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Review article

Oral pulsatile delivery systems based on swellable hydrophilic polymers

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Abstract

Upon contact with aqueous fluids, swellable hydrophilic polymers undergo typical chain relaxation phenomena that coincide with a glassy–rubbery transition. In the rubbery phase, these polymers may be subject to swelling, dissolution and erosion processes or, alternatively, form an enduring gel barrier when cross-linked networks (hydrogels) are dealt with. Because of the peculiar hydration and biocompatibility properties, such materials are widely exploited in the pharmaceutical field, particularly as far as hydrophilic cellulose derivatives are concerned. In oral delivery, they have for long been employed in the manufacturing of prolonged release matrices and, more recently, for pulsatile (delayed) release devices as well. Pulsatile delivery, which is meant as the liberation of drugs following programmed lag phases, has drawn increasing interest especially in view of emerging chronotherapeutic approaches. In pursuit of pulsatile release, various design strategies have been proposed, chiefly including reservoir, capsular and osmotic formulations. In most cases, water-swellable polymers play a key role in the overall delivery mechanism after being activated by physiological media. Based on these premises, the aim of the present review is to survey the main oral pulsatile delivery systems, for which swelling, dissolution and/or erosion of hydrophilic polymers are primarily involved in the control of release.

Keywords: Swellable hydrophilic polymers; Dissolution; Erosion; Swelling; Hydrophilic cellulose derivatives; Oral pulsatile/delayed release

1. Introduction

Water-swellable polymers are highly hydrophilic materials that, upon contact with aqueous fluids, typically undergo a glassy–rubbery thermodynamic transition, which is related to a distension of their macromolecular chains [1]. As a consequence of the hydration process, the polymer can be subject to an even greater volume increase (swelling). Swollen polymeric substrates may erode because of mechanical attrition phenomena and/or dissolve in the medium at a rate that chiefly depends on the relevant physical–chemical properties and solvent concentration [2]. In contrast to erodible polymers, cross-linked macromolecular networks (hydrogels) fail to dissolve even after extensive water uptake. When the aqueous solvent penetrates into swellable polymeric matrices, two differing fronts can in principle be distinguished: the swelling front, which is the boundary between glassy and rubbery matrix regions, and the erosion front at the interface between the rubbery polymer and outer medium [3–5]. Depending on the relative movements of these fronts, a gelled layer of varying thickness is formed. In insoluble hydrogel systems, such a layer keeps thickening until the swelling process is completed.

Because of the peculiar hydration behaviour, both erodible and non-erodible swelling polymers exhibit generally high biocompatibility as well as susceptibility to being activated by physiological fluids [6]. Such inherent characteristics have drawn remarkable interest to swellable hydrophilic materials, which have widely been employed in the pharmaceutical area over the past decades, especially as far as polysaccharidic compounds are concerned. In this respect, hydrophilic cellulose derivatives, alginic acid, carrageenans as well as guar, xanthan and locust bean gums represent the most popular examples, while polyvinyl

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alcohol (PVA) and polyethylene oxide (PEO) are non-saccharidic swelling polymers in common use. Due to their consolidated safety, versatility and broad availability profiles, cellulosic ethers, such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC) and calcium or sodium carboxymethylcellulose (CMC), have particularly been exploited in the pharmaceutical manufacturing either as conventional binding, film-coating and viscosity-building excipients or as functional formulation adjuvants governing drug release from advanced delivery systems [7]. In the specific field of oral modified release, their most prominent role has for long been related to the design and preparation of hydrophilic matrix systems for prolonged delivery. More recently, a further interesting application has been highlighted in connection with the accomplishment of pulsatile (delayed) release performances. In general, pulsatile release is meant as the timed liberation of drugs following programmable lag phases [8]. External stimuli are relied on to start the release step in triggered pulsatile delivery, whereas only inner mechanisms are operating in time-based release, which is expected to be independent of environment variables such as pH, ionic strength and temperature. Therefore, time-based pulsatile delivery can also be referred to as delayed release. After the lag phase, the drug liberation may be prompt and quantitative, sustained over a prolonged period of time or else repeated when multiple dose fractions are delivered following prefixed lag intervals.

Much emphasis has lately been laid on the potential of delayed release for meeting chronotherapeutical needs that are being recognised for a number of widespread chronic pathologies [9–12]. Particularly in the case of cardiovascular disease, bronchial asthma and rheumatoid arthritis, which mostly exhibit circadian manifestations in the early morning, the efficacy and tolerability of a therapy could notably be improved by delivery systems intended to timely release the drug few hours after bedtime administration, thus providing pharmacological protection when it is especially required without involving an unnecessarily extended patient exposure to the active molecule nor impairing the overall treatment compliance.

Furthermore, delayed release performances are also exploited to target proximal as well as distal colonic regions via the oral route [13,14]. Colon delivery has proved advantageous in the management of inflammatory bowel disease (IBD) and, in addition, is currently pursued as a potential approach to increase the oral bioavailability of peptides, proteins, oligonucleotides and nucleic acids [15–17]. In order to attain a time-controlled drug release into the colon, pulsatile delivery systems are basically provided with an outermost enteric film, which is effective in overcoming the generally high gastric emptying variability, and programmed to yield a lag period roughly suitable for covering the fairly constant small intestinal transit time of dosage forms [18].

Finally, when multiple-dosing daily regimens are dealt with, repeated pulsatile delivery patterns could help to enhance the treatment compliance in case the active ingredient is not eligible for prolonged release formulations, for example because of a strong first-pass effect or tolerance development [19].

Many efforts have been spent in the design of time-dependent pulsatile delivery systems, which have been presented in the form of reservoir, capsular and osmotic devices [8,14,19]. Reservoir formulations are based on a single- or multiple-unit drug core and one or more coating layers. According to the inherent characteristics of the coating materials, they have been distinguished in erodible, rupturable and diffusive systems, in which delayed release is, respectively, enabled by disruption and erosion of the coat layer or by drug diffusion phenomena through the coat layer itself. Disruption may in turn be promoted by an osmotic or swelling-induced increase in the core volume or result from the membrane strain produced by carbon dioxide that is formed from effervescent excipients. Capsular systems generally consist in a drug-filled insoluble body, which is sealed with a highly swellable, erodible or, alternatively, lipophilic matrix plug. This undergoes a timed removal either because of its water swelling and/or erosion processes or following a pressure rise that is caused by osmotic water uptake inside the capsule body. Lastly, osmotic devices are composed of a selectively permeable outer membrane that encloses the drug formulation coupled with an osmotic or swelling load. After a programmable activation time, the drug is pumped out at a constant rate through a calibrated orifice drilled in the membrane when an effective outward hydrostatic pressure is established.

For most aforementioned formulation types, swellable hydrophilic polymers indeed play a pivotal role in the composition of key items susceptible to solvent activation. In particular, these polymers are commonly exploited in reservoir systems to provide either erodible coating barriers or the swelling force required to break up rupturable films. Furthermore, in the case of capsule-shaped and advanced osmotic devices they are used as matrix-forming agents for the seal plug and the swelling push compartment, respectively. However, it is in the specific instances of erodible reservoir and original capsular formulations that swellable hydrophilic polymers prove to be chiefly responsible for the overall control of delivery. Accordingly, the present review article mainly focuses on the design and release features of such particular formulation types, especially addressing the role and behaviour of their swellable hydrophilic polymeric components.

2. Reservoir systems provided with swellable/erodible hydrophilic polymeric coatings

Because of their above-mentioned advantageous characteristics, hydrophilic cellulose derivatives have been employed to prepare most reservoir pulsatile delivery sys-

tems provided with erodible coatings, even though the use of different swellable polymers has also been described. Press-coating technique has chiefly been relied on for their application onto drug-containing units. However, organic and aqueous spray-coating, dipping and, more recently, powder-layering have been attempted as well. The mechanism by which hydrophilic cellulosic barriers delay release depends on the progressive hydration, dissolution and erosion phenomena they undergo when exposed to the aqueous medium, thus preventing the drug from being delivered until the inner core is reached by the solvent (Fig. 1). In immediate release tablet cores, even the disintegrant activation that is possibly induced by water penetration through the gelled polymeric layer may contribute to a complete removal of coat residues adhering to the inner drug formulation. In general, lag times shown by erodible reservoir systems depend on the physical–chemical properties of the applied polymer and on the coating level.

An early example of delivery system based on the erosion process of a hydrophilic polymeric item is a multilayer tablet for pulsed release, in which an intermediate HPMC barrier was encased between two drug compartments [20,21]. The device was coated with an impermeable film except for one drug layer surface that could freely interact with the aqueous medium, thus providing an immediate release pulse. A second pulse occurred after extensive erosion of the inner HPMC barrier. The lag phase was dependent on the viscosity of the polymer blend employed for such barrier. Reproducible plasma concentration curves of a model drug were attained in agreement with the observed *in vitro* performances. A subsequent evolution of this system led to the Chronotopic™ delivery platform, which consisted in a single- or multiple-unit drug core coated with a HPMC layer and, when proposed for time-based colon delivery, with an outer enteric film as well [22–29]. Particularly in early development stages of this technology, the achievement of the functional HPMC coat turned out to be a challenging step. The polymeric agents were initially applied in powder form by press-coating or as hydro-organic dispersions by spray-coating [22–24]. When double-compression was dealt with, uniform coat layers could hardly be obtained because of difficulties in having the core positioned in the die centre, thus potentially threatening lag time reproducibility. In addition, the need for special equipment and time-consuming multi-step processes was likely to impair scalability, whereas the relatively large polymer amount that it was necessary to employ involved important versatility constraints with respect to the starting core size and lag phase duration. In spite of the encouraging outcome, hydro-alcoholic film-coating was also ceased on account of the growing awareness of environmental and safety issues connected with the use of organic solvents. Aqueous spray-coating was then attempted with differing HPMC grades [25–28]. A low-viscosity polymer (Methocel® E50, Dow Chemical Co.) was demonstrated to offer an acceptable balance among various important aspects, such as process feasibility, effectiveness in delaying drug delivery, fine-tuning of lag time and moderate impact on the release rate. In Figs. 2 and 3, details of the HPMC layer in its glassy and swollen state are shown, respectively. The mechanism of delivery from Methocel® E50-coated devices was in-depth investigated, and a contribution of the core tablet disintegration was highlighted (Fig. 4). Programmable and reproducible lag phases followed by a fast drug liberation were achieved both *in vitro* and in healthy volunteers (Fig. 5). By the way, an agreement between *in vitro* and *in vivo* delays was assessed. The above findings were supported by γ-scintigraphic data, which also demonstrated the ability of the delivery platform to accomplish time-based colon targeting. Furthermore, Chronotopic™ systems were successfully prepared according to the above-described aqueous spray-coating procedure from hard- and soft-gelatin capsules [29]. The obtained systems exhibited the pursued physical–pharmaceutical requisites and release performances. Capsules were selected as alternative cores because of their

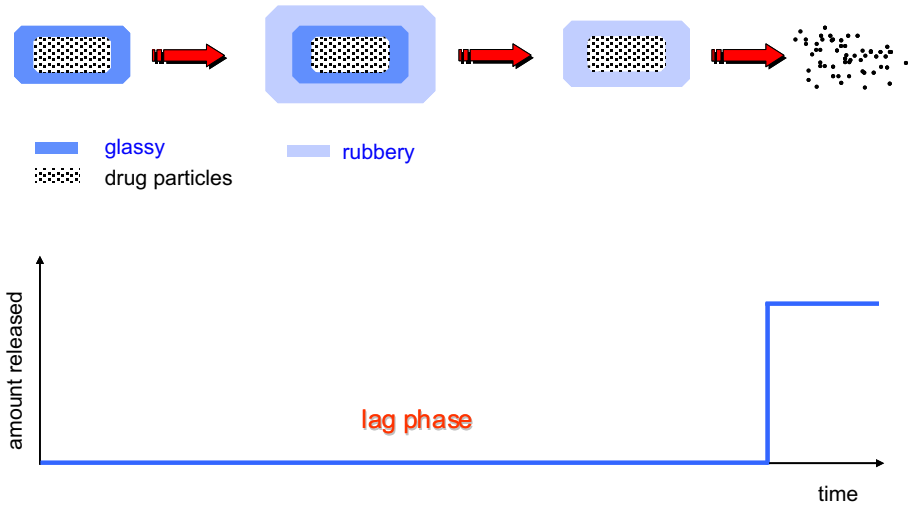

Fig. 1. Expected behaviour and release profile of swellable/erodible reservoir systems for oral pulsatile delivery.

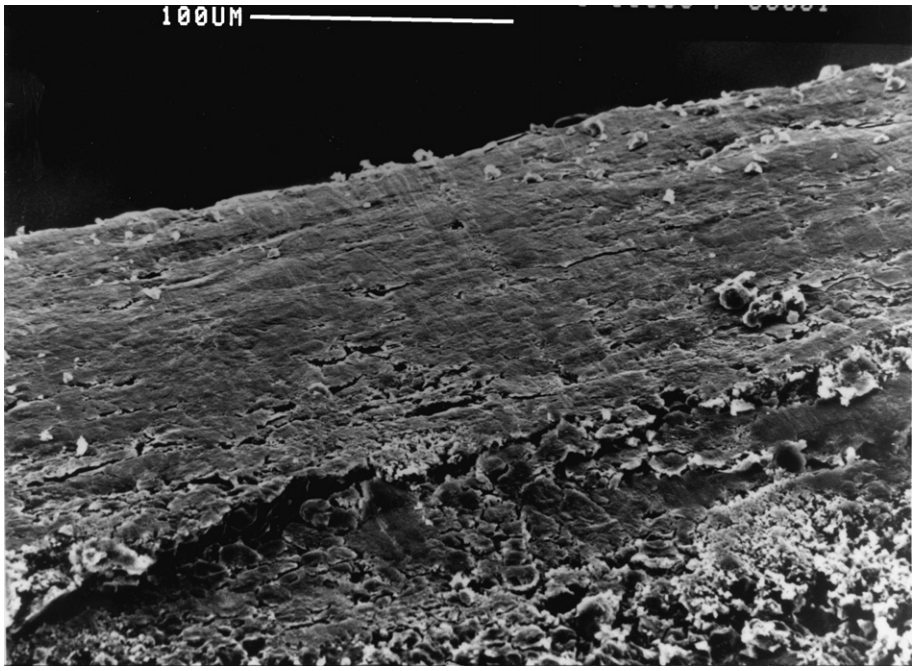

Fig. 2. SEM (scanning electron microscope) photomicrograph (magnification 317×) of a detail of the glassy HPMC layer in the Chronotopic™ system.

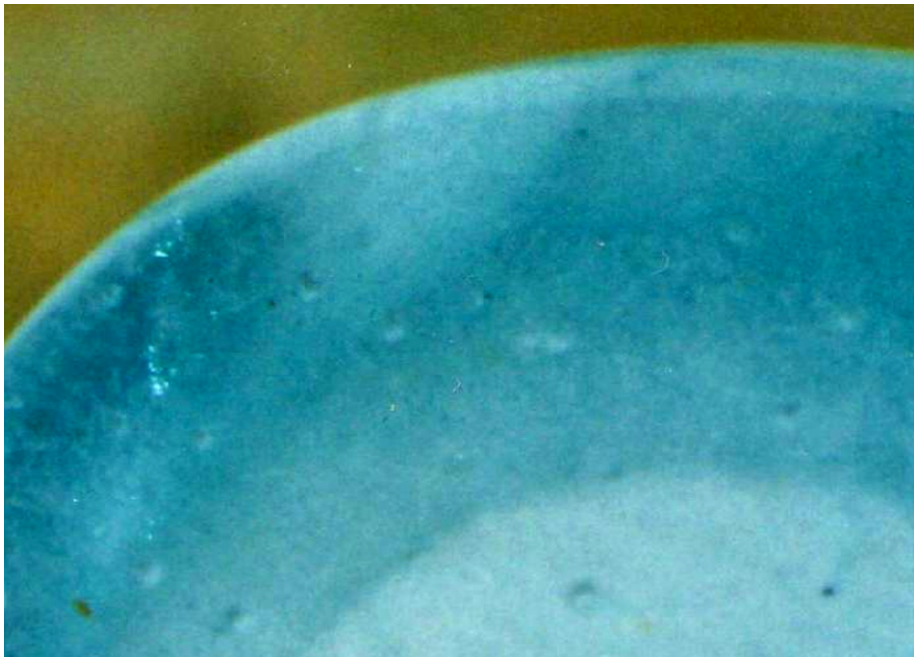

Fig. 3. Detail of the swollen HPMC layer in the Chronotopic™ system.

suitability for conveying dispersed and multiparticulate formulations, which were described in the literature as potentially useful vehicles for protecting protein drugs and aiding their absorption in the gastrointestinal tract [30,31]. More recently, the use of novel coating techniques, such as tangential spray-coating in rotary fluid bed and powder-layering, was explored with the aim of improving the yield and time of the manufacturing process, thus further enhancing its scalability potential [32,33].

Despite the practical drawbacks associated with press-coating, this technique was largely exploited to prepare reservoir systems with hydrophilic cellulose derivatives or other swellable polymers [34–48].

In particular, tablets provided with erodible or gellable barriers based on low- and high-viscosity HPMC, respectively, were proposed to achieve delayed release of drugs irrespective of their solubility and formulation characteristics [34,35]. After the lag phase, the rate of delivery was not

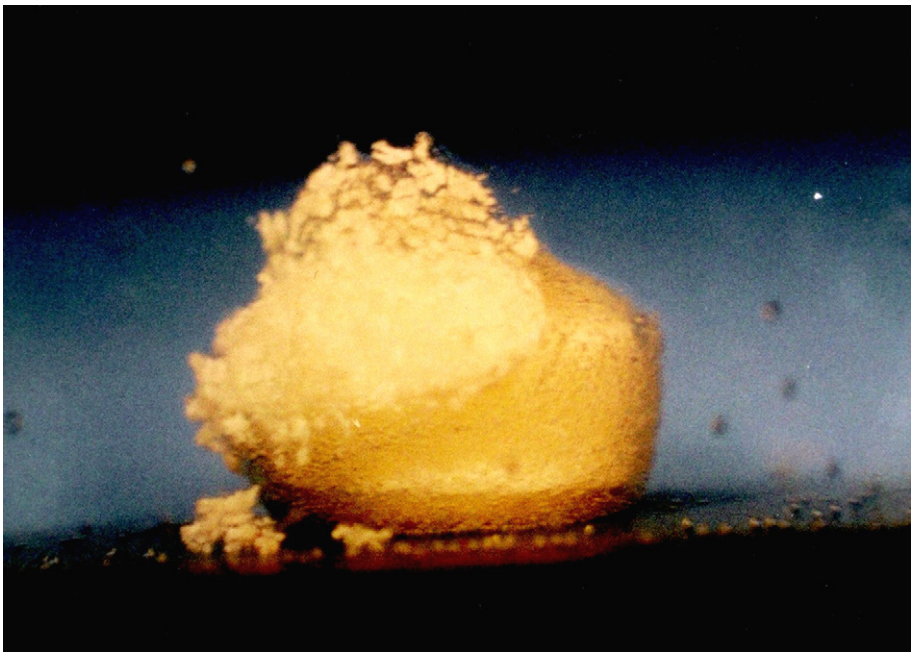

Fig. 4. Final release phase in a disintegrating core-based Chronotopic™ system.

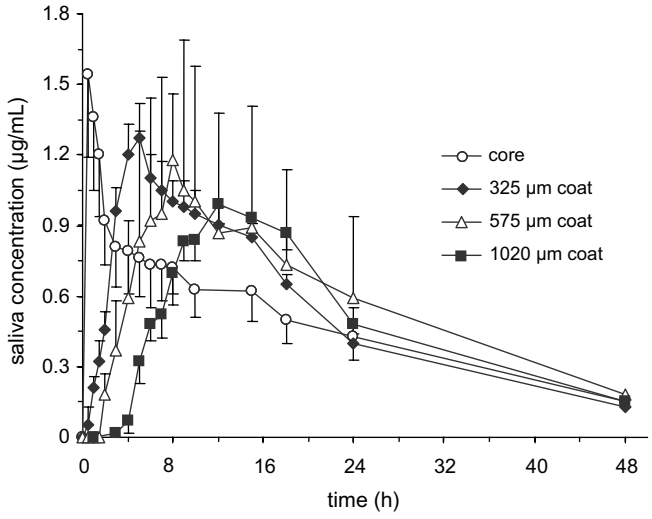

Fig. 5. Mean salivary concentration profiles of antipyrine after oral administration of tablet cores (155 mg weight, 6 mm diameter) and systems with increasing HPMC coat thickness (four fasting volunteers, bars indicate standard deviation) (Adapted from ref. [26]).

modified in the case of erodible coatings, whereas the release kinetics was controlled by swellable layers. High-viscosity HPMC, as such or blended with lower viscosity grades, was also used as the press-coating agent for a delivery system containing model drugs with differing solubility, which was aimed at the chronotherapy of early-morning diseases [36–38]. By raising the coating level or the high-viscosity polymer amount in the coat formulation, lag phases were extended and release was slower both *in vitro* and in healthy volunteers. Moreover, when the drug dose was split between the core and the outer layer, double-peak plasma levels were obtained. Another high-viscosity HPMC press-coated tablet was presented in a gastric-resistant configuration for time-based colon delivery [39]. By a preliminary imaging investigation, the system was demonstrated to disintegrate in the ascending colon.

Double-compression coating with HPMC was also exploited in the case of a multiple-unit device that comprised a number of cores with differing release behaviour contained in a hard-gelatin capsule [40]. By appropriately combining uncoated with HPMC-coated minitablets and HPMC minimatrices, versatile release performances were achieved, including multi-pulse delivery patterns.

Press-coated tablets prepared with HEC as the swelling hydrophilic material yielded lag times that were affected by the coat thickness, viscosity of the polymer and its particle size as well [41,42]. Larger particle dimensions were related to shorter delays, which were ascribed to an initially faster water uptake in the presence of a higher porosity structure. *In vivo* lag times in agreement with *in vitro* data were observed in healthy volunteers.

An analogous system based on HPC was described in [43]. When comparing *in vivo* delays assessed in a dog pharmacokinetic study with the corresponding *in vitro* results, consistent lag time values of 3 h were found. However, *in vitro* lag phases of 6 h turned out shortened *in vivo*. Such a discrepancy was less evident when a higher rotation speed was adopted for release tests. Provided with an enteric hydroxypropyl methylcellulose acetate succinate (HPMCAS) coating, this system was propounded for time-controlled colon targeting as well [44]. HPC was also used as the release-controlling agent in a tablet assembly device for pulsatile and time-dependent colonic delivery, which was manually prepared by inserting a cylindrical core unit

into a perforated erodible matrix and sealing their top and bottom surfaces with an impermeable film [45]. Drug release was delayed until radial erosion of the HPC shell was completed. The duration of the lag phase depended upon the thickness of such shell and the core composition. When employed in place of microcrystalline cellulose as the tablet filler, lactose promoted a faster water uptake owing to its marked osmotic effect. On the other hand, the use of a HPC matrix as the inner core led to prolonged release curves after the lag time.

Water-swellable materials other than cellulose ethers were also exploited to attain press-coated reservoir systems. For example, erodible coatings based on spray-dried composite lactose powders containing sodium alginate/chitosan complexes were shown to withstand acidic media and delay, through their hydration and erosion processes, the release of drugs from the core in pH 6.8 fluids [46]. Lag time was affected by the coating level and deacetylation degree of chitosan. Tablets loaded with a highly soluble excipient and dry-coated with PEO and macrogol 6000 blends were designed to face the bioavailabililty fall possibly connected with delivery of drugs into distal intestinal regions, where the water content is limited [47]. An increase in the coat tendency to erode, as indicated by a purposely introduced parameter, was associated with improved model drug (acetaminophen) bioavailability in a dog pharmacokinetic investigation. Recently, the SyncroDose™ delivery technology was developed, which envisaged a drug-containing tablet core and an erodible dry-coating layer composed of xanthan and locust bean gum mixtures [48]. By varying the ratio between these polysaccharides, the lag phase could be modulated according to differing chronotherapeutic needs.

In an attempt to overcome well-known drawbacks involved by conventional press-coating, alternative technologies were set up to obtain compression-coated pulsatile delivery systems. This is the case of the ENCORE™ and one-step dry-coated tablets (OSDRC), which were based on PEO/lactose blends and HPMC as the erodible barrier materials, respectively [49,50].

Finally, dip-coating technique was also employed for the application of erodible high-viscosity HPMC layers onto tablet cores [51]. In addition to the coating level, some further variables were demonstrated to affect the release performances in this particular instance. For example, when the organic versus water solvent ratio was enhanced or the HPMC concentration decreased in the coating dispersion, delay times turned out to be extended. Moreover, the release rate was reduced when the polymer was allowed to swell in the hydro-organic vehicle for longer time periods.

3. Capsular systems provided with swellable/erodible hydrophilic polymeric plugs

Capsular delivery systems intended for pulsatile release generally consist of an insoluble body, in which the drug formulation is incorporated, a soluble cap and a hydrophilic polymeric tablet plug that seals the open body end. According to the physical–chemical properties of the polymer it is formed from, the plug delays the onset of release through its erosion and/or swelling processes until timed removal from the capsule body and resulting liberation of the drug content into the aqueous medium. The plug matrix was originally composed of cross-linked polyethylene glycol (PEG 8000) hydrogel in the Pulsincap™, which was the very first capsule-shaped pulsatile delivery system described in the literature [52]. Although a body of proof-of-concept data was obtained through various imaging studies, possible constraints were related to the apparently complicated manufacturing and the use of a non-approved hydrogel polymer. However, the tolerability and patient compliance of one placebo treatment that involved a multiple-dosing daily regimen were assessed in volunteers over a 4-week test period [53]. When provided with an enteric coating, the system was proposed and evaluated for time-dependent colon delivery as well [54]. In this respect, scintigraphic investigations indicated that a selective plug ejection in the large bowel could be achieved. By coupling pharmacokinetic and imaging analytical techniques, non-invasive permeability studies were carried out in distal intestine regions with Pulsincap™ units containing appropriate marker compounds [55–57]. With the aim of circumventing the main limitations connected with the Pulsincap™ technology, the use of erodible capsule plugs was attempted in place of the originally employed hydrogel tablets [58–60]. Differing water-swellable materials, such as various HPMC viscosity grades, PVA and PEO, were examined for the plug preparation. The addition of highly swellable or effervescent excipients into the drug formulation was proven to aid a fast release step following lag time. The effect of wet-granulation on the performances of erodible plugs was also evaluated [61]. Wet-granulated plugs turned out to be more effective in delaying drug release than directly compressed ones. Hypotheses on the possible outcome of the wet-granulation process on the plug erosion behaviour were formulated according to microwave dielectric analysis results. Moreover, remarkable differences were found in the physical–pharmaceutical features and release patterns shown by erosion-based capsular devices, to which the impermeable ethylcellulose body film was applied by aqueous or organic spray-coating [62,63]. In particular, superior integrity characteristics on exposure to high moisture levels and a more reliable control of release were observed in the case of organic spray-coated capsules.

An alternative capsule-like design was envisaged for the Egalet® delivery platform [64,65]. When intended for pulsatile release, such a system comprised an impermeable cylindrical shell containing a drug core and two injection-moulded erodible plugs at each open end, which were based on high molecular weight PEG or PEO and PEG monostearate. By varying the size and composition of the plug and drug formulations, it was possible to define the onset and rate of delivery.

4. Conclusions

Over the past decade, increasing interest has been directed to oral pulsatile delivery especially because of its potential suitability for meeting chronopharmaceutical needs related to widespread diseases with circadian symptom variations. Accordingly, an array of design strategies and resulting delivery systems has been described in the literature, the vast majority of which comprise key formulation items based on swellable hydrophilic polymers. Notably, such materials are primarily relied on for the control of release in many instances. This is the case of reservoir and capsular devices, wherein a timed liberation of the active ingredient is enabled by the swelling and/or erosion processes of hydrophilic polymeric coatings and seal plugs, respectively. Polysaccharidic compounds, particularly with reference to cellulose derivatives, have mainly been exploited as components of delayed release formulations on account of a number of diverse benefits, which previously gained them popularity in the field of matrix systems for prolonged delivery. In view of those established advantages and the overall promising results thus far provided, the application of swellable hydrophilic polymers of consolidated pharmaceutical use is likely to further strengthen in the expanding area of pulsatile release. However, the actual development chances of delayed delivery platforms that involve their utilisation will presumably depend upon the proposition of innovative designs, the identification or set up of feasible and reasonably scalable manufacturing procedures and, finally, on an enhanced commitment to human proof-of-concept investigations.

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