	5.80 (26.15)	2.59 (12.00)	2.89 (28.56)
Ethyl cellulose/DBS	0.28 (22.66)	1.38 (33.20)	0.21 (11.60)	0.24 (39.45)

resulted in an increase in the time to flotation from 8 to 42 min at a coating level of 3.3% (w/w). A lower hardness resulted in tablets with a higher porosity, which facilitated the water penetration and therefore the effervescent reaction. In addition, the initial density of the softer tablets was lower. As expected, increasing the coating level increased the time to flotation.

Besides the tablet core formulation, the polymeric coating, in particular its permeability and mechanical properties, has a major impact on the performance of the delivery system. For the floating system, the ideal coating material should be highly permeable for dissolution or gastric fluids in order to rapidly initiate CO_2 formation and it should be impermeable for the generated CO_2 in the wet state to promote floating. The coating could also act as a rate-controlling membrane for the drug, however, preferably the release retarding effect should be obtained with the core.

Concerning the mechanical properties, the polymer films should be flexible enough in the wet state to avoid rupturing of the coating under the increasing CO_2 pressure. The polymers investigated in this study are widely used in the coating of solid dosage forms and were either of acrylic (Eudragit® RS 100, Eudragit® RL 100 and lyophilised Eudragit® NE 30 D) or cellulosic nature (cellulose acetate and ethyl cellulose). The elongation and puncture strength of dry and wet polymeric films with different plasticizers (TEC, ATBC or DBS) were investigated with a puncture test (Table 1). Films prepared from Eudragit® NE 30D resulted in high elongation values in both the dry and wet state. This polymer dispersion has a low minimum film formation temperature, does not require plasticizers and results in flexible films. Films prepared with Eudragit® RS or RL 30D and plasticized with the water-soluble TEC had higher elongation and lower puncture strength values (lower moduli) in the dry state when compared to films plasticized with the water-insoluble ATBC. In the wet state, the films were hydrated, water acted as an additional plasticizer. Hence, the values for puncture strength were lower when compared to the values of the dry state. Eudragit® RL has twice as many quaternary ammonium groups as Eudragit RS, the RL films were highly hydrated and swollen and therefore had lower elongation values than RS films. With Eudragit RS films, the water-soluble plasticizer, TEC, leached into the medium resulting in less flexible films when compared to films containing ATBC, a water-insoluble plasticizer, which remained in the film. Films plasticized with water-soluble plasticizers are therefore more permeable for the aqueous medium, but should rupture earlier than films prepared with water-insoluble plasticizers.

The cellulosic polymers were not suitable candidates for the floating delivery system. Cellulose acetate is a mechanically strong polymer, it was too rigid (puncture strength in the wet state, 7.11 MPa) and did not expand to a large extent in contact with dissolution media (elongation, 15.23%). Ethyl cellulose (plasticized with 20%, w/w, DBS) is a mechanically weak polymer (punc-

ture strength, 0.24 MPa), it was not flexible (elongation, 1.38%) and easily ruptured upon CO_2 formation, bubbles were released rapidly after the burst of the coating. In summary, the elongation of cellulose acetate and ethyl cellulose films in the wet state was much lower when compared to the elongation of the acrylic polymers, which were therefore further investigated. Parallel to the puncture test, tablet cores were dip-coated with organic solutions of the above-mentioned polymer–plasticizer combinations. The floating behaviour was evaluated in aqueous medium and confirmed the finding of the puncture test that the acrylic polymers were more suitable for the floating drug delivery system.

Based on these results, the time to flotation of various systems, which depends primarily on the rate of water penetration through the coating and the subsequent CO_2 formation, was visually determined. The time to flotation decreased with increasing Eudragit® RL content in Eudragit® RS/RL coatings (Fig. 2) and was longer with coatings containing ATBC as plasticizer than with coatings containing TEC (Fig. 3). As mentioned above, Eudragit® RL has twice as many quaternary ammonium groups and is more hydrophilic than Eudragit® RS. It therefore hydrated faster and resulted in a shorter time to flotation. The choice of the plasticizer not only affected the mechanical properties but also affected the time to flotation. Films prepared with the hydrophilic plasticizer, TEC, had a shorter time to flotation

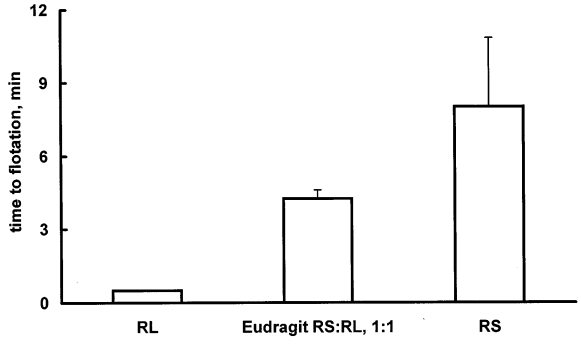

Fig. 2. Influence of the ratio of Eudragit® RS 100:RL 100 (20% ,w/w, ATBC; 3.4%, w/w, coating level) on the time to flotation (core, 20%, w/w, effervescent agents, 30 N).

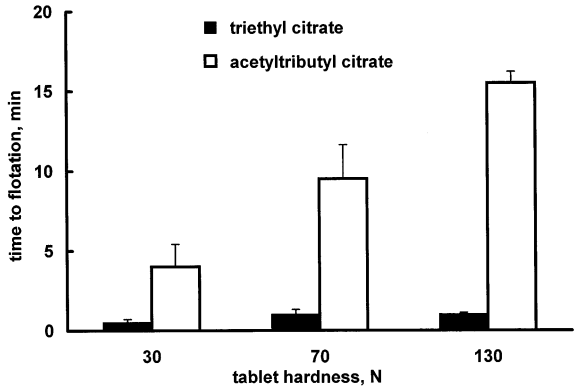

Fig. 3. Effect of type of plasticizer on the time to flotation (coating, Eudragit® RS 100, 2.0%, w/w, coating level; core, 20%, w/w, effervescent agents, 30 N).

because of the more hydrophilic nature of the films when compared to films containing the lipophilic plasticizer, ATBC. However, as reported above, TEC films were mechanically weaker in the wet state than ATBC films and therefore had a higher tendency to rupture upon CO_2 formation. Since the film integrity is of utmost importance for the floating system, ATBC was chosen as the plasticizer for Eudragit® RS/RL coatings.

The third acrylic polymer, Eudragit® NE (poly(ethylacrylate-methylmethacrylate)), which forms highly flexible films in the dry and wet state (Bodmeier and Paeratakul, 1994), was investigated as coating material of an effervescent core. Eudragit® NE-coatings were not permeable enough for the dissolution medium, the tablets did not float within a reasonable time period (< 15 min). PEG 1500, a water-soluble pore former, was added to increase the water permeability of the coating in order to shorten the time to flotation. PEG 1500 at a level of 15% (w/w) (based on the polymer) resulted in a still too long time to flotation (approx. 25 min), while PEG 1500 in excess of 30% decreased the time to flotation to less than 10 min. In practice, the tablets started to float rapidly, but because of the porous nature of the coating caused by the leaching of PEG 1500, the generated gas escaped and the tablets sank after a short time period of flotation. Eudragit® NE was therefore not further investigated.

Although rapid time to flotation was obtained after optimizing the core and coating formulation, the drug release was too fast and complete within 30 min (Fig. 4, one-layer tablet). A rapid water penetration of the coating resulted in a short time to flotation; however, the coatings were also highly permeable for the drug. The drug release could therefore not be controlled through the polymeric coating, but had to be controlled through the tablet core.

A two-layer tablet consisting of a drug-containing matrix layer, which retarded the drug release, and a second, effervescent layer, which was responsible for the floating, was prepared. Either the water-insoluble polymer, cellulose acetate (CA), or a high-molecular weight hydroxypropyl methyl cellulose (HPMC, Methocel® K4M), a water-soluble polymer frequently used in swellable/gellable sustained release matrix tablets, were evaluated as retarding materials. Increasing the CA content in the matrix core (from 10 to 50%, w/w) decreased the drug release; however, more than 80% drug was already released after only 3 h at a CA level of 50% (w/w) using chlorpheniramine maleate as a water-soluble model drug (Fig. 4A). Most CA layer tablets floated in less than 2 min (Fig. 4B); however, the tablets sank after 2 h because the water-insoluble polymer core did not swell upon uptake of the dissolution medium. The drug release was more retarded with the HPMC two-layer tablets, which also floated within minutes (Fig. 5A, B). Increasing the HPMC concentration decreased the drug release.

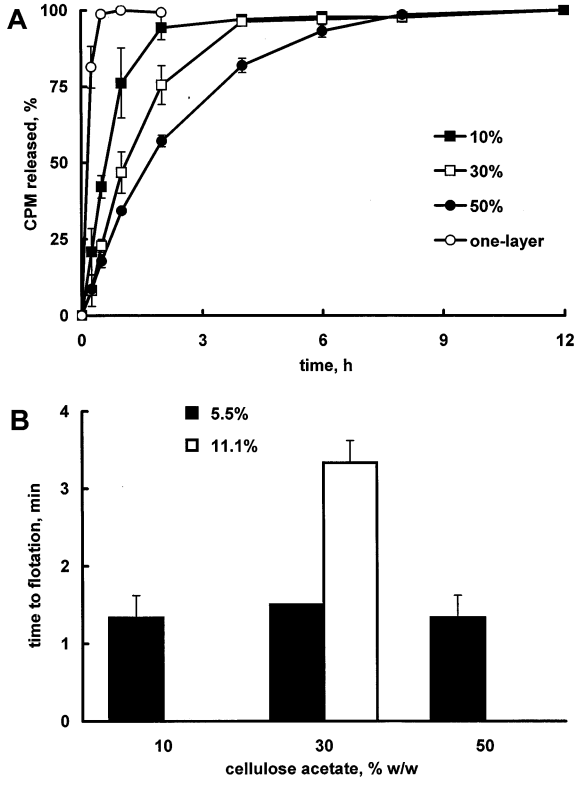

Fig. 4. Effect of the cellulose acetate concentration on (A) the drug release and (B) the time to flotation from two-layer effervescent tablets (coating, Eudragit® RL/ATBC 20%, w/w, 5.5%, w/w, coating level) and comparison to the release of a cellulose acetate-free one-layer tablet.

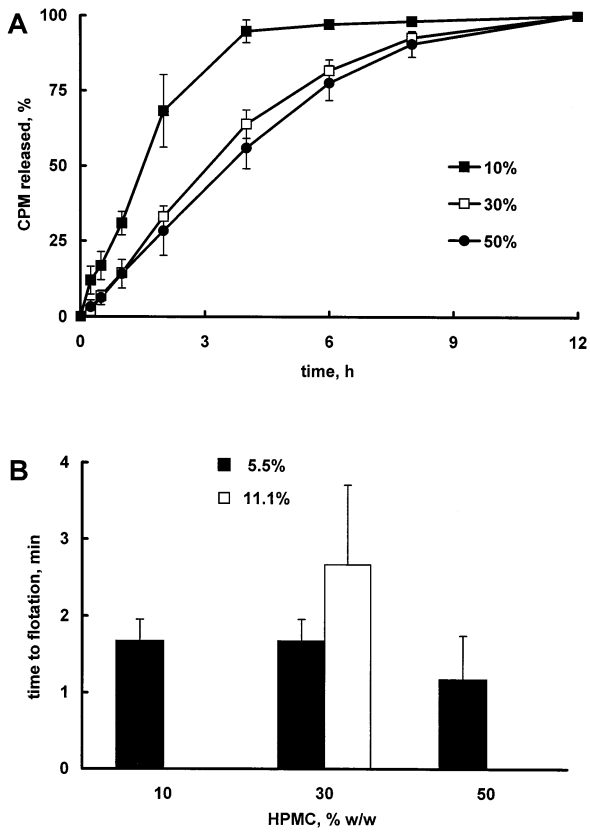

Fig. 5. Effect of the hydroxypropyl methyl cellulose concentration on (A) the drug release (5.5%, w/w, coating level) and (B) the time to flotation from two-layer effervescent tablets (coating, Eudragit® RL/ATBC 20%, w/w, coating level of 5.5 or 11.1%, w/w).

The swelling properties of HPMC supported the system, reaching a lower density as long as the volume expansion was faster than the weight gain. During the dissolution process, the collected CO_2 was displaced by the swollen HPMC and escaped through small fissures in the coating. The HPMC two-layer tablets, therefore, sank after 2–4 h.

In another modification, HPMC was incorporated within the effervescent drug core (single-layer system). The generated CO_2 was not separated from the HPMC layer as with the two-layer system, but was entrapped in the HPMC matrix and could therefore not escape from the gelled matrix. The time to flotation of these tablets was slightly higher than with the two-layer system, which could be explained by a slower CO_2 formation because of the presence of the effervescent agents within the HPMC matrix. Without HPMC, the drug was released completely within 30 min (Fig. 4A), while the inclusion of 10 or 20% (w/w) HPMC significantly retarded the drug release (Fig. 6A). At a 10% HPMC content in the one-layer tablet, the release was slightly faster without effervescent agents in the formulation. The generated gas within the gelled HPMC matrix probably formed an additional diffusion barrier for the drug. As expected, even rupturing of the coating had no influence on the drug release, because the polymeric coating was not a release-controlling barrier. The polymeric film prevented the disintegration of the HPMC tablet in the beginning and ensured gel formation, which was a prerequisite for the retarding effect and for the entrapment of the generated gas. Uncoated tablets rapidly disintegrated prior to gel formation because of the disintegrating effect of the effervescent agents. With increasing coating level, the floating started later due to the delayed water penetration through the thicker coating (Fig. 6B).

Under certain conditions, the polymeric film ruptured as a consequence of the generated CO_2 pressure. Although undesired with floating systems, the rupturing of the coating could be useful for pulsatile systems. For pulsatile delivery, the polymeric coating should burst after a specified time period. When compared to floating systems, immediate CO_2 generation and floating of the device is not needed for pulsatile systems. Ideally, the coating should retard the water uptake of the core and should be impermeable to the drug. After a certain time period, the coating should rupture as a consequence of the effervescent action and the drug should be released rapidly. In principle, polymeric films, which were not suitable for the floating systems because of a slow water penetration and/or a lack of flexibility, should be good candidates for pulsatile systems, while films with a high water penetration, usually combined with a high drug permeability and high flexibility, would not be suitable. The highly permeable Eudragit® RL was therefore not selected for pulsatile systems. Instead, the less permeable Eudragit® RS plasticized with the lipophilic plasticizer, ATBC, and ethyl cellulose plasticized with DBS were investigated.

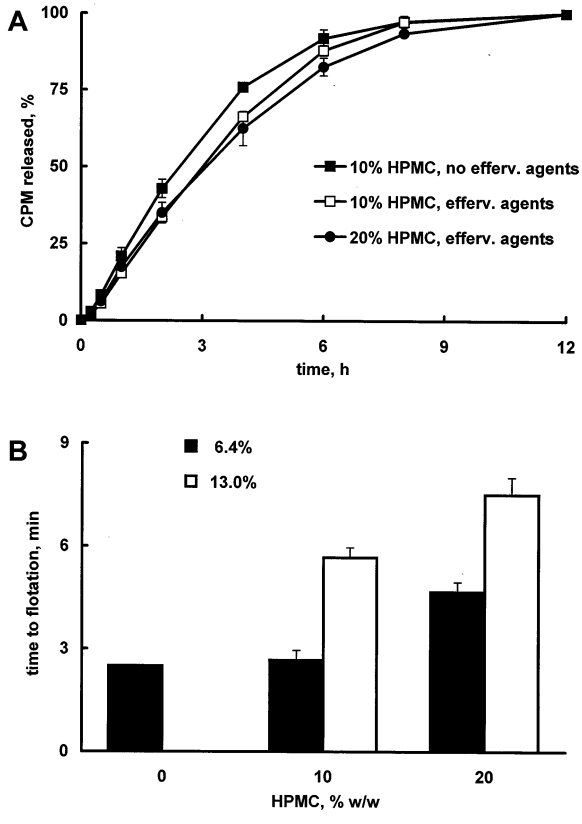

Fig. 6. Effect of the hydroxypropyl methyl cellulose and effervescent agent content on (A) the drug release (6.4%, w/w, coating level) and (B) the time to flotation of one-layer tablets (coating, Eudragit® RL/ATBC 20%, w/w, coating level of 6.4 or 13.0%, w/w).

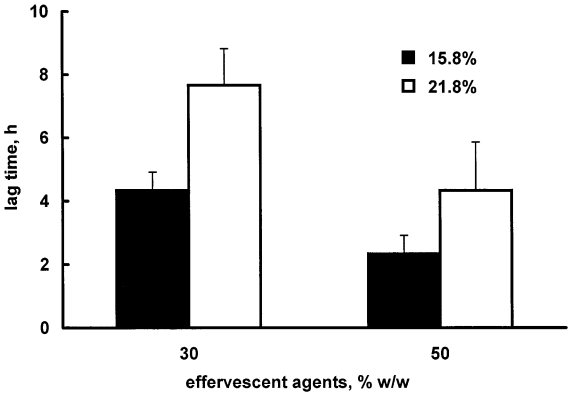

Fig. 7. Effect of the amount of effervescent agents and coating level (15.8 or 21.8%, w/w) on the lag time (coating, Eudragit® RS/ATBC 20%, w/w).

The lag time prior to drug release was a function of the coating and the core. For example, it could be controlled by the coating level and the concentration of effervescent agents in the core (Fig. 7). Increasing the Eudragit RS coating level from 15.8 to 21.8% almost doubled the lag time from approximately 4 to 8 h, while increasing the concentration of effervescent agents from 30 to 50% (w/w) (based on the layer weight) halved the lag time. With 30 or 50% (w/w) of effervescent agents and lactose as inert filler, the release after rupturing of the film was not pulsatile and not reproducible as shown by three individual release curves

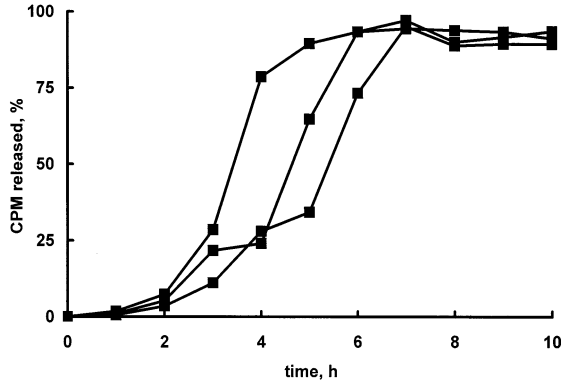

Fig. 8. Individual release profiles of effervescent tablets with a desired pulsatile release (coating, Eudragit® RS/ATBC 20%, w/w; 15.8%, w/w, coating level; core, 50%, w/w, effervescent agents, hardness 60 N, $n = 3$).

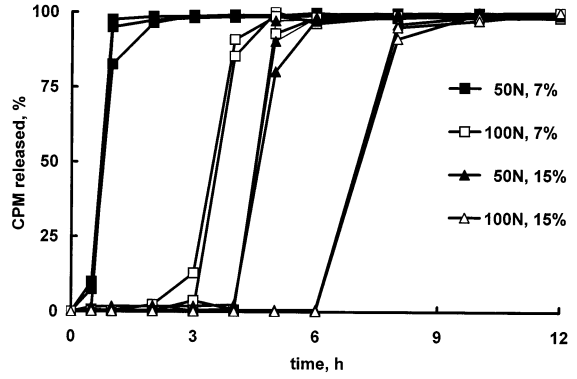

Fig. 9. Influence of the coating level (7 and 15%, w/w) and hardness (50 and 100 N) on the drug release/lag time (coating, EC/DBS; core, 30%, w/w, effervescent agents, microcrystalline cellulose, three replicates shown for each formulation).

(Fig. 8). Although the release profiles of dosage forms coated with Eudragit® RS/ATBC showed the expected lag time, the subsequent drug release was prolonged. The drug release from the core was hindered, because the film ruptured leaving only small fissures as pathways for the drug. Some core contents remained inside the ruptured coat and, after the end of the effervescent reaction, drug diffusion through the partially ruptured coating governed the drug release. Flat-shaped tablets instead of convex-shaped tablets were prepared with the goal to create weak points for easy rupturing at the edges of the tablet, where the coating was thinner. However, the release studies did not show the expected improvement because of the poor reproducibility (data not shown).

Next, another composition consisting of a core of chlorpheniramine maleate, 30% (w/w) effervescent agents and microcrystalline cellulose as an expanding filler, and an ethyl cellulose/DBS, instead of an Eudragit® RS, coating was investigated in order to achieve the pulsatile release profile. Ethyl cellulose plasticized with DBS had the desirable mechanical properties in the wet state for a pulsatile dosage form, it was weak and not flexible (Table 1). Dissolution studies of the coated expanding cores showed a pulsatile release profile. The lag time increased with increasing coating level (30 min at a coating level of 7%, 240 min at 15%) and at a higher core hardness (30 min at 50

N, 180 min at 100 N) (Fig. 9). Moreover, the disintegrant properties of microcrystalline cellulose as inert filler instead of lactose supported the film rupturing. Besides the core composition, also the mechanical properties of the film influenced the release behaviour. The less flexible ethyl cellulose films ruptured at the edge of the tablet upon increasing pressure leaving a wide orifice, whereas the more flexible Eudragit® RS films expanded, leading to only small fissures. The remaining empty ethyl cellulose coating had a shell-like shape. The pulsatile release from ethyl cellulose-coated tablets was also highly reproducible as shown with the three individual release curves for each formulation.

In conclusion, floating or pulsatile drug delivery systems based on effervescent cores were obtained depending on the choice of the polymeric coating and core components.

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