Pulsatile Drug Release from an Insoluble Capsule Body Controlled by an Erodible Plug

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Purpose. The objective of this study was to develop and evaluate a pulsatile drug delivery system based on an impermeable capsule body filled with drug and an erodible plug placed in the opening of the capsule body.

Methods. The erodible plugs were either prepared by direct compression followed by placing the tablets in the capsule opening or by congealing a meltable plug material directly within the capsule opening. The disintegration/erosion properties of these plugs were determined and optimized for the final delivery system. In order to assure rapid drug release of the capsule content after erosion of the plug, various excipients (fillers, effervescent agents) and drugs with different solubilities were evaluated. The lag time prior to drug release and the subsequent drug release were investigated as function of capsule content, plug composition, plug preparation technique, plug hardness, weight, and thickness.

Results. The erosion time of the compressed plugs increased with increasing molecular weight of the hydrophilic polymer (e.g. hydroxypropyl methylcellulose, polyethylene oxide), decreasing filler (lactose) content and decreased with congealable lipidic plugs with increasing HLB-value and inclusion of surfactants. For complete and rapid release of the drug from the capsule body, effervescent agents had to be included in the capsule content. The drug delivery system showed typical pulsatile release profiles with a lag time followed by a rapid release phase. The lag time prior to the pulsatile drug release correlated well with the erosion properties of the plugs and, besides the composition of the plug, could be controlled by the thickness (weight) of the plug.

Conclusions. A single-unit, capsular-shaped pulsatile drug delivery system was developed wherein the pulsatile release was controlled by the erosion properties of a compressed or congealed plug placed within the opening of the capsule opening.

KEY WORDS: controlled release; erosion; hydroxypropyl methylcellulose; lag time; pulsatile release.

INTRODUCTION

Drug delivery systems can be designed to release the drug over time in a linear (e.g. reservoir-systems), non-linear (e.g. matrix systems) or in a pulsatile fashion. With pulsatile systems, the drug is released rapidly within a short period of time after a specified lag time with no or little drug being released (1). Peroral pulsatile dosage forms can be classified into time-controlled or site-controlled delivery systems, with the release from the first group being primarily controlled by the system while the release from the second group is primarily controlled by the biological environment in the gastrointestinal tract (e.g. pH, enzymes). Site-specific delivery to the colon can possibly be achieved by the use of polymers, which are degraded specifically by enzymes present in the colon (2,3).

Most pulsatile delivery systems are reservoir devices covered with a barrier coating. The barrier can dissolve (4), erode (5–7) or rupture during/after a certain period of time, after which the drug is released rapidly from the inner reservoir core. The rupturing of the barrier is induced by an expanding core upon water penetration through the barrier coating. The expansion can be caused by effervescent excipients (8,9) or swelling agents, such as cellulose ethers. The time-controlled explosion system (TES) has a four-layer structure (10–12). The drug is layered on an inner core, followed by a swellable layer (e.g. hydroxypropyl cellulose) and an insoluble polymeric top layer (e.g. ethyl cellulose). Upon water ingress, the swellable layer expands resulting in the rupturing of the outer coating followed by rapid drug release. A three-layer-tablet consisting of two drug-containing layers separated by a drug-free gellable polymeric barrier layer was coated on three sides with an impermeable coating (13). Upon contact with dissolution fluids, the initial dose incorporated into the top layer was released rapidly from the uncoated tablet side. The second pulse in drug release was obtained from the bottom layer after the gelled barrier layer was broken by expanding disintegrants being present in the bottom layer.

Several single unit pulsatile dosage forms with a capsular design have been developed. The Pulsincap™ system consists of a water-impermeable capsule half, filled with the drug formulation (14–17). The capsule half is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution media or gastrointestinal fluids, the plug swells and is ejected from the capsule after a specific time interval, followed by rapid release of the capsule contents. Another delivery system, the Port® system, consists of a gelatin capsule coated with a semipermeable membrane, an insoluble plug and an osmotic charge within the capsule shell (18). In contact with aqueous media, water diffuses across the semipermeable membrane, resulting in an increasing inner pressure and ejection of the plug after a certain lag time. In the Chronset® system from Alza, the driving force for the drug release is an osmotically active compartment in the semipermeable cap, which pushes the capsule cap off the capsule body after a predetermined time interval (19).

The objective of the present study was to develop and evaluate an alternative pulsatile drug delivery system consisting of an impermeable capsule body and an erodible plug, which was either formed by compression or from a melt (20). A system based on a compressed plug consisting mainly of lactose and additives like polyvinylpyrrolidone, magnesium stearate or Eudragit® L100-55 has been described in the patent literature (21). Ideally, the drug would be released after complete erosion of the plug, with the lag time prior to drug release being controlled by the rate of erosion of the plug material.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as received: ibuprofen and chlorpheniramine

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maleate (CPM, Dolorgiet GmbH, Bonn, Germany), pseudoephedrine HCl (PSE, Moeller New Chemic, Xinjiang, China), hydroxypropyl methylcellulose (HPMC, Methocel® E3, E5, K4M, K15M, K100M, Colorcon Limited, Orpington, UK), polyvinyl alcohol (PVA, Mowiol® 40-88, Hoechst, Frankfurt, Germany), polyethylene oxide (PEO, Polyox® K100 and K8000, Union Carbide, Danbury, CT, USA), lactose (Tablettose® 80, Meggle, Wasserburg, Germany), saturated polyglycolated glycerides (Gelucire® 44/14 and 50/13, Gattefossé s.a., Saint Priest, France), distilled glyceryl monooleate (Myverol® 18-99, Eastman Fine Chemicals, Kingsport, TN, USA), Tween® 80 and Tween® 60 (polyethylenglycol sorbitan fatty acid ester, Atlas Chemie, Essen, Germany), Pluronic® F-68 (polyoxyethylene-polyoxypropylene block polymer, Serva Feinbiochemica, Heidelberg, Germany), sodium dodecyl sulfate (SDS, E. Merck, Darmstadt, Germany), bile salts (approx. 50% sodium cholate and 50% sodium deoxycholate, Sigma-Aldrich Chemie GmbH, Deisenhofen, Germany), sodium bicarbonate, anhydrous citric acid, (E. Merck, Darmstadt, Germany), mannitol and dextrose (Roquette, Lestrem, France), microcrystalline cellulose (Avicel® PH-102), Ac-Di-Sol® (cross-linked carboxymethylcellulose sodium) (FMC Corporation c/o Lehmann und Voss, Hamburg, Germany), dibasic calcium phosphate (Emcompress®, E. Mendell Co., Inc., Patterson, USA), polypropylene capsules with an inner diameter of 8 mm and a volume of 1.5 ml (Eppendorf-Netheler-Hinz-GmbH, Hamburg, Germany), Eudragit® RS 100 or RL 100 [poly (ethylacrylate-methylmethacrylate-trimethylammoniumethyl-methacrylate chloride)], Eudragit® NE 30 D [poly (ethylacrylate-methylmethacrylate)] (Röhm GmbH, Darmstadt, Germany), acetyltributyl citrate (ATBC, Morflex, Inc., Greensboro, USA), magnesium stearate, talc, isopropyl alcohol, methylene chloride (Sigma-Aldrich Chemie GmbH, Deisenhofen, Germany).

Methods

Filling of the Capsule Bodies

The drug and excipients were sieved (315 μm sieve), blended in a Turbula®-mixer (W.A. Bachhofen Maschinenfabrik, Basel, Switzerland) for 15 min followed by hand-filling the capsule bodies up to the top. The drug content was 10% w/w (total fill weight: 400–600 mg). To investigate the influence of effervescent agents on the drug release, 10 or 20%w/w $NaHCO_3$: citric acid (1:0.76 w/w) were mixed with lactose and 50 mg chlorpheniramine maleate to a total fill weight of 600 mg.

Preparation of Compressed Plugs

The powder was sieved through a 315 μm sieve and blended in a Turbula®-mixer for 15 min (if the plug consisted of two or more components). The plugs were prepared by direct compression of mixtures listed in Table I with a single punch press (EK0, Korsch, Berlin, Germany). A suspension of magnesium stearate in isopropyl alcohol was used as an external lubricant to avoid sticking of the tablets to the punches. The diameter of the compressed plugs was 8 mm and the weight and hardness were varied between 100–200 mg and 40–120 N.

Preparation of Meltable Plugs

In order to determine the erosion properties of the meltable plugs, they were prepared by melting and pouring the melt into a mould (height: 13–14 mm, diameter: 11 mm). Gelucire® 44/14 and 50/13 were investigated as pure material or in mixtures (Table I). The sieved sodium dodecyl sulfate (SDS) was added to the molten Gelucire® 50/13. Paraffin was used to lubricate the mould. Plugs consisting of Myverol® 18-99 or mixtures of Myverol® 18-99 with bile salts, Tween® 80 or Pluronic® F-68 were poured into small petri dishes and, because of their semi-solid consistence, investigated for erosion in that form.

Preparation of the Complete System

The compressed plugs were placed by hand on top of the filled powder in the open end of the capsule with the top of the capsule body and the plug being even. The meltable plug materials (90–220 mg) were molten and filled with a pipette on top of the capsule content.

Preparation of Coated Plugs

Plugs were compressed as described above and dipcoated with the following organic polymer solutions: 10% w/w Eudragit® RS or RL 100 or lyophilized Eudragit® NE 30 D-powder in methylene chloride or isopropyl alcohol. Acetyltributyl citrate was used as plasticizer for Eudragit® RS and RL 100 (20% w/w based on the polymer). Dextrose (20% w/w) was used with Eudragit® NE 30 D-powder as a pore-forming agent.

Determination of the Time of Erosion of the Plugs

The time for complete erosion of the plugs (compressed plugs: 200 mg, 40 N) was determined with a disintegration tester (Erweka ZT 3, Erweka GmbH, Heusenstamm, Germany) (900 ml pH 7.4 phosphate buffer USP XXIII, 37°C, n = 3).

Dissolution Studies of the Filled Capsule Bodies Without Plugs

USP XXIII paddle dissolution apparatus (Vankel VK800, Vankel Industries, Edison, NJ, USA) (500 ml pH 7.4 phosphate buffer USP XXIII, 37°C, 50 rpm, n = 3). The capsule bodies were fixed at the paddles in an upright position to avoid their floating. Samples were taken at predetermined time points and analysed with a spectrophotometer (Shimadzu UV-2101 PC, Shimadzu Europa GmbH, Duisburg, Germany) (chlorpheniramine maleate at 261 nm and ibuprofen at 224 nm).

Determination of the Release and Lag Time of the Complete Drug Delivery System

The capsules were fixed at the bottom of transparent plastic dissolution flasks (Nalgene®) and were placed in a horizontal shaker (GFL® 3033, Gesellschaft für Labortechnik mbH, Burgwedel, Germany) (500 ml pH 7.4 phosphate buffer USP XXIII, 37°C, 70 rpm, n = 3). Samples were withdrawn at predetermined time points and analysed as described above.

RESULTS AND DISCUSSION

Prior to developing pulsatile systems based on erodible plugs, an attempt was made to develop a pulsatile system analogous to the Pulsincap™ system, which consists of an insoluble capsule half and a hydrogel plug, which is ejected from the

Table I. Erosion Properties and Erosion Times of Different Plug Materials Determined in a Disintegration-tester in Distilled Water at 37°C[a]

	Compressed plugs		
Plug material	Dissolution	Swelling	Time of erosion, min
HPMC E3	+	+	102
HPMC E5	+	+	155
HPMC K4M	○	++	>480
HPMC E5 : lactose, 1:1	++		11
HPMC E5 : lactose, 1:2	+		5
PVA		+	>480
PVA: lactose, 1:1	+	+	220
PVA: lactose, 1:2	++	+	83
PEO K100	+	+	84
PEO K100 : lactose, 1:1	++		44
PEO K100 : lactose, 1:2	++		29
PEO K8000	○	++	>480
PEO K8000 : lactose, 1:1	○	+	>480
PEO K8000 : lactose, 1:2	+	+	342
	Congealed plugs		
Plug material	Dissolution	Swelling	Time of erosion, min
Gelucire® 44/14	++		27
Gelucire® 48/09	○		>480
Gelucire® 50/13;	○	+	>480
Gelucire® 44/14:50/13, 1:1	++		130
Gelucire® 44/14:50/13, 1:2	+	+	280
Gelucire® 50/13, 10% Tween® 80	+		430
Gelucire® 50/13, 10% SDS	++		235
glycerol monooleate	○	++	not determined
glycerol monooleate, 10% bile salts	++	++	not determined

[a] ++ very good; + good; ○ not good.

capsule after water uptake and swelling (14). In the Pulsincap™-system, the polymers [e.g. Desmodur W (bis-(4-isocyanato cyclohexyl)methane) crosslinked with hexane triol and polyethylene glycol of different molecular weight] used for the hydrogel plug are crosslinked, which controls the degree of swelling and assures the ejection of the plug in one piece. Unfortunately, the used plug materials are not FDA-approved. To overcome this problem, a novel coated swellable plug design composed of approved materials was envisaged (Fig. 1A). The core of the plug consisted of a swellable polymer such as hydroxypropyl methylcellulose or polyethylene oxide. These polymers swell in contact with aqueous media and then erode. In order to obtain ejection of a swollen, but intact plug, the core was coated with a polymer. Ideally, the coating material should be permeable to water to allow the swelling of the core and be flexible enough not to rupture during the expansion of the core in order to keep the plug in one piece. The ejection of the coated plug could be controlled by the swelling properties of the core materials and the permeability and mechanical properties of the coating. Various frequently used hydophilic polymers and coating materials were evaluated for the new plug design. The acrylic polymers, Eudragit® RS 100, RL 100 or NE 30 D resulted in flexible films (22,23) and the water permeability was controlled by the ratio of Eudragit® RL/RS and with Eudragit® NE 30 D by the inclusion of hydrophilic materials (e.g. dextrose). While coated plugs not placed within the capsule body swelled and kept an intact coating, two major problems were observed after placing the plugs in the capsule opening. First, the coatings ruptured at the edges of the plugs before their complete ejection. This was caused by the swelling of the plug in only one direction, along the axes of the compressed plug, when compared to the free plugs resulting in a higher swelling pressure on the coating. Secondly, the coating material adhered to the capsule wall, which affected the ejection of the plug negatively and also contributed to the rupturing of the coating. Especially Eudragit® NE 30 D, which has a low glass transition temperature (T_g = -8°C) adhered strongly to the capsule wall (24). To reduce the adhesion to the capsule wall, magnesium stearate, talc or silicone grease were used as lubricants, unfortunately without satisfactory success. To avoid rupturing, thicker coatings could not be used because they would negatively affect the swelling of the core. Tablets with round edges somewhat reduced the problem. However, since reproducible results were not obtained with this plug design, it was not further investigated and the emphasis shifted to plug materials which were not ejected in one piece but were eroded as a function of time.

A pulsatile capsule-shaped delivery system was developed, whereby the pulsatile drug release occurred after erosion of the plug material rather than after ejection of an intact plug (25). A schematic diagram of the delivery system is shown in Fig. 1B. The capsule shell consisted of polypropylene and was insoluble and impermeable to aqueous fluids. With

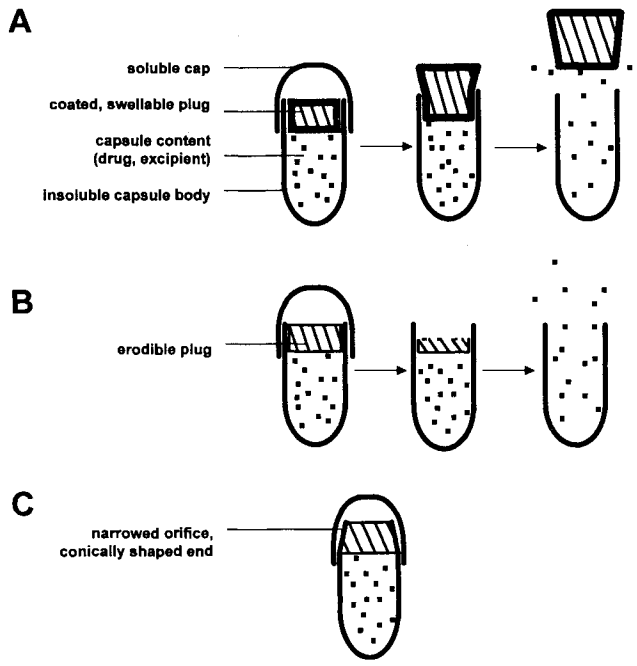

Fig. 1. Capsular pulsatile drug delivery systems consisting of an impermeable capsule body, the capsule contents and a plug; A: coated swellable plug, which is ejected after swelling; B: erodible plug, either compressed or congealed; C: special form of the capsule body to avoid premature ejection: conical shape at the end.

an optimally formulated system, the drug within the capsule content should be released rapidly after erosion of the plug material, which was used to close the capsule. The effect of various parameters of the plug (type of material, thickness and hardness) and the capsule content (type of excipient, amount of effervescent agents) were investigated in order to characterize the lag time prior to drug release and the drug release profiles of the capsules.

The plug was either formed by compression followed by placing the tablet onto the capsule content to close the capsule opening or by pouring a melt of the plug material onto the capsule content followed by congealing the melt into a plug, which closed the capsule. A tight fit between the plug and the impermeable capsule shell was very important in order to prevent water penetration to the capsule content and drug release prior to complete erosion of the plug material. In order to identify proper plug materials, the erosion properties and erosion times of different plug materials were investigated (Table I). Ideally, the plug should erode only from the surface exposed to the release medium. The water-soluble polymers hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA) or polyethylene oxide (PEO) appeared attractive as erodible plug materials because of their frequent use in hydrophilic matrix tablets. Depending on the molecular weight of HPMC, the polymer matrix degrades at different rates by erosion/dissolution of the polymer (26-28). Three different viscosity grades of HPMC (Methocel® E3, E5 and K4M) were evaluated. The higher molecular weight HPMC K4M swelled, but eroded too slowly to be a suitable choice for the pulsatile system. The lower viscosity grades were preferred, because they did not form a strong gel and eroded faster due to the dissolution of the polymer in the medium. Like with HPMC plugs, the erosion time of the PEO plugs decreased with decreasing molecular weight. PEO K100 eroded very fast even without addition of lactose. The PVA matrix swelled and eroded upon contact with water, after 480 minutes a small rest of the tablet remained. To control and to increase the erosion rate, a water-soluble filler, lactose, was added to the hydrophilic matrices. Pure lactose was compressed easily, however it dissolved too fast to be considered as a single plug material. All matrices eroded/dissolved faster with increasing lactose content. Considering that the exposed surface area of the plug positioned within the capsule body is limited to one side and is therefore much smaller than the surface area of free plugs, only plug compositions which disintegrated in less than two hours were used for further investigations.

From a manufacturing point of view, a compressed plug has to be prepared by first blending the plug materials, followed by compression and positioning of the plug within the capsule body. Because of fewer preparation steps, the formation of an erodible plug by congealing of a melt within the capsule body was investigated as an alternative to compressed plugs. In addition, a tight contact between the plug and the capsule body was obtained with the melt method. The meltable material then eroded by dissolution or dispersion/emulsification. In order to evaluate the erosion properties, the molten material was poured into moulds, congealed and then evaluated for its erosion potential. Gelucires® are lipidic materials based on saturated polyglycolated glycerides with varying melting points and HLB-values. High HLB-grades have been reported to disperse in water, while low HLB-grades, depending on their melting point either melt or remain physically unchanged in contact with aqueous media at body temperature. The high HLB-value Gelucires® 44/14 and 50/13 (the first number specifies the melting point, the second number the HLB-value) were evaluated as plug materials. Both melt at low temperatures, but

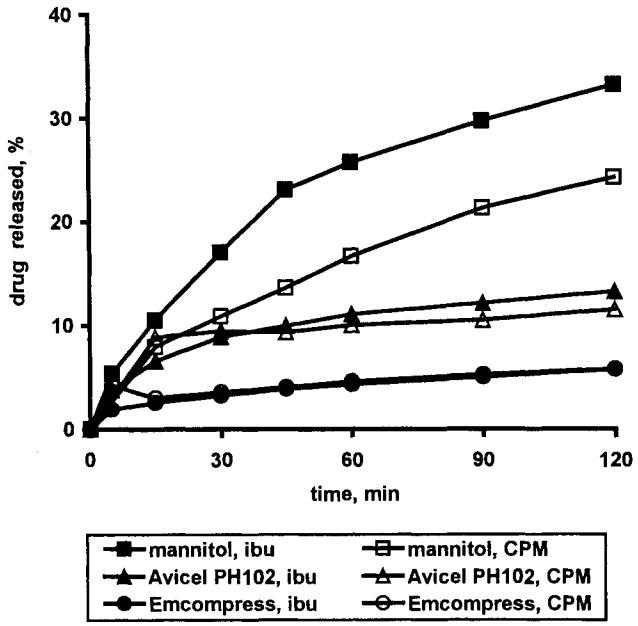

Fig. 2. Effect of excipients on the release of ibuprofen and chlorpheniramine maleate from capsules without plugs.

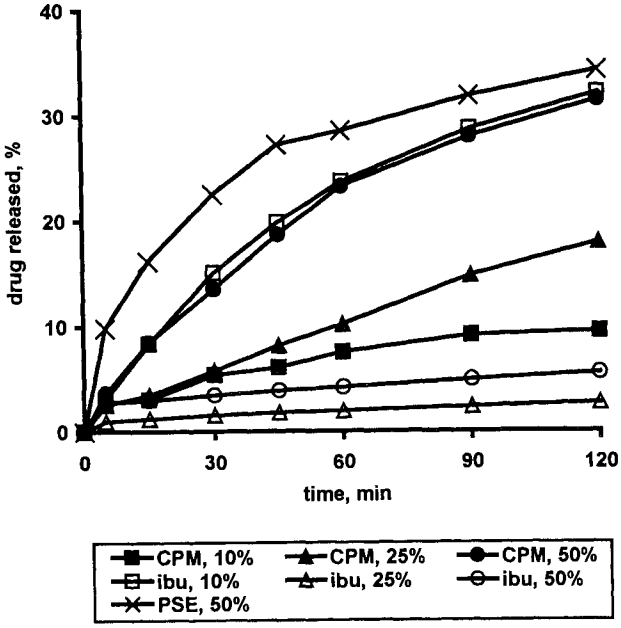

Fig. 3. Effect of drug type and drug concentration on the drug release from capsules without plug.

above body temperature (in order not to melt at higher storage temperatures or at body temperature) and form a low viscosity, easily pourable melt. The plug prepared from Gelucire® 44/14 dispersed too rapidly in buffer fluids, while the higher melting Gelucire® 50/13 swelled but remained intact. A 1:1 mixture of both Gelucire® types had satisfying properties, it dispersed slowly. Increasing the amount of the lower melting Gelucire® 44/14 increased the rate of dispersion. Gelucire® 48/09 remained unchanged after 8 hours in aqueous solution. The anionic surfactant, sodium dodecyl sulfate (SDS), and the non-ionic surfactant, Tween® 80, were investigated as additives in order to improve the erodability of the higher melting Gelucire® 50/13 by possibly forming a self-emulsifying system. The dispersability of the plug was more improved by the addition of SDS. Another meltable material investigated was glyceryl monooleate (GMO). GMO without additives swelled in contact with water, but formed a highly viscous gel-like product (cubic phase), which did not erode. The addition of bile salts (10% w/w), which have been reported to result in the dispersion of cubic phase drug delivery systems (29–31) resulted in the disintegration of the plug, the monoglyceride was dispersed into the aqueous phase. However, when compared to the other meltable plug materials, the monoglyceride was probably too soft to be a viable candidate.

While the extent of the lag time prior to the drug release is primarily controlled by the rate of erosion of the plug material, the subsequent drug release phase will be determined by the composition of the capsule content. The effect of various excipients on the drug release of a hydrophilic and a lipophilic model drug, chlorpheniramine maleate or ibuprofen, from the open capsule body (without plug) is shown in Fig. 2. Less than 40% of the drug was released within two hours with all formulations. The highest amount of drug was released with mannitol (water-soluble), followed by microcrystalline cellulose (Avicel®) (water-insoluble, but swelling and disintegrating properties) and the dibasic calcium phosphate (Emcompress®, water-insoluble). The type of drug had little influence on the release at the relatively low drug loading of 10% w/w. Increasing the drug loading increased the drug release of the hydrophilic drug, chlorpheniramine maleate, but resulted in a decrease with ibuprofen because of a more lipophilic nature of the capsule content (Fig. 3). At a higher loading (50% w/w), the drug release for the different drugs was controlled by the solubility of the drug and increased with increasing water solubility in the order of pseudoephedrine HCl > chlorpheniramine maleate > ibuprofen. However, even with the very water-soluble pseudoephedrine HCl, less than 40% drug was released within 2 hours, this being too slow for a desired pulsatile release after erosion of the plug. In general, the slow release was probably caused by the small fluid volume and the low hydrodynamic motion within the capsule body, resulting in saturated drug solutions within the capsule body. In addition, the polypropylene capsule body was poorly wetted by the dissolution medium.

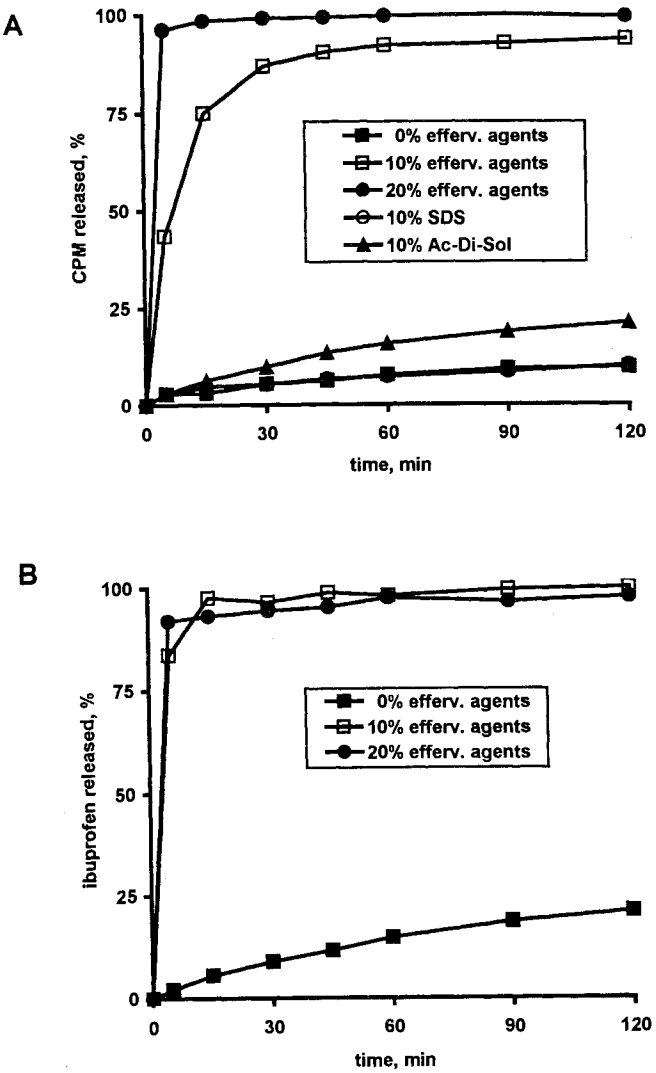

Fig. 4. Influence of additives [effervescent agents (0, 10 or 20% w/w), sodium lauryl sulfate (SDS) or Ac-Di-Sol® (disintegrant)] on the drug release from the capsules without plug. A. chlorpheniramine maleate, B. ibuprofen.

To achieve pulsatile release, the drug should be released rapidly once the capsule content is exposed to the medium. The addition of effervescent agents, disintegrating agents and surfactants was investigated to accelerate the release from the capsule body. A rapid release for both chlorpheniramine maleate and ibuprofen was achieved by the addition of effervescent agents to the capsule content (Fig. 4). The drug release increased with increasing concentration of effervescent agents. The addition of 20% effervescent agents resulted in a complete drug release within 5 min. The addition of the superdisintegrant, Ac-Di-Sol®, marginally improved the release, while SDS had no effect.

After evaluating the plug material and the capsule content separately, the complete pulsatile delivery system was investigated next. It consisted of the impermeable polypropylene capsule body, a capsule content of chlorpheniramine maleate, lactose and effervescent agents (20% w/w) and various plugs. The lag time before the pulsatile release was controlled by the properties of the plug. Variables such as the composition, the thickness or weight and the hardness of the plug were investigated in order to control the erosion time of the plug and hence the lag time. One initial problem was the reproducibility of the release due to the differences in the erosion of each single plug. Sometimes the whole plug was ejected by the increasing inner pressure resulting from the generated CO_2. This problem of premature and irreproducible ejection of the plug was avoided by using a specially shaped capsule body. It was not straight cylindrical, but the end of the orifice was conically shaped (Fig. 1C). The narrowed opening avoided the premature ejection of the plug.

The effect of plug composition on the chlorpheniramine maleate release is shown in Fig. 5. The release profiles revealed pulsatile characteristics. After a lag time with no drug release, the drug was released within a relatively short time period. The lag time correlated well with the erosion data obtained with

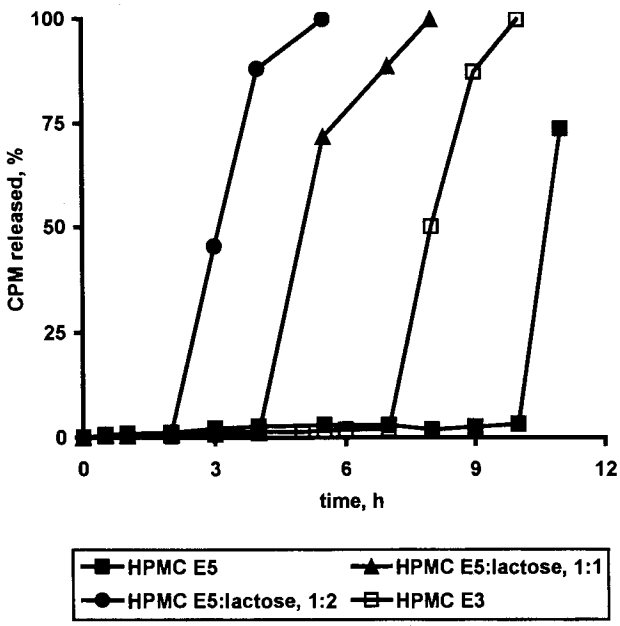

Fig. 5. Pulsatile release of chlorpheniramine maleate as a function of differently composed HPMC-plugs (weight = 100 mg, thickness = 1.8 mm, hardness = 40 N).

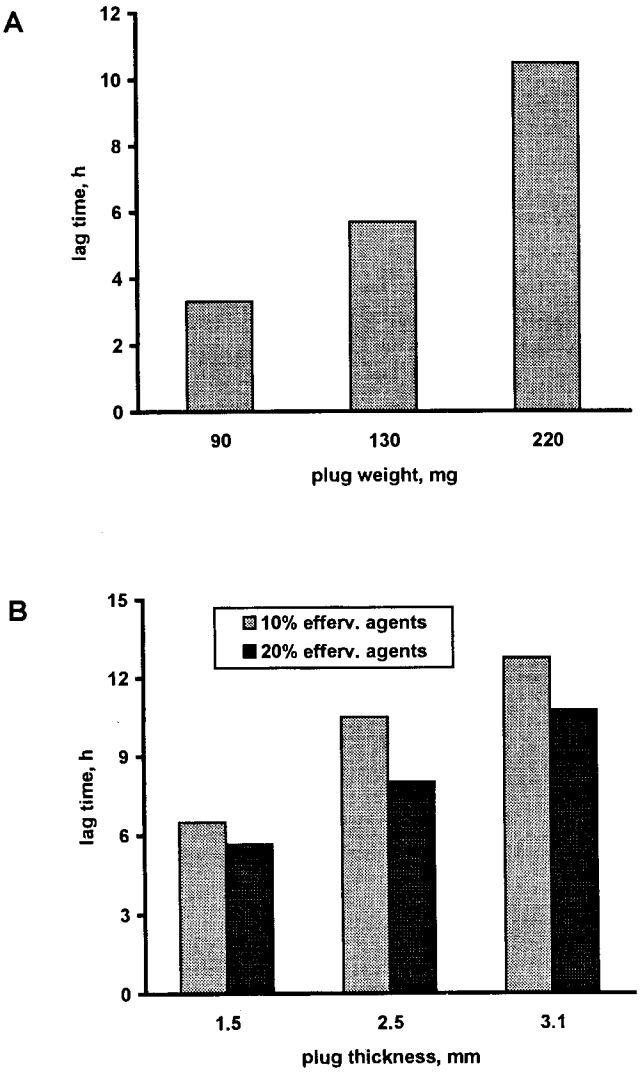

Fig. 6. Influence of A. the plug weight (Gelucire® 44/14: 50/13; 2:1) and B. the plug thickness and concentration of effervescent agents (PVA: lactose, 1:2; 50 N) on the lag time.

the free plugs (Table I). Increasing the amount of lactose in the HPMC plug and using the lower viscosity grade HPMC (E3 vs E5) resulted in a faster erosion and shorter lag times. The lag time was not affected by the hardness of the plug in the hardness range investigated (20, 60, 120 N, corresponding thickness: 2.7, 2.3, 2.2 mm) (data not shown). The lower porosity of the harder plugs was probably offset by the smaller plug thickness. The system was therefore not sensitive to the hardness of the plug, which might be important from a manufacturing point of view.

Other important variables are the plug position (which was kept constant in this study, the plug was even with the capsule end) and the thickness of plug. The thickness of the plug was difficult to measure with plugs prepared by the melt pouring method. The weight of the plug, which correlated to the thickness, was easily measurable gravimetrically and was therefore varied. Increasing the weight of plugs prepared from a blend of Gelucire® 44/14 and 50/13 (2:1) increased the lag time from 4 to almost 12 hours (Fig. 6A). The same trend was seen

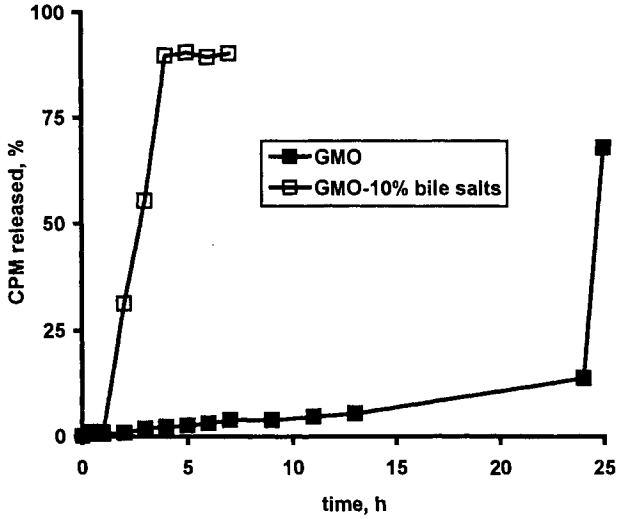

Fig. 7. Release of chlorpheniramine maleate from capsules containing glycerol monooleate (GMO) and GMO-bile salts (10% w/w) as plug material (120 mg).

with compressed PVA-lactose plugs (Fig. 6B). More time was necessary for the erosion of the thicker plugs. Varying the plug thickness was therefore a simple mean to control the lag time prior to the pulsatile release behaviour. The lag time was also affected by the amount of effervescent agent in the capsule content (Fig. 6B). At the 20% level of effervescent agents, the lag time was shorter than at the 10% level for all plug thicknesses. At the higher level, the pressure of the CO_2 generated prior to complete erosion of the plug caused the push-out or rupture of some of the hydrated plug material, thus resulting in shorter lag times.

The pure glycerol monooleate (GMO) plug formed a highly viscous cubic system, resulting in a long lag-time. The inclusion of only 10% w/w bile salts into GMO plugs significantly shortened the lag time from 24 hours to 2 hours. A self-emulsifying plug and an easily erodible material was formed (Fig. 7).

In conclusion, pulsatile drug release was achieved with a capsular device based on an impermeable capsule body and an erodible plug. The pulsatile release could be controlled by the properties of the plug (e.g. composition and thickness) and of the capsule content (e.g. inclusion of effervescent agents).

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