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Review

Oral pulsatile delivery: Rationale and chronopharmaceutical formulations

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This review article is dedicated to Professor Maria Edvige Sangalli, who provided a notable contribution to the field of oral pulsatile delivery.

Keywords:
Oral drug delivery
Pulsatile release
Delayed release
Chronotherapy
Lag time

ABSTRACT

Oral pulsatile/delayed delivery systems are designed to elicit programmable lag phases preceding a prompt and quantitative, repeated or prolonged release of drugs. Accordingly, they draw increasing interest because of the inherent suitability for accomplishing chronotherapeutic goals, which have recently been highlighted in connection with a number of widespread chronic diseases with typical night or early-morning recurrence of symptoms (e.g. bronchial asthma, cardiovascular disease, rheumatoid arthritis, early-morning awakening). In addition, time-based colonic release can be attained when pulsatile delivery systems are properly adapted to overcome unpredictable gastric emptying and provide delay phases that would approximately match the small intestinal transit time. Oral pulsatile delivery is pursued by means of a variety of release platforms, namely reservoir, capsular and osmotic devices. The aim of the present review is to outline the rationale and main formulation strategies behind delayed-release dosage forms intended for the pharmacological treatment of chronopathologies.

Contents

1. Introduction

It has recently been reported that the time of drug administration can play a key role in determining the efficacy and tolerability of a pharmacological therapy. Indeed, the temporal rhythms of bodily functions have been shown to affect not only the incidence or severity of a number of disease conditions but also the pharmacokinetics as well as pharmacodynamics of most bioactive compounds in use (Lemmer, 1991; Hrushesky, 1994; Smolensky et al., 1999; Youan, 2004). Accordingly, chronotherapeutic treatments tailored to supply the patient with the appropriate dose of the required drug when this is especially needed are gaining increasing interest.

In the field of drug delivery, dosage forms designed to elicit a programmed liberation of drugs after lag phases that commence upon administration are recognized as potentially suitable tools for meeting chronopharmaceutical demands (Maroni et al., 2005; Gazzaniga et al., 2008). Such a release mode is commonly referred to in the literature as pulsatile and/or delayed delivery in spite of a non-full compendial compliance of these terms. In the Eur. Ph. 6th Ed., in fact, "pulsatile" is intended as sequential, i.e. repeated. On the other hand, even though the pharmacopoeial definition of "delayed" apparently matches the concerned release mode (programmable lag phase prior to drug liberation), delayed-release systems also include enteric-coated formulations. For the above-stated reasons, delivery devices able to predictably delay drug release will hereinafter be indicated as "pulsatile" and/or "delayed".

The pulsatile/delayed release process may be started in response to external signals (e.g. chemical, thermal, electric and magnetic

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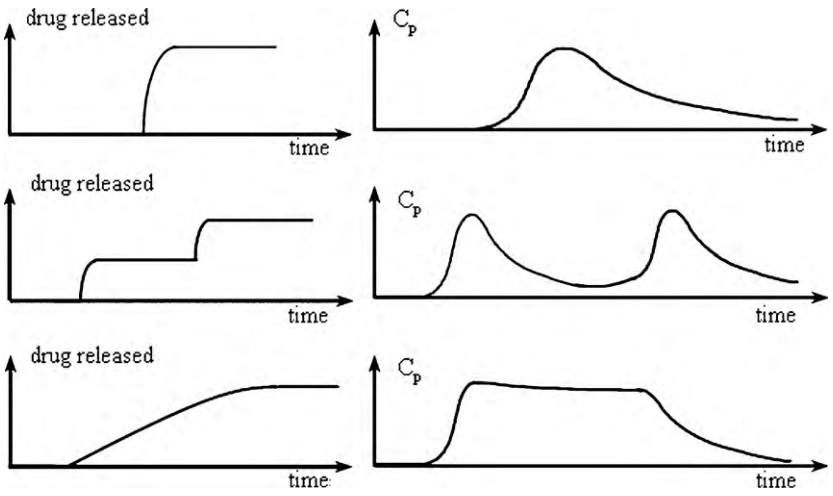


Fig. 1. Expected *in vitro* release (left) and plasma concentration (right) curves of pulsatile delivery systems with prompt and quantitative (top), repeated (middle) or prolonged (bottom) release patterns after the lag phase.

stimuli) or, alternatively, be regulated by inherent mechanisms, as in the case of time-controlled devices that are expected to perform consistently irrespective of major physiological variables (e.g. pH, ionic strength, temperature). After the lag phase, pulsatile delivery systems may give rise to a prompt and quantitative, repeated or prolonged release pattern depending on their formulation characteristics (Fig. 1).

Due to constraints related to the gastrointestinal transit, circadian or ultradian variation patterns of disease symptoms are the only viable targets for orally-administered pulsatile delivery devices. Indeed, these could profitably be used in the management of pathologies with prevailing night or early-morning manifestations, such as cardiovascular disease, bronchial asthma, rheumatoid arthritis and sleep disorders. In these instances, pulsatile-release medications could provide a timely pharmacological effect following evening dosing, without either entailing an unnecessary sustained exposure of the patient to the drug molecule or requiring the interruption of normal sleep patterns, which would result in impaired compliance.

Besides chronotherapeutic applications, oral pulsatile delivery systems may offer a number of different advantages. When designed to yield repeated release profiles, they could accomplish multiple daily dosing regimens for those drugs that fail to be candidate for prolonged-release formulations, e.g. because of a strong first-pass effect or pharmacological tolerance. Recently, multi-pulse delivery of antibiotics has also been described as a means of limiting the development of resistant bacterial strains thus possibly improving the outcome of infectious disease therapy (Saigal et al., 2009). Moreover, delayed-release dosage forms have been proposed to prevent the occurrence of detrimental drug–drug interactions without modifying the administration schedule of combined medications, which could negatively affect the patient compliance (Sawada et al., 2003a).

In addition, pulsatile release is exploited to attain oral colon delivery based on a time-dependent approach that relies on the relative consistent small intestinal transit time (SITT) of dosage forms (Davis, 1985; Gazzaniga et al., 1994a, 2006). For this purpose, an outer enteric-soluble film is generally applied to pulsatile delivery systems in order to overcome unpredictable gastric emptying. Moreover, *in vivo* lag periods should be modulated to roughly correspond to SITT. Colon delivery is extensively investigated in view of its proven advantageousness in the treatment of inflammatory bowel disease (IBD) and potential role in the chemoprevention of colorectal adenocarcinoma (Takayama et al., 2009). Furthermore, in spite of modest absorption properties, the large bowel is currently recognized as a gateway to the systemic circulation. In particular, colonic release has been hypothesized to enhance the oral bioavailability of peptides, proteins, oligonucleotides and nucleic acids, which mostly exhibit poor gastrointestinal stability and permeability characteristics thus generally requiring parenteral administration (Haupt and Rubinstein, 2002; Bourgeois et al., 2005). As a matter of fact, a large number of such drugs have become available on a production scale thanks to the recent advances in biotechnology, thus strengthening the need for non-invasive delivery modes with higher patient compliance. In this respect, the oral route would represent a preferred administration option.

For pulsatile release purposes, a variety of design strategies have been attempted. Several coated, capsular and osmotic formulations have indeed been described (Bussemer et al., 2001; Maroni et al., 2005; Gazzaniga et al., 2008). In the present article, the main oral pulsatile delivery systems proposed are surveyed with regard to the relevant formulation characteristics and release performance.

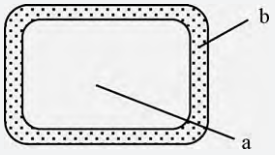
2. Delivery systems based on release-controlling coatings

Coatings with differing compositions are applied to solid cores that contain the active ingredient in order to defer the onset of its release (Table 1). Either single- or multiple-unit dosage forms are used as core substrates, the latter offering typical advantages in terms of performance consistency especially because of a lower impact of gastric residence. According to the coating agent(s) employed, various release mechanisms can be involved, such as in the case of erodible, rupturable or diffusive reservoir systems.

Erodible devices are provided with hydrophilic polymeric coatings of adequate thickness (Gazzaniga et al., 2008). When exposed to aqueous media, these undergo swelling, dissolution and/or erosion phenomena that result in a delayed release of the drug from the core formulation. Lag time is basically programmed by selecting the appropriate polymer and coating level. For this purpose, hydrophilic cellulose derivatives, such as hyroxypropyl methylcellulose (HPMC), hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC), are typically utilized because of their established safety and versatility profiles.

An early pulsatile delivery system based on hydrophilic cellulose ethers was a three-layer tablet including two immediate-release drug compartments and a functional HPMC interlayer (Conte et al., 1989, 1992). The device was coated with an impermeable ethylcellulose (EC) film except for the free surface of one drug-containing layer. By promptly interacting with the aqueous medium, this could provide an immediate release pulse. A delayed pulse would take

Table 1
Outline of pulsatile delivery systems based on release-controlling coatings and references listed according to key formulation characteristics.



Legend	References
(a) Drug-containing core (tablet, capsule, multiple units)	
(b) Release-controlling layer:	
Swellable/erodible	Cao et al., 2004; Conte et al., 1989, 1992; Del Curto et al., 2009; Efentakis et al., 2006; Fukui et al., 2000; Gazzaniga et al., 1994b,c, 1995, 2009, 2010; Ghimire et al., 2007; Halsas et al., 1998a,b, 2001; Karavas et al., 2006a,b; Li and Zhu, 2004; Maffione et al., 1993; Maroni et al., 2009; Matsuo et al., 1995, 1996; Ozeki et al., 2004; Pozzi et al., 1994; Qureshi et al., 2009; Sangalli et al., 2001, 2004; Sawada et al., 2003b, 2004; Staniforth and Baichwal, 2005; Takeuchi et al., 2000; Zema et al., 2007, 2009; Zou et al., 2008
Rupturable	Bussemer et al., 2003a,b,c; Bussemer and Bodmeier, 2003; Dashevsky et al., 2004; Fan et al., 2001; Feng et al., 2008; Hata et al., 1994; Ishino et al., 1992a,b; Krögel and Bodmeier, 1999a; Lin et al., 2001a,b, 2002, 2004a,b, 2008; Liu et al., 2009; Mohamad and Dashevsky, 2006a,b, 2007; Morita et al., 2000; Murata et al., 1998; Rane et al., 2009; Schultz et al., 1997; Schultz and Kleinebudde, 1997; Sungthongjeen et al., 2004; Ueda et al., 1994a,b,c,d; Zhang et al., 2003
Increasingly permeable	Narisawa et al., 1994, 1995, 1996, 1997

place following extensive erosion of the intermediate HPMC barrier. The lag phase elapsing between the two pulses was shown to depend on the composition of such a barrier. Reproducible double-peak plasma levels of a model drug were observed consistent with the *in vitro* performance. Starting from this technology, the Chronotopic™ system was subsequently proposed, which consisted in a drug-containing core entirely coated with HPMC. By combining coated units with uncoated ones, two-pulse release patterns could indeed be obtained while avoiding the poorly scalable manufacturing involved by the previous multi-layer device. The Chronotopic™ system, however, was chiefly intended for single-pulse chronopharmaceutical and colonic delivery. The application of the functional HPMC layer was initially accomplished by press-coating and hydro-organic spray-coating (Maffione et al., 1993; Gazzaniga et al., 1994b,c). Both techniques were later abandoned due to a number of relevant drawbacks. Indeed, press-coating entailed remarkable versatility constraints, whereas the use of organic solvents was hampered by major environmental and safety issues. Aqueous spray-coating of tablet cores was therefore performed with differing HPMC grades (Gazzaniga et al., 1995; Sangalli et al., 2001, 2004; Zema et al., 2007). A low-viscosity polymer (Methocel® E50) was proven to offer an advantageous balance of various key aspects, such as process feasibility, effectiveness in delaying the drug liberation, flexibility in lag time modulation and limited impact on the release rate. Programmable and reproducible lag times followed by a fast delivery phase were elicited both *in vitro* and in healthy volunteers by Methocel® E50-coated devices (Sangalli et al., 2001). These results were supported by γ-scintigraphic data, which confirmed the ability of the system to yield time-controlled colon targeting when provided with an outermost gastric-resistant film. The aqueous spray-coating procedure employed was successfully applied to hard- and soft-gelatin capsule cores (Sangalli et al., 2009). Such dosage forms might indeed convey multi-particulate formulations (micro- and nanoparticles) that are described as potentially beneficial to the intestinal absorption of protein drugs (Carino and Mathiowitz, 1999; Jung et al., 2000). Furthermore, systems based on bovine insulin tablet cores, with or without enzyme inhibitor and absorption enhancer compounds, were prepared and evaluated pointing out adequate stability and *in vitro* release characteristics (Maroni et al., 2009; Del Curto et al., 2009). The use of innovative coating techniques, such as powder-layering, was also explored in an attempt to increase the yield and reduce the duration of the manufacturing process, thus further improving its potential for industrial scale-up (Sangalli et al., 2009).

High-viscosity HPMC grades or combinations of high- and low-viscosity ones were used for the preparation of a press-coated erodible system containing model drugs with differing solubility properties (Halsas et al., 1998a,b, 2001). When raising the coating level or the high- to low-viscosity polymer ratio, longer lag phases and slower absorption were observed. However, no satisfactory *in vitro–in vivo* correlation could be established. In addition, biphasic slow release patterns with no lag time and double-peak plasma concentration curves were achieved when splitting the drug dose between the core and the coating formulation.

In a different instance, a low-viscosity HPMC press-coated tablet was provided with an outer sodium bicarbonate-containing HPMC buoyant layer thus resulting in a floating pulsatile delivery device (Zou et al., 2008).

High-viscosity HPMC/polyvinylpyrrolidone (PVP) composite materials, in which the two polymers were bound by weak interactions rather than simply mixed with each other, were employed as press-coating agents for a chronopharmaceutical felodipine delivery system in pursuit of improved reproducibility of performance (Karavas et al., 2006a,b). Lag time was proven to extend by increasing the HPMC to PVP content ratio. The dissolution rate of felodipine was enhanced through incorporation into a PVP matrix core as an amorphous nanodispersion in order to achieve a fast release after the delay phase.

Double-compression coating based on high-viscosity HPMC was also exploited in the case of a multiple-unit dosage form that consisted of subunits with differing formulation and release characteristics conveyed in a hard-gelatin capsule (Li and Zhu, 2004). By properly combining such subunits, versatile release patterns were achieved including multi-pulse delivery.

In an attempt to overcome the drawbacks associated with conventional compression-coating, the low-viscosity HPMC erodible barrier of the one-step dry-coated tablet (OSDRC) was obtained by a novel single-step procedure enabled by a purposely devised tableting machine (Ozeki et al., 2004).

High-viscosity HPMC was alternatively applied to tablet cores by the dipping method (Cao et al., 2004). In this case, some further variables besides the coating level were proven to affect the release performance. For example, lag time was extended when the aqueous to organic solvent ratio or the polymer concentration of the coating dispersion were diminished. In addition, the

release rate decreased when HPMC was allowed to swell longer in the hydro-organic vehicle.

When HEC or HPC were used as the press-coating agent, *in vitro* and *in vivo* delay times were also demonstrated to lengthen as a function of the amount and viscosity grade of the cellulose derivative applied (Matsuo et al., 1995, 1996; Fukui et al., 2000; Qureshi et al., 2009). Furthermore, melt-granulated mixtures of low-substituted HPC (L-HPC) and glyceryl behenate were employed to prepare the erodible barrier of the press-coated tablet (PCT) (Ghimire et al., 2007). Following administration to beagle dogs, theophylline-containing PCT prototypes elicited reproducible lag times increasing as a function of the percent amount of glyceryl behenate in the coating formulation.

Recently, HPC was subjected to injection-molding for the manufacturing of novel swellable/erodible shells (ChronoCap) able to convey differing formulations and release a variety of bioactive compounds after the required lag phases (Gazzaniga et al., 2009, 2010). The peculiar advantages of this technology include a high versatility and, in principle, the possibility of handling the drug formulation separately from the release-controlling device, thus potentially limiting the technical and regulatory burden connected with pharmaceutical development.

In order to prepare press-coated systems, swellable hydrophilic materials other than cellulose ethers were also exploited. For example, erodible coatings based on spray-dried composite lactose powders containing sodium alginate/chitosan complexes were demonstrated to withstand a prolonged contact with acidic fluids and delay drug release in pH 6.8 media (Takeuchi et al., 2000). The duration of the lag phase was affected by the amount and deacetylation degree of chitosan. Moreover, tablets press-coated with polyethylene oxide (PEO) and polyethylene glycol (PEG) 6000 blends were provided with a highly water-soluble excipient load in order to avoid the possible decrease in the oral bioavailability of drugs delivered into distal intestinal regions, where a limited water content is present (Sawada et al., 2003b). A greater erosion of tablet cores, as indicated by a novel index named "core erosion ratio", was indeed associated with higher acetaminophen bioavailability in beagle dogs. Analogous preparations containing nifedipine were later investigated *versus* an extended-release dosage form to explore the impact of formulation variables on the relevant suitability for chronotherapy (Sawada et al., 2004). PEO was also used to prepare a swellable layer applied to the free surface of a core tablet that was encased in a partial impermeable shell (Efentakis et al., 2006). When PEO was replaced by sodium carboxymethylcellulose or sodium alginate, respectively, longer and shorter delay phases were observed in agreement with the swelling properties of the materials investigated. On the other hand, the SyncroDose™ delivery platform consisted of a drug-containing tablet and an erodible press-coated layer formed from the bacterial exopolysaccharide xanthan gum and the plant galactomannan locust bean gum (Staniforth and Baichwal, 2005). The lag phase would be modulated by varying the ratio between the two polysaccharides in the coating mixture.

In contrast to the aforementioned devices, which were based on hydrophilic release-controlling polymers, the erodible layer of the Time-Clock® system was composed of natural waxes and surfactants (Pozzi et al., 1994). These were applied to tablet cores by aqueous spray-coating under relatively elevated temperature conditions. The delay preceding drug release was due to a progressive dispersion of the hydrophobic coating agents into the aqueous fluid. *In vivo* pharmacokinetic and γ-scintigraphic investigations pointed out reproducible lag times irrespective of food intake.

In rupturable delivery systems, the time-programmed liberation of bioactive compounds is enabled by the disruption of moderately water-permeable films based on insoluble polymeric materials often in admixture with pore-formers and/or plasticizers. The disruption step is brought about by an increase in the core volume that may in turn result from an osmotically-driven water influx or from the hydration of swellable polymers. The release onset is mainly controlled by the thickness and composition of the rupturable coating.

In the pulsatile release tablet (PRT), for example, the rupture of a press-coated layer composed of melted-granulated hydrogenated castor oil and PEG 6000 was induced by the swelling process of calcium carboxymethylcellulose in the core (Ishino et al., 1992a). The delay phase was modulated by changing the thickness and PEG 6000 content of the coating. An *in vivo* evaluation of diltiazem hydrochloride PRT prototypes on beagle dogs pointed out a marked inter-subject variability under fasted conditions and a more reproducible pulsatile release performance in the fed state (Ishino et al., 1992b).

Croscarmellose sodium (Ac-Di-Sol®) was selected among various swelling agents for application to gelatin capsules and tablets in order to form an expanding layer interposed between the drug-containing core and the outer rupturable film (Bussemer et al., 2003a,b; Bussemer and Bodmeier, 2003; Dashevsky et al., 2004; Mohamad and Dashevsky, 2006a; Sungthongjeen et al., 2004). Typical delayed release patterns were shown by both capsule- and tablet-based systems. Longer lag times were generally observed by increasing the thickness of the rupturable membrane or decreasing its channelling agent content. An opposite effect was noticed when raising the swelling polymer coating level. However, this finding was not confirmed when tablets were used as cores, probably because the hydrated Ac-Di-Sol® layer could hamper the relevant disintegration process (Sungthongjeen et al., 2004). The pH dependence of the superdisintegrant performance, which might be reflected in an erratic release onset, was prevented by including fumaric acid in the formulation of the expanding layer (Mohamad and Dashevsky, 2006a). Owing to the inherent brittle characteristics, which would lead to extensive disruption rather than to the formation of small breaches in response to tensile stress, plasticized EC films containing HPMC as a pore-former were proven superior to Eudragit® RS membranes in controlling drug release from such devices (Bussemer and Bodmeier, 2003; Bussemer et al., 2003c).

Polyvinyl alcohol (PVA) was added to the core tablet of the swelling controlled release system (SCRS) to provide the swelling pressure required to rupture its outer EC film (Morita et al., 2000). The amounts of PVA and of a swelling-limiting salt (trisodium citrate dihydrate) in the tablet as well as of HPMC in the coat were demonstrated to be the chief determinants of the lag phase duration and the release rate. Relatively high PVA and limited HPMC percentages, coupled with the lack of trisodium citrate dihydrate, led indeed to a burst-like disruption of the outer membrane with consequent rapid liberation of the model drug.

EC films, in which HPMC was incorporated as the pore-former, were also proposed to coat tablet cores containing high-viscosity HPMC as the swellable excipient (Lin et al., 2008). Various quali-quantitative compositions were investigated for both the core and the coating. The lag phase was concluded to depend on the thickness of the EC membrane and the relevant hydrophilicity degree as imparted by HPMC.

Furthermore, EC was mixed with the enteric-soluble methacrylic copolymer Eudragit® L to prepare pH-dependent rupturable devices based on differing core formulations, such as a diltiazem hydrochloride immediate-release tablet including crospovidone as the swelling agent or a hydrophilic matrix intended for the prolonged release of propranolol hydrochloride (delayed-onset sustained release tablet, DST) (Fan et al., 2001; Feng et al., 2008). Even though an agreement was found between *in vitro* and *in vivo* data for both systems, they might fail to elicit the programmable pulsatile release behavior pursued owing to the well-known variability encountered in the gastric

residence of non-disintegrating single-unit dosage forms. Indeed, the relevant lag time would most likely encompass an initial phase of unpredictable duration preceding stomach emptying that could ultimately impair the outcome of cardiovascular disease chronotherapy.

In a different instance, the hydrostatic pressure responsible for the disruption of the EC membrane was exerted by carbon dioxide generated inside the core tablet after dissolution of effervescent excipients (Krögel and Bodmeier, 1999a). The lag phase could be modulated by varying the core hardness and/or the coating level. Interestingly, when EC was replaced by Eudragit® RL, floating dosage forms were obtained because of the higher water permeability and flexibility characteristics of the films.

EC was also applied by double-compression technique (Lin et al., 2001a,b; Rane et al., 2009). In these cases, the delayed onset of release was related to the split of the coating shell into two halves following formation of symmetrical breaches within its lateral structure due to a hypothetically lower inherent packing density. Lag time was proven affected by the thickness and/or compression force of the coating and the particle size of EC powder. Indeed, larger particle dimensions were associated with a higher porosity thus resulting in enhanced shell permeability. As expected, the incorporation of swellable (HPMC, sodium starch glycolate, sodium alginate, glycine max husk) and osmotic (sodium chloride) excipients into the core formulation or of hydrophilic compounds (HPMC, spray-dried lactose) into the outer shell was reflected in shorter delay phases (Lin et al., 2002, 2004a; Rane et al., 2009). Modifications of half of the coating formula were demonstrated to be a further means of modulating the lag phase. The obtained bipartite shells, however, possibly involved release mechanisms other than that observed when testing units coated with EC only (Lin et al., 2004b).

Eudragit® RS/Eudragit® RL mixtures were alternatively used as rupturable film-forming agents for pulsatile delivery purposes (Zhang et al., 2003). In particular, they were applied to drug-containing tablet cores provided with an osmotic charge and a low-viscosity HPMC swelling coat. Due to the permeability characteristics imparted by positively-charged quaternary ammonium groups, the acrylic membrane allowed water to enter the system upon contact with aqueous fluids. Micrometric fissures were formed within its structure as a consequence of expansion of the underlying compartments. The drug was thus released by diffusion as well as osmotic pumping phenomena. Lag time was dependent on the thickness of the Eudragit® RS/RL film.

Multiple-unit rupturable formulations were also described, such as in the case of the time-controlled explosion system (TES). This device was based on inert sucrose seeds coated with overlapping drug and L-HPC layers, and with an outermost EC film (Ueda et al., 1994a,b,c). While the delay time was related to the EC coating level, a thickness threshold of 180 μm was necessary for the L-HPC swelling layer to elicit the pursued pulsatile release performance. The system behavior was not influenced by the solubility and amount of the active ingredient, the pH of the medium and the particle size of subunits. *In vivo* absorption profiles consistent with *in vitro* release ones and unaffected by feeding were highlighted by a human pharmacokinetic investigation (Hata et al., 1994). However, dog studies revealed a decreased extent of absorption in the case of TES formulations with a longer *in vitro* lag time (Ueda et al., 1994d; Murata et al., 1998). This result was attributed to the limited volume of water available for dissolution in the distal intestine (Murata et al., 1998).

Pellets with an inner croscarmellose sodium swelling coat and an outer EC film were later proposed, which exhibited *in vitro* lag phases influenced by the pH and ionic strength of release fluids and, when administered to healthy volunteers, a decrease in the extent of absorption as compared with a reference immediate-release preparation (Mohamad and Dashevsky, 2006b, 2007). A multiple-unit dosage form with an analogous design concept was devised in order to attain a chronotherapeutic delivery of isosorbide 5-mononitrate, i.e. the main active metabolite of the anti-anginal drug isosorbide dinitrate (Liu et al., 2009).

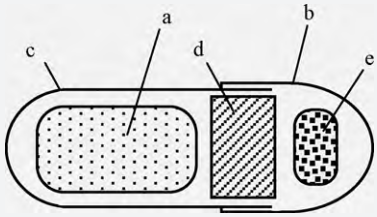
The use of cellulose acetate to prepare the rupturable film of a multiple-unit delivery system was also reported (Schultz and Kleinebudde, 1997). Pellets provided with a semi-permeable membrane were thus obtained, which were subject to disruption as a consequence of the water influx promoted by an osmotically-active excipient. A linear relationship was found between lag time and coating level beyond a minimum 2 mg/cm^2 value. The addition of plasticizers to the cellulose acetate film resulted in longer delay and slower release phases as a function of the relevant lipophilicity (Schultz et al., 1997). However, the tensile properties of the membrane turned out to be influenced by the amount rather than the type of plasticizer added.

Further reservoir systems present diffusive release-controlling coats. In particular, an increasingly permeable polymeric film based on Eudragit® RS was applied to nonpareil seeds loaded with drug/succinic acid mixtures to prepare the sigmoidal release system (SRS) (Narisawa et al., 1994, 1995). The delay observed *in vitro* and confirmed *in vivo* on beagle dogs was a function of the Eudragit® RS coating level. The typical release pattern of SRS was ascribed to an initially limited inward water diffusion, which would result in the partial ionization of the organic acid incorporated in the intermediate layer (Narisawa et al., 1996). The ionized and non-ionized acid forms were elucidated to induce a synergic fast increase in the permeability of the outer membrane by interacting with the positively-charged quaternary ammonium groups of the methacrylic copolymer and partitioning into its hydrophobic segments, respectively. Because prolonged lag times and lower release rates were noticed when the osmolarity of the medium was raised, an osmotic pumping effect was also hypothesized to be operating (Narisawa et al., 1997).

3. Delivery systems based on release-controlling plugs

A number of capsular systems were described from which pulsatile delivery was obtained through the timely ejection of a hydrophilic matrix plug sealing the drug formulation in an impermeable capsule body (Table 2). Upon contact with aqueous fluids, a rapid dissolution of the gelatin cap would occur and the plug could indeed undergo a gradual swelling process until expulsion from the body, thus allowing the drug to be delivered. The lag phase prior to release coincided with the time needed for plug removal, and its duration depended on the physical-chemical nature, size and position of the plug itself. This was composed of cross-linked PEG 8000 hydrogel in the original Pulsincap™ device, the suitability of which for time-controlled release was extensively assessed by human imaging investigations (Wilding et al., 1992; Hebden et al., 1999; Stevens et al., 2002). Although regulatory concerns were raised by the use of the hydrogel polymer, the tolerability and patient compliance of a four-week *placebo* treatment that involved multiple daily dosing were established (Binns et al., 1996). However, erodible hydrophilic polymers, such as HPMC of various viscosity grades, PVA, PEO, guar gum and sodium alginate, were later employed as alternative matrix-forming agents to prepare the release-controlling plug (Krögel and Bodmeier, 1998; Ross et al., 2000; Gohel and Sumitra, 2002; Mastiholimath et al., 2007; Nayak et al., 2009; McConville et al., 2009). In some instances, effervescent or highly swellable (e.g. L-HPC) excipients were incorporated into the capsule body to aid a fast release step following the lag phase. Wet-granulated plugs composed of low-viscosity HPMC and lactose were proven more effective than directly compressed ones

Table 2
Outline of pulsatile delivery systems based on release-controlling plugs and references listed according to key formulation characteristics.



Legend	References
(a) Drug formulation (osmotic, effervescent or swellable excipients optionally present)	
(b) Soluble capsule cap	
(c) Capsule body:	
Impermeable	Bar-Shalom et al., 2009; Binns et al., 1996; Gohel and Sumitra, 2002; Hebden et al., 1999; Krögel and Bodmeier, 1998, 1999b; Lee et al., 2000; Mastiholimath et al., 2007; McConville et al., 2004, 2005, 2009; Nayak et al., 2009; Ross et al., 2000; Stevens et al., 2002; Sutch et al., 2003; Wilding et al., 1992
Semi-permeable	Crison et al., 1996; Löbenberg et al., 2005
(d) Release controlling plug:	
Swellable	Binns et al., 1996; Hebden et al., 1999; Stevens et al., 2002; Wilding et al., 1992
Swellable/erodible	Bar-Shalom et al., 2009; Gohel and Sumitra, 2002; Krögel and Bodmeier, 1998, 1999b; Lee et al., 2000; Mastiholimath et al., 2007; McConville et al., 2004, 2005, 2009; Nayak et al., 2009; Ross et al., 2000; Sutch et al., 2003
Hydrophobic	Crison et al., 1996; Löbenberg et al., 2005
(e) Optional immediate-release drug dose	Crison et al., 1996; Löbenberg et al., 2005

in delaying the drug liberation (McConville et al., 2004). Moreover, notable differences were found in the performance of such erosion-based capsular systems when the impermeable EC film was applied by aqueous rather than organic spray-coating to the drug-containing body (Sutch et al., 2003; McConville et al., 2005). Superior mechanical properties upon exposure to high-moisture conditions and a better release control related to a tighter plug seal were indeed observed in the case of organic film-coated capsules. Erodible tablet plugs were also prepared from pectin/pectinase blends (Krögel and Bodmeier, 1999b). Started upon contact with aqueous fluids, the progressive enzymatic degradation of the polysaccharide was demonstrated to defer drug release when the plug pH was buffered in the 4–8 range needed for pectinolytic activity.

On the other hand, an insoluble plug was employed to seal the opening of a semi-permeable capsule body containing the active ingredient along with an osmotic charge in the programmable oral release technologies (PORT™) device (Crison et al., 1996; Löbenberg et al., 2005). The influx of water into the capsule would lead to a surge in its internal pressure ultimately resulting in the plug expulsion and drug liberation into the medium. Lag time was shown to depend upon the permeability of the capsule wall, osmotic strength of the inner formulation and length of the plug. Reproducible delay phases were observed in human γ-scintigraphic and dog pharmacokinetic studies.

Finally, a capsule-like design was exhibited by the Egalet® delivery platform (Lee et al., 2000; Bar-Shalom et al., 2009). When intended for pulsatile release, this system consisted of a drug core embedded in a hollow impermeable shell provided with an injection-molded erodible plug (PEO, high molecular weight PEG) at both open ends. By varying the size and composition of plugs or the drug formulation, it was possible to define the onset and rate of delivery. Proof-of-concept data were achieved through imaging investigations carried out on volunteers.

4. Delivery systems based on osmotic pumping

Osmotic pumping was relied on to develop a once-a-day controlled-onset extended-release (COER-24) formulation of verapamil hydrochloride (Gupta et al., 1996; Prisant and Elliott, 2003). In accordance with the OROS® Push–Pull™ technology, COER-24 consisted of a bipartite core tablet including an expanding polymeric compartment and a drug compartment. The core was entirely coated by a semi-permeable film with laser-drilled orifices connecting the drug tablet with the outer medium. A hydrophilic coat was interposed between the core and the outer membrane to further prolong the delay preceding the onset of release (Fig. 2). Upon water ingress, the active ingredient dissolved and the push compartment started swelling. As a result, the drug solution was pumped out at a constant rate through the orifices of the semi-permeable film. Sustained release of verapamil was demonstrated to occur after lag times of 4–6 h, and a good *in vitro–in vivo* correlation was assessed (Gupta et al., 1996). The suitability of COER-24 for meeting the well-established chronotherapeutic requirements of cardiovascular disease was confirmed by clinical trials (Hermida et al., 2007). Notably, this technology underlies the chronopharmaceutical product Covera-HS that is available on the marketplace.

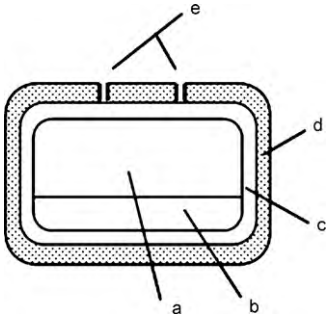


Fig. 2. Outline of the COER-24 delivery system: (a) drug formulation, (b) swelling polymeric compartment, (c) hydrophilic polymeric coating, (d) osmotic membrane and (e) laser-drilled orifices.

5. Conclusion

The large variety of oral pulsatile delivery systems described in the literature highlights the current interest in this particular area of pharmaceutics. Indeed, the assessment of temporal rhythms in an increasing number of disease states, the consolidation of chronotherapeutic approaches and a growing awareness of the impact of patient compliance are likely to strengthen the

research efforts towards the design, preparation and evaluation of such devices. Innovation, scalability, lack of severe regulatory constraints and availability of human proof-of-concept results, however, are expected to play a key role for a successful development of the delivery technologies proposed.

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