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Oral pulsatile drug delivery systems

Alessandra Maroni, Lucia Zema, Matteo Cerea & Maria Edvige Sangalli†
†*Istituto di Chimica Farmaceutica e Tossicologica, Università di Milano, V. le Abruzzi 42, I-20131 Milan, Italy*

In the field of modified release, there has been a growing interest in pulsatile delivery, which generally refers to the liberation of drugs following a programmable lag phase from the time of administration. In particular, the recent literature reports on a variety of pulsatile release systems intended for the oral route, which have been recognised as potentially beneficial to the chronotherapy of widespread diseases, such as bronchial asthma or angina pectoris, with mainly night or early morning symptoms. In addition, time-dependent colon delivery may also represent an appealing related application. The delayed liberation of orally administered drugs has been achieved through a range of formulation approaches, including single- or multiple-unit systems provided with release-controlling coatings, capsular devices and osmotic pumps. Based on these premises, the aim of this review is to outline the rational and prominent design strategies behind oral pulsatile delivery.

Keywords: chronotherapy, delayed release, lag phase, pulsatile release, rupturable film, swellable/erodible coating

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1. Introduction

Drug delivery systems have drawn an increasing interest in the pharmaceutical field over the last few decades. Indeed, they have proven suitable for meeting increasingly sophisticated therapeutic needs, which have been highlighted by impressive advances in the medical and pharmacological areas. This goal has been accomplished by most modified-release dosage forms through a temporal and/or spatial control exerted on drug liberation or, in different instances, through an improvement in the poor bioavailability proper to the vast majority of biotech molecules and many others as well [1].

Up to the early nineties, great efforts have been spent in the design of delivery systems able to release active ingredients over an extended time lapse at a theoretically constant rate; in this respect, the principle of homeostasis, has deeply affected the interests and objectives of pharmaceutical scientists. As a result, their research activity has been grounded on the construct according to which all physiological functions are kept relatively constant in time by inherent mechanisms that are triggered by variations derived from the environment [2-4]. From this standpoint, as compared with multiple dosing regimens implied by sustained treatments based on immediate-release medications, the consistent delivery of drugs in an extended fashion could definitely offer considerable benefits. Among them, particular emphasis has been given to the avoidance of the typical plasma concentration peak–trough fluctuations, reduced administration frequency, consequently improved patient compliance, and lowered overall drug dose required within a given therapy interval [5].

More recently, increased attention has been focused on the advantages likely to arise from opportunely timed drug treatments. Such a shift in interest is clearly related to the advent of thoroughly innovative chronotherapeutics views [6]. In fact, periodicity as a key feature of living organisms has been noticed since ancient times and, in the twentieth century, the assessment of cyclical phenomena at each level of

life organisation has been witnessed along with the at least partial elucidation of its underlying genetic and biomolecular mechanisms [3]. Nevertheless, the impact of basic chronobiology concepts on the practice of medicine is still ongoing. It has been established that 24 h variation frames, circadian rhythms, which are by far prevailing over shorter (ultradian) and longer temporal cycles (circamensual or circannual) as an adaptation to light–darkness alternations, can heavily influence the outcome of a number of therapies and diagnoses due to their neat effect on most physiological parameters. Values of heart rate, blood pressure, platelet adhesiveness, fibrinolysis, blood cell count, respiratory rate, airway resistance, immune system reactivity, hormone secretion, urine output, tissue perfusion, gastric pH, body temperature, mental activity and alertness, to mention but a few relevant examples, are all predictably undergoing marked daily fluctuations. It ensues that the incidence and/or severity of many disease states display a characteristic temporal occurrence rather than being randomly distributed throughout the 24 h day [2-4,7-9]. Ischaemic heart disease and rheumatoid arthritis, most often experienced on awakening, and bronchial asthma, exhibiting by far more frequent dyspnoea episodes within the night or in the early morning, are definitely among the most popular 'chronopathologies' owing to their prominently circadian recurrence as well as high morbidity and, especially as far as myocardial infarction is concerned, mortality indices [2,4,6,10]. Sleep disorders and Parkinson's disease represent further examples of pathologies showing cyclical symptomatology variations. Moreover, the physiological periodicity observed in so many bodily functions is unavoidably reflected in the pharmacokinetic processes relevant to countless drug molecules. Hence, pharmacokinetics can in turn be strikingly variable depending on the time of intake, thereby affecting the onset, magnitude and duration of drug action. Less evident but also documented are circadian patterns in pharmacodynamics, which may relate to the number, binding capacity and susceptibility of receptors being stimulated upon specific drug interaction, thus starting the biological cascade that finally leads to the therapeutic effect. Administration time may therefore play a pivotal role in determining the efficacy and safety of pharmacotherapy [3,7,8].

Based on the above hints, chronotherapy is generally meant as a treatment schedule that takes account of any possible time-dependent variation in the risk or symptomatology of disease, as well as in the pharmacokinetics or pharmacodynamics of the employed drugs when a pharmacological therapy is dealt with. The emerging chronotherapeutic requirements have led to much interest on systems able to release drugs according to a pulsatile pattern [6]. Pulsatile delivery or delayed release are terms usually referred to for the purpose of describing the liberation of a drug after a programmed lag phase starting at the time of administration. At the end of the delay period, drug release takes place either in a prompt or sustained fashion, and thereafter it can also be repeated in one or more further pulses. However, patterns envisaging single or multiple rapid and transient drug outputs are generally considered as the most challenging and even appealing mode of liberation [11,12]. In some instances, release can be triggered by outer events, thus being initiated in response to chemical, thermal, electrical, magnetic and ultrasonic stimuli or enzymatic reactions. In others, it can be governed via biofeedback, typically featuring the glycaemia-dependent delivery of insulin. In contrast to triggered pulsatile release, for time-based delivery systems, merely inherent mechanisms are only exploited to control the onset of drug liberation, irrespective of environment variables such as pH, ionic strength, temperature etc. [13]. Whatever the underlying working principle, the great potential for pulsatile release systems chiefly resides in their suitability for supplying the patient organism with therapeutic plasma levels of an adequate active principle (i.e., affording effective drug disposition at the biophase, when these are especially required). Such biopharmaceutical performances are expected to allow the therapy efficacy to be improved, while enabling a reduction in the side effects likely connected to an excessive, or excessively long-lasting, unnecessary body exposure to the drug molecule. In principle, this would apply to the treatment of chronopathologies [11-13] as well as to replacement [14], cancer [15,16] and, according to recent findings, infectious disease therapy [201]. In pursuit of pharmacological treatments that might be tailored to meet diverse chronotherapeutic needs, an increasing number of devices for pulsatile delivery have been proposed in scientific literature [11-13]. As commonly observed in any domain of pharmaceutics, the oral route is by far preferred, mainly due to cost-effectiveness and generally high patient compliance. Oral pulsatile delivery systems have increasingly been suggested as an especially appropriate means of implementing chronotherapy for circadian illness states that are more frequently recurring within the night hours or soon after awakening [11,12,17]. In fact, provided that the device is purposely programmed to set off release when symptoms are usually encountered, the bedtime intake of medication would yield pharmacological protection when the risk of disease occurrence is higher, thus sparing the patient from being awoken for drug administration or, even worse, as a consequence of his pathology. This could be highly beneficial primarily in the case of aforementioned asthma and ischaemic heart disease. Particularly in the latter case, a chronomodulated antihypertensive approach based on evening dosing has been proven suitable for reducing the incidence of cardiovascular events without increasing that of cerebrovascular damage and optic neuropathy connected to an excessive hypotension condition which may arise following bedtime administration of immediate or prolonged-release formulation [2,18,19].

Besides chronotherapeutic goals, a further interesting application for oral pulsatile release systems results from their possible exploitation to achieve drug delivery into the large bowel, including the caecum and ascending colon which cannot otherwise be reached via rectal route [11,12,20]. For the purpose of colon targeting, an external gastric-resistant film is usually envisaged to overcome highly variable stomach

Table 1. Schematic presentation of quoted oral pulsatile delivery systems according to relevant formulation strategies.

	Coated systems			Capsular systems	Osmotic systems
	Rupturable coating	Swellable/erodible coating	Increasingly permeable coating		
Single-unit reference	[25-30] [31] [32] [33,34] [35] [36-40] [41]	[49,50] [51] [52-65] [67,68] [69-71] [72] [73] [74] [75] [76-78] [79] [80-82] [83,84]	N/A	[92-101] [102,103] [104] [105,106] [107-109]	[19,110-114]
Multiple-unit reference	[42-45] [46] [47,48]	[85] [86] [87]	[88-91]	N/A	N/A

N/A: Not applicable.

emptying. After dissolution of the enteric coating, the onset of release is programmed to take place in 3 – 4 h, which has been demonstrated to roughly correspond to the average small intestinal transit time, practically independent of characteristics of the dosage form, as well as of the fasted or fed state of the subject [20-22]. Despite its relatively poor absorptive characteristics, the colon does represent an interesting release site for absorbable molecules that may cause irritation or be degraded in upper gastrointestinal districts, as well as for non-absorbable ones that are supposed to act in the gut lumen. At present, considerable attention is directed to colon delivery in that it could improve the treatment and prevention of widespread inflammatory bowel disease (IBD) and colorectal adenocarcinoma. Moreover, expectations are being turned to colonic release as a possible strategy to increase the oral bioavailability of peptide and protein drugs, which are known to be less prone to enzymatic degradation in the large, rather than in the small, bowel [20,21,23].

Finally, oral pulsatile delivery systems with a repeated release pattern may be taken into account to enhance patient compliance when multiple-dosing daily regimens are prescribed, but the indicated drug fails to constitute a suitable candidate for prolonged release; for example, this may concern molecules that undergo a strong first-pass effect in the liver or else develop pharmacological tolerance [11-13].

From the formulation viewpoint, oral pulsatile delivery systems have been distinguished in either reservoir or capsular devices respectively provided with release-controlling layers or plugs [11-13] and osmotic pumps. The coatings of reservoir systems, which embody the most numerous and diversified group, work differently according to their composition. Namely, they may, in turn, act as rupturable membranes sensitive to inner pressure rises, swellable/erodible barriers or, finally, as increasingly permeable boundaries. Both single- and multiple-unit devices have been described, the latter intended to provide established benefits, such as gastrointestinal spread, lower influence of gastric emptying variability, improved consistency of biopharmaceutical performance, circumvented risk of dose dumping and possibility of matching subunits with distinct delivery behaviour within one formulation [11,12,24]. These aspects are considered as major advantages, particularly when modified-release dosage forms are dealt with.

Details relevant to the main design and release features of different oral time-controlled pulsatile delivery system prototypes chiefly reported in the primary literature are presented and outlined in the following sections. In Table 1, all systems quoted in the body of the review are listed according to the involved formulation strategy.

2. Delivery systems provided with rupturable coating layers

A considerable number and variety of both single- and multiple-unit oral pulsatile delivery systems are devised as a drug reservoir provided with an outer release-controlling water-insoluble but permeable coating subject to mechanically induced rupture phenomena. Such membrane undergoes partial or complete breakup within a programmable time period after the systems are immersed in the aqueous fluids, thus allowing the inner drug formulation to be exposed directly to the bulk medium. The film rupture responsible for drug release occurs as a consequence of an increasing outward pressure, which results from expansion of the inner core. This may in turn be attained by including swellable, osmotic or effervescent additives in the drug reservoir.

Recently, different systems based on hard [25,26] or soft [27] gelatin capsule and tablet [28] cores were described, all coated by an inner swellable and outer rupturable layer. The authors

also undertook in-depth investigations into the mechanical and swelling properties of films obtained from different materials in order to identify potentially suitable candidates for the preparation of both the breakup and expansion barriers [29,30]. In particular, dry and wet ethylcellulose (EC) and methacrylic copolymer (Eudragit® RS) films with different quali-quantitative composition in plasticisers and pore-former were evaluated in terms of puncture strength, strain, energy at break and modulus as a function of the time of exposure to the aqueous fluid. The study was performed with the aid of a purposely developed test procedure, which allowed subsequent measurements to be carried out on the same specimen. Eudragit® RS afforded very flexible films that underwent small cracks instead of extensive rupture upon stress application, whereas EC films completely broke up owing to their brittle characteristics. EC blends with hydroxypropyl methylcellulose (HPMC) as a pore former (60:40) and hydrophilic plasticiser triethyl citrate (TEC) 20% weight/weight (w/w) turned out to be a promising formulation [29]. As far as the expanding layer is concerned, the superdisintegrant sodium croscaramellose (Ac-Di-Sol®) was proven superior to other screened swellable materials, such as low-substituted hydroxypropylcellulose (L-HPC), sodium starch glycolate, crospovidone and low-viscosity HPMC. Thanks to its remarkable swelling force, Ac-Di-Sol® could yield a complete breakage of the overlapped layer, thus leading to a rapid drug release at the end of the lag phase [30]. From both opportunely formulated hard- and soft-gelatin capsule-based systems, pulsatile delivery patterns were achieved encompassing a lag time followed by a fast release phase. The lag time increased as a function of the outer coating level and was decreased by including therein higher percentages of HPMC, or else by enhancing the thickness of the underlying swelling layer. Shorter lag times were obtained from coated soft-gelatin as compared with analogous hard-gelatin systems. This result was explained by the possibility that in hard-gelatin units, which were not completely filled with powder, the swelling pressure could partly be discharged inwards. Differently, due to the complete liquid filling of soft-gelatin capsules, the whole pressure developed by the swelling layer was directed onto the outer film, which was consequently subject to an earlier breakup [25,27]. Analogous data were attained in the case of tableted cores as regards the influence of the above formulation variables on pulsatile release performances, although lag phases were unexpectedly shown to lengthen as the Ac-Di-Sol® amount increased. In this respect, it was hypothesised that the sodium croscaramellose layer might delay, by imparting higher hardness characteristics to the system and hindering water penetration when in the hydrated state, the contribution of the core disintegration to the overall swelling force exerted on the EC film [28].

A further example of a single-unit device based on the swelling-induced rupture of an outer EC membrane was proposed by Morita and colleagues [31]. On account of the relevant working principle, it was named Swelling Controlled Release System (SCRS). In more detail, an inner tablet core, which contained emedastine difumarate and polyvinyl alcohol (PVA), respectively, as the hydrophilic model drug and swellable material, was coated with EC and HPMC blends in different weight ratios. PVA was selected in view of its peculiar swelling behaviour, which can be modulated depending on the hydrolysis degree (i.e., the percentage substitution of acetate groups with hydroxyls, and the presence of salts). In fact, ions compete with PVA for interaction with water molecules, thereby hampering the polymer swelling process. When organic or inorganic salts were added (sodium chloride, trisodium citrate dihydrate, sodium sulfate), and high HPMC amounts were included in the external membrane composition, the swelling of PVA slowed down and the drug could meanwhile diffuse outwards through the hydrophilic pore net, thus resulting in a prolonged release fashion. Differently, the avoidance of salts along with the inclusion of a relatively high PVA quantity in the core and restrained HPMC content in the rupturable film (EC:HPMC 75:25, TEC 10% w/w) finally led to a burst-like breakup of the latter, which was caused by the rapid swelling agent expansion. Prior to membrane disruption, the model drug release was prevented due to the poor permeability of EC film, comprising only small amounts of hydrophilic pore-former. Therefore, typical pulsatile release profiles were achieved, in which the delay phase was extended in duration as a function of the rupturable film thickness.

Fan and colleagues [32] devised another swelling-based rupturable system in the form of a coated tablet, prepared with crosslinked polyvinylpyrrolidone (PVP) as the hydrophilic swellable polymer and diltiazem hydrochloride as the model drug. The rupturable film was composed of EC and the gastric resistant acrylic resin Eudragit® L in a 1:2 ratio. The system proved to withstand the acidic pH value typical of gastric fluid and, after an additional off-release phase from the pH switch to 6.8, a rapid liberation of the active ingredient was observed. Lag time was primarily affected by the weight gain determined by the coating application. A key step in the overall release control was identified in the pH-dependent dissolution of the Eudragit® L component, which caused pores to form within the EC membrane. The resulting penetration of water into the core brought about an increase in the swelling agent volume, until breakage of the outer insoluble film. The performances of the device were also explored *in vivo* on eight volunteers versus an immediate-release tablet containing an equal dose of diltiazem hydrochloride. The appearance of detectable drug amounts in the plasma was clearly delayed by the delivery system in exam. No significant differences were found in the area under the plasma concentration versus time curve from t = 0 to t = 24 h (AUC_{0-24}) and maximum plasma concentration (C_{max}) relevant to the compared formulations, thus suggesting that neither the *in vivo* rate of release nor that of absorption were altered by the device. On the other hand, lag time (t_{lag}) and maximum time (t_{max}) were prolonged and demonstrated to be in good agreement with *in vitro* data.

The same swelling-dependent working principle and core form characterised a system previously proposed by Ishino and colleagues [33]; however, these authors described an outer release-controlling barrier composed of co-melted polyethylene glycol (PEG) 6000 and hydrogenated castor oil mixtures in various ratios, which were applied onto isoniazid and calcium carboxymethylcellulose-containing tablets by presscoating technique. The system afforded a rapid drug release following delay phases, which could be programmed through the opportune modification of the thickness and/or PEG 6000 content of the external coat. The *in vivo* evaluation on beagle dogs of diltiazem hydrochloride-based prototypes pointed out an ample inter-individual variability in the fasted state and more reproducible performances in fed subjects [34].

Recently, a single-unit rupturable system was designed by Zhang *et al.* [35], in which both swelling and osmotic excipients contributed to the water uptake required for the breakup of an insoluble but permeable surrounding membrane. The system consisted in a tablet core containing the potent bronchodilator terbutaline sulfate, which could be indicated in the chronotherapy of nocturnal asthma attacks, and sodium chloride as an osmotic agent. An inner low-viscosity HPMC (Methocel® E5) coating was applied as the swelling layer, whereas mixtures of Eudragit® RS and RL were used to prepare the rupturable membrane. The latter methacrylic copolymer was added to enhance the aqueous flux across the external film, due to its two fold higher number of positively charged quaternary ammonium groups. The system was shown to give rise to *in vitro* pulsatile delivery performances only when both sodium chloride and HPMC were comprised in the formulation. In particular, a prompt drug release was preceded by lag phases of increasing duration as a function of the outer coating level. Scanning electron microscope-aided analysis elucidated that the drug liberation occurred through few micrometer-sized gaps formed in the release-controlling membrane as a result of the core expansion.

EC, commonly used as the main component of rupturable films, was also applied by press-coating onto pure sodium diclofenac tablet cores [36]. A delayed-onset and rapid-completion delivery of the inner drug was achieved from this system as well. In the course of *in vitro* studies, a link was highlighted between breakup of the EC shell into upper and lower halves and the occurrence of the release process. The authors hypothesised that a different packing density of the polymer powder between side and upper/lower regions could account for the observed EC matrix symmetrical disruption. Less dense packing characteristics were imparted by press-coating procedure to the side structure as compared with the upper and lower surfaces. The loose density was deemed responsible for the formation of the lateral breach in the EC shell. The silent phase duration turned out to be markedly affected by the particle size of the employed EC type. Indeed, larger particle dimensions were related to a higher porosity of the coating layer, thus resulting in enhanced water permeability. Accordingly, the longest delays were attained when micronised powders of the polymer were used. In a subsequent research step, increasing lag times were achieved by applying higher compression forces as well as thicker micronised EC layers onto the drug tablet [37]. Moreover, when embedding in the core either swellable (HPMC, sodium starch glycolate) or osmotic (sodium chloride) excipients, the latter proved more effective in bringing forward the onset of release, even in the presence of model drugs different from diclofenac sodium (theophylline and salbutamol sulfate) [38]. The addition of hydrophilic adjuvants, such as sprayed-dried lactose or HPMC, into the outer shell formulation also resulted in shortened induction phases. Because they did not cause any concomitant alteration of the release rate, these materials appeared to constitute a potentially suitable tool for the modulation of lag time [39]. Finally, while keeping the composition of the lower shell layer constant (EC with average particle size of 167.5 µm), many different formulations were evaluated for the upper layer, encompassing mixtures of the same EC powder with micronised EC or various excipients (microcrystalline cellulose, spray-dried lactose, dibasic calcium phosphate anhydrate, HPMC). The overall findings seemingly suggested that the preparation of a bipartite coating, in which the upper part was based on blends of the above-mentioned materials, could provide a further means of regulating the delay phase and, depending on the physicochemical properties of the specific additive, may involve release mechanisms other than the shell split into two halves shown by the original device [40].

Krögel and Bodmeier [41] proposed a single-unit system, which exploited a different rupture-inducing mechanism. Namely, carbon dioxide, developed by a typical citric acid/sodium bicarbonate effervescent mixture contained within a core tablet, determined the outward expansion required for breakage of the external release-controlling membrane. EC plasticised with 20% w/w dibutyl sebacate was selected as the film-forming agent. A fast liberation of chlorpheniramine maleate was attained after reproducible lag times, which could be programmed by varying the core hardness and/or coating level. Interestingly, when Eudragit® RL was used in place of EC, floating dosage forms were achieved because of the higher permeability and flexibility characteristics of the films, which allowed water to diffuse into the inner tablet without any delay and underwent no disruption caused by subsequent gas development.

Rupturable systems for oral pulsatile release were also designed in multiparticulate form. A frequently quoted example relates to the Time-Controlled Explosion System (TES) [42]. These authors reported the preparation of the system from inert sucrose seeds, which were coated with overlapping layers. The inner layer contained the active ingredient, the intermediate layer composed of highly swellable L-HPC, and the external membrane was based on EC [43]. The swelling-dependent rupture occurred as previously described in regard to analogous single-unit devices. A thickness threshold of 180 µm was assessed for the L-HPC layer, below which

diffusion-controlled release was observed instead of sudden delivery following the silent phase. Moreover, the influence of drug solubility, drug content and medium pH on the release behaviour was excluded through the comparative use of model molecules with different physicochemical properties. The particle size of subunits was also shown not to impact on the delivery mode. Afterwards, the role of the EC film was investigated more in-depth [44]. It was demonstrated that the thickness of such membrane primarily affected lag time, irrespective of the pH values in the release environment. The addition of an equal amount of talc into the membrane composition resulted in shortened delay phases. TES prototypes containing a vasodilator and antiplatelet drug were also evaluated *in vivo* [45]. Results collected from a bioavailability study performed on nine volunteers indicated that *in vitro* release and *in vivo* absorption data were consistent. Furthermore, AUC was not significantly different after TES administration to fasting and fed subjects, nor following intake of TES and of an immediate-release single-unit dosage form in fasted conditions. Relying on the above findings, the authors hypothesised a potential suitability of this TES formulation for twice-daily dosing chronotherapy of ischaemic heart disease, which could also limit first-pass effect and tolerance drawbacks entailed by the loaded active ingredient.

Rupturable pellets based on a plasticised (15% w/w dibutyl sebacate) EC film were proposed by Hartman Kok *et al.* [46], who thereby aimed at < 1 h lag phases. The pellets contained sodium chloride as an osmotic agent, with or without a swellable polymer to enhance the core expansion. The addition of the swelling excipient was demonstrated to shorten lag time but, contrary to the authors' expectations, was not effective in increasing the release rate. Fast delivery was proven achievable when uniform-sized subunits were employed.

Another rupturable multiparticulate system in the form of pellets was previously designed by Schultz and Kleinebudde [47]. In this instance, however, the expansion process responsible for the formation of micrometric fissures in an outer semipermeable cellulose acetate membrane was only related to an osmotic gradient established across the membrane itself due to the presence of sodium chloride in the pellet formulation. In order to obtain delayed release of the model drug acetaminophen, a minimum quantity of coating material (2 mg/cm^2) was required. Beyond such value, a linear correlation was found between duration of the lag phase and coating level. The addition of plasticisers (TEC, tributyl citrate or diethyl phthalate) into the composition of films led to a decrease in the relevant water permeability as a function of the excipient lipophilicity, eventually resulting in an extended lag time and a lowered release rate [48]. On the other hand, the mechanical film characteristics, evaluated by means of a tensile testing apparatus, were more affected by the content rather than the type of the added plasticiser. Lastly, it was assessed that the presence of talc within the membrane structure only influenced the duration of the delay phase.

3. Delivery systems provided with swellable/erodible coating layers

There are several examples in the literature of reservoir systems provided with barrier coatings which may swell, erode and/or dissolve upon contact with aqueous fluids. In most instances, hydrophilic cellulose derivatives, such as hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC) and HPMC, are employed as the main components of the release-controlling coat in view of their in principle adequate swelling behaviour, consolidated safety profile, ease of handling, general availability in several grades and reasonable costs. Press-coating technique is primarily exploited for the application of such polymers onto single- or, in a few cases, multiple-unit drug cores.

Tablet cores dry-coated with HEC were prepared and evaluated by Matsuo *et al.* [49]. Pulsatile delivery of diltiazem hydrochloride, selected as the model drug due to its applicability in the chronotherapy of cardiovascular disease, was achieved by this system and the time to release onset was found to depend on the thickness of the coating layer; furthermore, a minor role was played by the polymer particle size. With increasing particle dimensions, in fact, shorter induction phases were noticed, which the authors attributed to an initially facilitated water uptake by powders with higher porosity. Moreover, the viscosity grade of HEC was also demonstrated to affect the duration of lag time, both *in vitro* and *in vivo* on five volunteers [50]. Longer delays corresponded to more viscous polymers. Although AUC did not significantly vary, C_{max} underwent a progressive decrease as t_{lag} was lengthened. Consistent *in vitro* and *in vivo* lag time values were highlighted, even if the latter tended to last slightly less.

An analogous diltiazem hydrochloride-containing tablet system was presented by Fukui and colleagues [51], for which, however, HPC was employed as the coating material. This system also proved able to delay drug delivery for a time period increasing as a function of viscosity as well as applied amount of the swellable polymer, without causing any alteration of the relevant rate. Prototypes with *in vitro* lag times of 3 and 6 h, respectively, were evaluated on four beagle dogs. An agreement was found between *in vitro* and *in vivo* lag times referred to the first prototype. On the other hand, the *in vivo* delay phase imparted by the latter system was shorter than *in vitro*. Such discrepancy was reduced when the *in vitro* study was performed at the paddle rotation speed of 150 rpm.

Many researchers focused on the use of HPMC as the release-controlling polymer; for example, various coating techniques aimed at the application of HPMC barriers were investigated throughout the development of the Chronotopic™ system [52-65]. This device was conceived by Gazzaniga and colleagues as a single- or multiple-unit drug-containing core, coated with hydrophilic swellable HPMC of different viscosity grade. The authors reported that, upon hydration, such a layer underwent increasing permeability, swelling, erosion and/or dissolution phenomena, which

finally resulted in the delayed onset of a rapid and quantitative release of drugs. The duration of the lag phase was dependent on the physicochemical properties and amount of the applied polymer, as well as on the employed coating technique. By introducing appropriate design modifications, colon delivery was pursued relying on the time-based approach [53,56,58]. For this purpose, the application of a sufficient quantity of release-controlling polymer and of an outer enteric film, which might overcome the influence of highly variable gastric emptying time, was required. The possibility of attaining selective drug delivery into the colon was highlighted through γ-scintigraphic and pharmaco-scintigraphic studies by Sangalli *et al.* [60,66]. The achievement of the HPMC coat represented a challenging technological aspect for the system preparation. Initially, press-coating [55,57] and hydro-alcoholic spray-coating of high-viscosity HPMC grades (Methocel® K4M and K15M) [52-58], which were assumed to be more effective in deferring drug release but had never been used before in the role of spray-coating agents, were attempted by Gazzaniga and co-workers. Although in both cases a successful outcome was obtained in terms of physical-technological requisites and release performances, considerable drawbacks were connected with either technique. Besides entailing general operational disadvantages, dry-coating would have hindered the preparation of the system in multiparticulate forms. On the other hand, the use of organic solvents, which was well-known to raise major environmental, safety-related and consequent regulatory problems, remained an open issue. Therefore, the feasibility of HPMC-based aqueous spray-coating procedures was explored [59,61]. As compared with higher viscosity grades, Methocel® E50, in particular, was shown to afford feasible coating operations both in fluid bed and rotating pan, reasonable process time and robust formulations. These benefits were coupled with a satisfactory capability of delaying drug delivery without decreasing its rate, and an appreciable flexibility in the modulation of lag time without implying excessive coat thickness values. An *in vivo* pharmacokinetic study involving four fasting volunteers pointed out the delayed appearance of the model drug antipyrine in saliva, with lag time increasing as a function of the coating level [60]. *In vitro* and *in vivo* delays were of the same rank order. Moreover, the possibility of preparing the Chronotopic™ system starting from hard- and soft-gelatin capsules was investigated [62,63]. The use of such dosage forms as cores for the device could enable a time-controlled liberation of liquid or semisolid incorporated formulations. This appeared potentially interesting in view of pursuing time-based colon delivery to enhance the oral bioavailability of peptides and proteins. The aqueous Methocel® E50-based spray-coating procedure was successfully performed following a progressive adjustment of operating parameters, with no need for the application of a subcoating to protect the gelatin shells. Coated capsules with good physical-technological requisites were obtained, which proved capable of giving rise, *in vitro* as well as on six fasting volunteers, to programmable delays prior to a prompt release of the model drug acetaminophen. Lastly, more recent studies were undertaken with the aim of further improving the overall time and yield of the coating process [64,65]. In this respect, tangential spray-coating in rotary fluid bed and powder-layering turned out to be potentially advantageous techniques.

Either gellable or erodible HPMC barriers applied by dry-coating were also exploited by Conte *et al.* [67,68] to attain delayed release from tablet cores regardless of the solubility and formulation characteristics of the inner drug. Erodible layers, which were based on low-viscosity HPMC (Methocel® E3, E5 and E50), were shown not to alter the release kinetics after the initial lag phase, whereas the rate of delivery could be controlled by swellable shells based on high-viscosity HPMC (Methocel® K4M and K100M).

Halsas *et al.* [69] proposed another high-viscosity HMPC (Methocel® K4M) dry-coated tablet, in which the total amount of ibuprofen, chosen as the model active ingredient on account of its potential suitability for a chronotherapeutic approach to rheumatoid arthritis, was either contained in the core or divided between the core and coat. When the whole drug content was located in the inner tablet, slow release and slowly increasing drug plasma concentration preceded by a lag time were obtained *in vitro* and *in vivo* (two randomised crossover single-dose studies involving four groups of eight healthy volunteers), respectively. With higher applied amount of HPMC, lag phases were prolonged and both the rate of release and bioavailability diminished. Differently, when fractions of the overall drug dose were introduced into the outer shell, a biphasic slow delivery pattern with no lag time was observed, which was reflected in double-peak plasma drug concentration profiles. Finally, sodium alginate was also investigated as the swellable material. Its use apparently led to a faster release of the core drug fraction both *in vitro* and *in vivo*. Furthermore, the effect of blending different HPMC viscosity grades (Methocel® K100 and K4M) in the coat formulation was explored [70]. Such combinations turned out to constitute an interesting means of adjusting the ibuprofen release performances from the system. In particular, shorter lag time and faster release were attained when low versus high-viscosity HPMC ratio was enhanced. Qualitatively analogous results were collected from two randomised crossover single-dose studies involving four groups of eight healthy volunteers. However, no satisfactory correlation could be established between *in vitro* and *in vivo* data. In order to evaluate the appropriateness of this press-coated system to convey highly soluble drugs, pseudoephedrine hydrochloride was employed in place of previously used sparingly soluble ibuprofen [71]. When the whole drug dose was contained in the core tablet, prompter pulsatile release and corresponding faster *in vivo* absorption after a lag time were achieved in the case of Methocel® K100-based coating. The use of the higher viscosity HPMC resulted in prolonged *in vitro* and *in vivo* lag phases as

well as in slower release and absorption processes. The authors concluded that time-controlled delivery of drugs with different water solubility at 6 to 8 h after intake, as possibly required by evening chronotherapies of early-morning diseases, could be attained through an opportune formulation within the described press-coated system [70,71].

Recently, high-viscosity HPMC was used to coat nifedipine-containing tablets by the dipping method [72]. Delayed release curves were obtained *in vitro*, with lag time and delivery rate affected by the coating level and adopted coating conditions. In particular, when ethanol/water ratio was raised or HPMC concentration decreased in the vehicle, longer silent phases were observed. On the other hand, the rate of nifedipine release diminished by extending the time during which the polymer was allowed to swell in the hydro-organic mixture prior to the dipping step. Such results were ascribed to the influence exerted by the above-mentioned parameters on the morphology and barrier properties of the HPMC layer.

In pursuit of time-based colon delivery, Takeuchi *et al.* [73] prepared by spray-drying composite lactose, sodium alginate and chitosan particles, in which a sodium alginate/chitosan complex was formed. These powders, which showed good flowability and compaction characteristics, were applied onto acetaminophen-containing tablet cores by press-coating. Release was prevented, or at least considerably slowed down, in media with pH of 1.2 – 5. Gelification and the erosion phenomena of the coating layer occurring in pH 6.8 fluid delayed drug delivery as a function of the amount and deacetylation degree of chitosan.

The possibility of achieving pulsatile release from press-coated tablets was also pursued by utilising non-conventional dry-coating techniques. Such alternative procedures were primarily devised for the purpose of overcoming practical drawbacks typically implied by double-compression, such as the difficult location of the inner core exactly in the die centre, the need for longer and more complicated multiple-step processes and, consequently, the possible lack of reasonable scale-up prospects. In this respect, the ENCORE™ and OSDRC (one-step dry-coated tablets) systems are worth mentioning [74,75]. In the first instance, time-controlled delivery of theophylline was obtained from 35% polyethylene oxide (PEO) and 65% lactose coated tablets [74]. The latter system yielded acetaminophen release patterns with lag time increasing as a function of the lateral HPMC shell thickness and the compression pressure [75].

In some cases, compression techniques were exploited to prepare multilayered or concentric tablets, which were provided with a partial outer coating aimed at protecting only specific peripheral areas of the system from the bulk medium. A first example was represented by a three-layer tablet with a release-controlling intermediate hydrophilic barrier based on a mixture of high-viscosity HPMCs (Methocel® K4M and K15M), interposed between two ibuprofen-containing compartments [76]. The lateral surface of the separation barrier, along with the entire surface of the bottom drug layer, were covered with a 0.2-mm thick impermeable EC film, thus allowing the exposed area of the top layer to interact freely with the aqueous fluids. The *in vitro* release pattern included two subsequent release pulses, one immediate and one delayed in time. The first pulse was related to the prompt liberation of ibuprofen from the upper uncoated layer, whereas the lag phase preceding the second pulse was due to the progressive hydration of HPMC polymers present in the intermediate barrier. Once water molecules were able to reach the superdisintegrants contained in the bottom layer (crosslinked PVP and sodium starch glycolate), these swelled greatly, thereby promoting disintegration of both the barrier and underlying tableted compartments. A partial loss of efficiency of superdisintegrants, attributed to their gradual hydration mode, was indicated as the likely reason for a slower second-pulse delivery. Double-peak plasma concentration curves in agreement with the corresponding *in vitro* release profiles were obtained after single administration of the system to two volunteers. Lag time was programmable by varying the percent amount of the employed HPMC grades [77]. A further *in vivo* study carried out on three fasting volunteers with a formulation devoid of drug in the top layer, pointed out that the onset of detectable plasma levels of the active principle was fairly reproducible in time. Another development stage of this system envisaged the application of a high-viscosity HPMC in-lay shell via press-coating instead of the manually prepared partial EC seal [78].

A system based on a cylindrical inner core inserted into a hollow HPC matrix was also devised [79]. The upper and lower bases of the resulting tablet assembly were protected by impermeable ethylene vinyl acetate copolymer seals. All preparation steps (i.e., the outer matrix perforation, opportune combination of the two parts and selective impermeable coating application) were manually performed. *In vitro* lag times were shown to last until complete radial erosion or detachment of the external shell. The relevant duration was dependent on the thickness of the shell itself and on the core formulation. As compared with microcrystalline cellulose, lactose, for example, exerted a strong osmotic action, thereby leading to a faster release onset determined by early separation of the two concentric tablets. Prolonged drug delivery was also achieved when a HPC matrix was used as the inner core. On account of the achievement of delays on the order of few hours, such a device was proposed by the authors as a potential means of colon targeting.

Hydrophobic blends of natural waxes (carnauba and white beeswax) and surfactant (polyoxyethylene sorbitan monooleate) were employed as the release-controlling material for the Time-Clock® system [80]. Such mixtures were applied by spray-coating of water dispersions kept at 75°C. When exposed to the aqueous fluids, the hydrophobic barrier was subject to a progressive redispersion, thus delaying drug release for a time period correlated with its original thickness. Within pharmacokinetic and γ-scintigraphic investigations,

each carried out on six volunteers under different digestive conditions, the system demonstrated to afford reproducible lag times, which were not affected by food intake. AUC and C_{max} values, relevant to the model drug salbutamol sulfate, were not decreased as compared with those pertaining to a corresponding immediate-release formulation; however, a considerable gap was noticed between *in vitro* and *in vivo* delays, as the lag phases observed *in vivo* were by far longer. A good agreement was assessed when the *in vitro* test was performed in 120 cps viscous media. Provided with an external enteric coating, this device was proven suitable for time-dependent colon targeting by γ-scintigraphy [81,82].

A peculiar example of single-unit system for pulsatile release was that prepared by Three Dimensional Printing™, a novel technique allowing dosage forms with highly complicated internal structures to be microengineered [83]. It envisaged computer-aided spreading of thin powder layers alternated with printing of binder droplets. Extremely accurate spatial placement of material amounts even on the order of micrograms was enabled by such a process. The resulting device was based on Eudragit® E, which is soluble below and permeable above pH 5, and contained chlorpheniramine maleate in the central region. Delayed release of this drug was observed, showing a progressive rate decrease connected with lengthening lag phases. The delay time was dependent on Eudragit® E content; moreover, double-pulse pH-dependent release was obtained by printing diclofenac sodium into two different Eudragit® L internal domains or by combining external Eudragit® L and inner Eudragit® E compartments, all housing drug-printed regions inside [84].

Finally, only a few examples of swellable/erodible multiple-unit systems for pulsatile delivery were proposed. Still exploiting the hydration properties of HPMC (Methocel® K100M), Li and Zhu [85] devised a multiparticulate system based on subunits with different delivery behaviour contained within a hard-gelatin capsule. Minitablets with or without an external HPMC press-coating and HPMC minimatrices were prepared to afford immediate, prolonged and delayed-release features. Through the proper combination of diverse subunits, the authors achieved versatile nifedipine delivery patterns, also including multi-pulse release profiles.

Pellets coated with Eudragit® L30D55, in which a network of crosslinked pentaerythritol triacrylate was incorporated, were devised by Hartman Kok *et al.* [86]. After coating, pellets maintained in a fluidised state were exposed to a UV light of 365-nm wavelength, so that crosslinking might be initiated. Such a reaction was essential to opportunely modify the dissolution characteristics of the employed acrylic resin, which is normally soluble at pH values > 5.5. In contrast, the resulting material was shown to swell and become permeable as a consequence of water uptake. As pursued, fast release of the pellet contents was obtained after predetermined lag times on the order of few minutes. The delays were dependent on the coat thickness as well as on the time of UV exposure.

Another multiparticulate system provided with a methacrylic copolymer-based release-controlling barrier was formerly described by Kao *et al.* [87]. This device consisted in nonpareil seeds loaded with diltiazem hydrochloride and externally coated by a Eudragit® RS membrane plasticised with TEC. Pulsatile release profiles were attained, with lag phases lengthening as a function of the applied polymer amount and of curing time. The delay phase was ascribed to the time taken by the polymeric layer to fully hydrate, thus enabling a prompt outward diffusion of drug. Hence, the authors suggested that Eudragit® RS coatings might be suitable for deferring the release onset of drug molecules with high and pH-independent water solubility, thereby affording selective delivery into different gastrointestinal sites.

4. Delivery systems provided with increasingly permeable coating layers

Based on the observation that the release rate of theophylline from Eudragit® RS-coated beads was considerably improved in organic acid solutions, Narisawa and colleagues [88] designed a multiple-unit system comprising a drug (theophylline or acetaminophen)/succinic acid mixture loaded on nonpareil seeds and an outer Eudragit® RS film applied by aqueous spray-coating. Sigmoidal *in vitro* release curves were obtained for both model drugs, with lag phases increasing in duration as a function of the coating level. Thereafter, the device was named Sigmoidal Release System (SRS). A pharmacokinetic study carried out on three fasting beagle dogs confirmed the *in vitro* findings by providing almost superimposed lag time values. The release behaviour of SRS containing either theophylline or propranolol hydrochloride (i.e., model drugs with markedly different water solubility) was subsequently investigated [89]. For this purpose, 100 mg amounts of product lodged inside small polyester-net bags, which were proven not to alter mechanical stress nor delivery phenomena undergone by the beads in the gastrointestinal tract, were administered to two fasting beagle dogs at subsequent time intervals. After recovery, the beads were analysed for residual drug content. The *in vivo* release data of propranolol hydrochloride were in good agreement with those attained *in vitro*. On the other hand, theophylline was not completely delivered from the formulation, although *in vitro* and *in vivo* lag times were quite similar. The different *in vivo* release performances of theophylline were ascribed to the possible influence of the limited fluid volume in the distal gastrointestinal tract on the dissolution process of poorly water-soluble drugs. The working principle of the device was also explored through various dissolution, ion exchange and glass transition temperature experiments, particularly with regard to the release-controlling mechanism operated by the Eudragit® RS coat [90]. It was elucidated that both the ionised and nonionised forms of organic acids were involved in enhancing the water permeability of the polymeric membrane through a corresponding improvement in the relevant

hydration rate. This was accomplished by ionic interaction of the carboxylic anions with the positively charged quaternary ammonium groups and partitioning of the nonionised acid molecules into the hydrophobic segments of Eudragit® RS, respectively. Moreover, following the observation that lag time was prolonged and release rate diminished by increasing the medium osmotic pressure through the addition of a non-ionisable excipient (glucose), an osmotic pumping effect was also supposed to contribute to the overall SRS delivery mechanism [91]. Namely, it was hypothesised that said effect could drive the liberation of drugs in a saturated solution after the critical point was reached (i.e., a time at which water influx and efflux across the polymeric membrane balanced each other).

5. Capsule-shaped delivery systems provided with release-controlling plugs

Many single-unit devices for pulsatile release were designed in the form of capsules, which were characterised by the presence of an additional element besides the cap and body components. Namely, all of them were provided with a release-controlling plug inserted into the body open end, which worked according to the physicochemical properties of the material it was composed of. The Pulsincap™ was the first capsular delivery system to be proposed for time-controlled release [92,93]. It essentially consisted of a water-soluble cap and a rigid, insoluble and impermeable body, which was filled with the drug formulation and sealed by a hydrogel plug based on crosslinked PEG 8000. When in contact with the aqueous fluids, the cap rapidly dissolved and the plug began to swell as a result of water uptake, thus gradually increasing in volume until ejection from the body and consequent release of the capsule contents. The time taken for the plug removal depended on the size and position of the plug itself within the capsule body. Noteworthy reproducibility of *in vitro* and *in vivo* lag times was highlighted through γ-scintigraphy imaging on eight volunteers. Despite the smart design, some concerns were raised by the apparently complicated manufacturing process and, above all, in connection with the use of non-approved crosslinked hydrogel for the plug preparation. In this respect, various investigations were undertaken both on animals and humans to assess the safety profiles of either placebo or drug-containing Pulsincap™ units [94]; in particular, the general tolerability related to repeated administrations of placebo Pulsincap™ was assessed on 12 volunteers through a twice-daily dosing regimen extended over a 28-day period. For this study, a 190 mg hydrogel plug was employed because such weight represented the maximum compatible with the largest capsule size envisaged for the system (size 0). The treatment was well tolerated, as no adverse reactions or side effects could be attributed to the product under examination, and was also fully complied with, as none of the enrolled volunteers exited the 28-day trial prior to completion. The Pulsincap™ was also presented in gastro-resistant configuration, so as to exploit the time-based approach to colon delivery [95]. The plug was shown by γ-scintigraphic analysis to be selectively propelled out of the capsule body within the caecum or ascending colon regions in all cases (nine volunteers). By combining scintigraphic imaging and pharmacokinetic techniques, the authors could take advantage of systems containing opportune marker drugs to carry out non-invasive evaluations of the inherent permeability characteristics and absorption potential of the large bowel [96-98]. With the aim of simplifying the original Pulsincap™ technology, systems based on an erodible plug in place of the hydrogel one were also proposed [99]. In fact, it would have been thereby possible to overcome drawbacks related to the use of crosslinked PEG, as well as to the need for achieving plugs with accurate dimensions and highly reproducible position within the capsule body. Accordingly, EC-coated capsules containing a propranolol hydrochloride tablet on top of a L-HPC filling were sealed by an erodible plug with varied composition and evaluated *in vitro*. L-HPC was included in the formulation because it was expected to promote the tablet expulsion after erosion of the plug owing to its marked swelling characteristics. The use of lactose and Methocel® K100LV mixtures as the plug-forming material demonstrated to yield the pursued pulsatile release performances. The rapid and complete drug liberation occurred following a lag phase, which could be modulated by changing the weight (i.e., the thickness and/or percent composition of the plug). The effect of wet granulation on the erosion behaviour and release control displayed by such plugs was explored through various experimental techniques [100]. Longer lag times were attained in the case of wet granulated as compared with directly compressed plugs. The prolongation of delay was more evident for formulations with low HPMC content (15%). Microwave dielectric analysis helped to elucidate that in the course of wet granulation processes performed on blends with smaller polymer percentages, a higher water mobility could enable greater disentanglement and spreading degree of macromolecular chains within the wet mass, thus resulting in a more homogeneous and intimate mixture of the tablet components. Recently, nuclear magnetic resonance studies were carried out in order to investigate whether any possible difference in the routes and/or timescale of inward water transport might account for the unlike behaviour of capsules which the EC film was applied on by aqueous or organic spray-coating [101]. It was hypothesised that the reason for the less effective and more variable performances of aqueous-coated capsules could reside in a less tight seal operated by the lactose and dibasic calcium phosphate-based plugs. In such systems, water influx was therefore allowed to occur through the gap between plug and inner wall of the capsule body, thus resulting in premature and erratic delivery of the contents.

Devices comprising a polypropylene impermeable capsule body, a swellable/erodible plug and effervescent excipients included in the drug formulation were proposed by Krögel and Bodmeier [102]. Aiming at a Pulsincap™-like ejection mechanism of hydrated plugs, the authors first explored the outcome of swellable tablets coated with Eudragit® RS100,

RL100 or NE30D; however, those films underwent early rupture phenomena and, moreover, hindered the gradual plug displacement, even when lubricants were used. Hence, uncoated tableted plugs composed of various HPMC viscosity grades (Methocel® E3, E5, K4M, K15M and K100M), PVA (Mowiol 40-88) and PEO (Polyox® K100 and K8000), were prepared and evaluated. Alternatively, melted saturated polyglycolated glycerides (Gelucire® 44/14 and 50/13) or distilled glyceryl monooleate (Myverol® 18-99) were poured into the capsule opening and directly congealed in the final plug position. The release of different model drugs (chlorpheniramine maleate and ibuprofen) was delayed for time lapses which were dependent on the weight of the plug as well as the physicochemical properties and percent amount of the employed swellable polymer. Following the lag phase, a fast delivery was obtained when adding sodium bicarbonate and citric acid into the capsule body. Plug tablets formed from natural polysaccharide pectin and enzyme pectinase were also envisaged for the above-described system [103]. Upon contact with the aqueous fluids, the progressive enzymatic degradation of the polymer substrate was initiated. The time to release could be modulated by changing the polymeric substrate/enzyme ratio and the total weight of the tablet. The presence of an appropriate buffering agent (potassium dihydrogen phosphate) in the formulation allowed the pH value in the very proximity of the plug to be maintained close to the optimum 4 – 8 range for this enzyme activity. Besides, it prevented pectinase from being degraded via pepsin catalysis in acidic media.

More recently, analogous diltiazem hydrochloride-containing capsular systems provided with high-viscosity HPMC (Methocel® K4M) or guar gum swellable/erodible plugs either in tablet or powder form were proposed, in which the capsule body was rendered insoluble and impermeable through the exposure to formaldehyde vapour, which resulted in crosslinking of gelatin [104].

An alternative capsule-shaped design was conceived for the Programmable Oral Release Technologies (PORT™) system [105]. It consisted of a hard-gelatin capsule, a semipermeable cellulose acetate coating applied onto the capsule body, an insoluble lipid (Gelucire® 50/02) plug, and an osmotic charge/drug mixture as the inner formulation. Optionally, an immediate-release drug dose could be housed in the cap above the plug, in order to allow double-pulse delivery. The working principle of this device relied on the time-controlled expulsion of the lipid plug following a surge in the capsule internal pressure, which, in turn, was brought about by osmotically induced water influx across the semipermeable membrane. The delay phase could be controlled by modifying the thickness of the outer coat, the length of the plug and/or the osmotic strength of the body contents. A γ-scintigraphic study carried out on six volunteers under fasted and fed conditions highlighted that the time to release of a radiolabelled compound was reproducible and not greatly affected by the presence of food. Furthermore, the *in vivo* release onset was predictable from *in vitro* data, as a good agreement was found between *in vitro* and *in vivo* lag times [106].

In view of close design and, in some instances [99,102,104], working principle similarities with capsular devices, it is finally worth mentioning the Egalet® technology, which was proposed for both prolonged and pulsatile release of even poorly soluble drugs [107-109]. In its 'Burst-Egalet®' configuration, such a system envisaged a cylindrical impermeable outer shell composed of cetostearyl alcohol and EC. The shell enclosed an inner drug core and two plugs sealing each open end, which were based on high molecular weight PEG or PEO and PEG monostearate. The release-controlling plugs and drug-containing unit were all embedded in the shell by injection-moulding. When in contact with the aqueous fluids, the outer plugs underwent surface erosion processes. After complete erosion, the inner formulation was exposed to the medium and drug release was enabled. Through opportune modifications in the dimensions and composition of plugs and drug core, the time and rate of delivery could be controlled. The pursued release performances were achieved also *in vivo*, as established by γ-scintigraphic studies carried out on six and eight fasting volunteers [107,108].

6. Osmotic delivery systems

Gastrointestinal Therapeutic Systems, more commonly referred to as osmotic pumps, were originally conceived in pursuit of zero-order release kinetics; however, the intrinsic need for an activation phase prior to the slow drug liberation was purposely relied on, in order to achieve a once-a-day Controlled-Onset Extended-Release (COER-24) formulation of verapamil hydrochloride, intended to meet chronotherapeutic requirements related to cardiovascular disease [19,110]. The device was based on a bipartite tablet core, comprising an osmotic drug-containing compartment and a hydrophilic swellable polymer push compartment. The core was entirely coated by a semipermeable cellulosic membrane provided with a couple of laser-drilled micropores connecting the drug tablet with the aqueous fluids of the external environment. Between the core and the semipermeable film, an additional hydrophilic layer was applied, which contributed to defer the system activation. According to the OROS® Push-Pull™ working principle, water penetrated into the core across the outer coat, eventually resulting in dissolution of the active ingredient on one hand, and swelling of the hydrophilic polymer on the other. The consequent expansion of the push compartment led to a constant-rate expulsion of drug solution through the laser-drilled holes. Due to the sophisticated underlying technology, verapamil hydrochloride could be released in a prolonged fashion over a period of several hours after a 4 – 5 h delay. This was confirmed by pharmacokinetic investigations, which

pointed out a good correlation between the rate of *in vitro* release and *in vivo* absorption processes, thus suggesting that drug absorption be controlled by the osmotic system [111]. Such unique delivery performances allowed higher verapamil plasma levels after evening dosing to be aligned with peak blood pressure, heart rate and myocardial oxygen demand occurring around awakening time [112]. Multi-centre clinical trials highlighted the actual benefits connected with the chronopharmacological treatment in exam, as well as the lack of adverse events differing in type or magnitude from those reported in the case of other verapamil hydrochloride formulations [112-114]. Notably, Covera-HS®, a well-known antihypertensive medicinal product available on the US market, is merely based on the previously discussed COER-24 technology.

7. Expert opinion and conclusion

Remarkable emphasis has been recently laid on the potential of oral pulsatile delivery. The rapidly growing interest in this particular research area is primarily related to the pursuit of high-compliance drug treatments which may fulfill chronotherapeutical requirements highlighted for a number of widespread pathologies. In addition, colon delivery, which is attainable relying on time-controlled release performances, is presently holding appeal for pharmaceutical scientists, after it has been ascertained that the large bowel not only is endowed with non-negligible absorption properties, but may also represent a favourable release site for numerous drugs with stability and/or permeability limitations. Accordingly, a vast array of different design strategies and technologies have been proposed for delayed release of orally dosed active ingredients. This has resulted in a considerable number and variety of devices, the most prominent examples of which have been reviewed above. The majority of these systems are based on fairly novel and/or innovative technical approaches. Hence, it is worth wondering what kind of future prospects are to be expected in the field. It can reasonably be assumed that the current focus on oral pulsatile release is liable to further increase owing to consolidation of chronotherapeutic principles and relevant translation into the clinical practice. Meanwhile, a more attentive consideration is being directed to the patient compliance with drug treatments and, in addition, circadian patterns are being identified for many illness states other than those commonly referred to (i.e., ischaemic heart disease, rheumatoid arthritis and bronchial asthma). Moreover, the incidence of such typical chronopathologies is bound to keep high, or even display a rising trend, in the light of population ageing and, in the case of asthma, of more threatening environmental conditions. It should also be underscored that the availability on a large scale of several biotech molecules, most of which are likely to be undeliverable via the oral route when formulated for immediate-release, could strengthen the present interest in colon targeting and related delivery platforms. For all these reasons, and probably some others as well, it can be presumed that great expectations will be placed in the forthcoming evolution of oral pulsatile release systems. In order to seize such an opportunity, however, such devices will have to yield something beyond originality and enhanced pharmacotherapy chances. Firstly, in spite of even complicated designs, they will have to involve only feasible and hypothetically easily scalable manufacturing processes, possibly based on conventional pharmaceutical equipment. In this respect, any technique implying manual operations or not fully automated multi-step procedures might fail to meet feasibility and scale-up criteria. Furthermore, the regulatory burden connected with particular formulation or processing choices will have to be taken into account since very early development stages. In principle, technologies that completely circumvent the use of organic solvents should thus be preferable. Besides raising toxicological concerns, organic vehicles definitely clash with today's higher awareness of environmental and work safety-related problems. Above all, the selection of excipients which have not extensively been studied from the tolerability standpoint and/or may not rely on a long-lasting employment within the food or pharmaceutical industry could turn out detrimental even when affording noteworthy technical advantages. This is especially true for synthetic polymers, biodegradability being a key requisite for acceptable utilisation in drug formulations. On the other hand, with reference to proof-of-concept studies, it has been noticed that adequate *in vivo* testing on humans has not yet been envisaged for many of the herein reviewed techniques. Hence, it is conceivable that more in-depth *in vivo* investigations will be undertaken, with the aim of evaluating the impact of physiological and pathological gastrointestinal conditions on the release behaviour and relevant reproducibility. Inter- and intra-subject variability of data, in fact, represents one of the most challenging aspects which are to be faced in the course of any pharmaceutical development. Finally, in view of establishing due *in vitro*-*in vivo* correlations, greater effort and improved skills could be required by the design and implementation of biorelevant and discriminating *in vitro* dissolution tests.

Therefore, despite the broad scientific involvement in this specific area, many different biological, technical and regulatory issues will have to be thoroughly addressed before patients may finally benefit from the emerging pulsatile delivery technologies.

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Affiliation

Alessandra Maroni, Lucia Zema, Matteo Cerea & Maria Edvige Sangalli†
†Author for correspondence
Istituto di Chimica Farmaceutica e Tossicologica, Università di Milano,
V. le Abruzzi 42, I-20131 Milan, Italy
Tel: +39 02 503 17533; Fax: +39 02 503 17565;
E-mail: maria.sangalli@unimi.it