ERODIBLE DRUG DELIVERY SYSTEMS FOR TIME-CONTROLLED RELEASE INTO THE GASTROINTESTINAL TRACT

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Abstract

In oral delivery, lag phases of programmable duration that precede drug release may be advantageous in a number of instances, e.g. to meet chronotherapeutic needs or pursue colonic delivery. Systems that give rise to characteristic lag phases in their release profiles, i.e. intended for time-controlled release, are generally composed of a drug-containing core and a functional polymeric barrier. According to the nature of the polymer, the latter may delay the onset of drug release by acting as a rupturable, permeable or erodible boundary layer. Erodible systems are mostly based on water swellable polymers, such as hydrophilic cellulose ethers, and the release of the incorporated drug is deferred through the progressive hydration and erosion of the polymeric barrier upon contact with aqueous fluids. The extent of delay depends on the employed polymer, particularly on its viscosity grade, and on the thickness of the layer applied. The manufacturing technique may also have an impact on the performance of such systems. Double-compression and spray-coating have mainly been used, resulting in differing technical issues and release outcomes. In this article, an update on delivery systems based on erodible polymer barriers (coatings, shells) for time-controlled release is presented.

Keywords

Oral pulsatile release, Oral colon delivery, Coating, Swellable/erodible hydrophilic polymers, Injection-molding, Fused deposition modeling 3D printing.

Introduction

Oral delivery systems for time-controlled release are able to defer the onset of drug release into the gastrointestinal tract for a programmable lag period independent of pH, ionic strength, enzyme concentration and other physiological parameters. It is by now recognized that a delay prior to release may be advantageous for effective pharmacological treatment of several pathologic conditions [1]. This is typically the case with a variety of high-morbidity rheumatic, cardiovascular and respiratory chronic diseases, which show cyclic patterns in their signs and symptoms [1,2]. When these mainly recur at night or in the early morning hours, bedtime administration of drug products having a proper lag phase in their release profile would help provide pharmacological protection as needed. On the other hand, both untimely awakenings, as an immediate-release dosage form would require, and exposure to unnecessarily sustained therapeutic drug levels, as prolonged-release formulations taken before sleep would entail, could thereby be overcome. As a result, not only the efficacy and safety of a treatment but also the relevant patient compliance may greatly be enhanced through the use of chronopharmaceutical delivery systems.

Besides, a lag phase prior to release allows to target the colonic region with drug molecules intended for either a local action, e.g. to treat Inflammatory Bowel Disease (IBD), or for systemic absorption, especially of biotech molecules that pose stability issues in the proximal gut and may benefit from the aid of enhancers for mucosal permeation [3,4]. When colon delivery is sought, the lag phase is expected to last throughout the entire small intestinal transit (3 h ± 1 SD), which was reported not to be strongly influenced by the characteristics of dosage units and by food intake [5,6]. Moreover, the lag period should be started upon emptying from the stomach rather than

on administration, owing to the high variability of gastric residence that cannot reliably be predicted. Hence, in order to attain colonic release based on a time-controlled approach, enteric coating is generally required.

Repeated lag phases, each followed by the release of a drug dose fraction, may be exploited to fulfill multiple daily administrations regimens when prolonged release is not a viable option, e.g. because of pharmacokinetic (strong first-pass effect) or pharmacodynamic (tolerance) constraints. Successive release pulses are also proposed as an alternative strategy in antibiotic therapy, possibly resulting in restrained growth of resistant bacterial strains [7].

Finally, properly modulated lag phases prior to the release of co-administered bioactive compounds may avoid undesired drug-drug interactions in the gastrointestinal tract and overcome the need for differing dosing schedules, thus improving the overall patient convenience and compliance [8].

Peroral delivery systems for time-controlled release are expected to yield lag phases on the order of few hours, which may be consistent with their mean residence time within the digestive tract. These are often pursued through functional polymeric barriers that enclose an inner drug formulation [9,10]. According to the physico-chemical properties of their polymeric components and type of excipients added (plasticizers, pore formers, bulking agents), such barriers delay the onset of release via differing mechanisms. They may indeed undergo time-programmed disruption, become leaky or be subject to progressive erosion/dissolution. In particular, erodible systems are generally single-unit dosage forms based on a drug containing-core, such as an immediate-release tablet or capsule, and a swellable hydrophilic barrier of adequate thickness and polymer viscosity. Such a barrier may be a coating or, in more recent and

innovative instances, a freestanding release-modifying shell available for filling with any drug formulation.

Because of the inherent safety and biocompatibility profile as well as of their availability in a range of grades and reasonable costs, hydrophilic cellulose derivatives, namely hydroxypropyl methylcellulose (HPMC) and, less frequently, hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC), are broadly used as the functional polymers in erodible delivery systems [11]. Other polysaccharides, including galactomannans, alginates, xanthan gum, and non-saccharide hydrophilic polymers, such as polyvinyl alcohol (PVA) and polyethylene oxide (PEO), are nonetheless also employed. All of these materials are largely utilized in the food, pharmaceutical, nutraceutical and cosmetic industries mainly as rheology-modifiers, stabilizers, binders and film-coating agents.

Upon water uptake, such polymers typically go through a glassy-rubbery thermodynamic transition that is associated with distension and disentanglement of their macromolecular chains [12-14]. Consequently, the polymer structure may expand, erode due to mechanical attrition and/or dissolve at a rate that chiefly depends on the relevant physico-chemical characteristics and on the ionic strength and temperature of the medium. As the aqueous fluid penetrates into the polymeric layer, a swelling front, i.e. the boundary between the glassy and the rubbery domain, and an erosion front, at the interface between the rubbery polymer and the outer medium, are identified. Depending on the relative movements of the swelling and erosion fronts, which in turn are governed by the hydration, dissolution and viscosity properties of the polymer, a gel layer of varying thickness is formed.

In a few instances, insoluble materials are added to the hydrophilic polymers to modulate the degree of hydration of the barrier, or even used as the main components of mechanically erodible coatings. In the latter case, their erosion in aqueous fluids would need to be promoted by surfactant excipients.

Drug release from hydrophilic erodible systems is in principle deferred until the entire polymeric layer is in the swollen state, i.e. when the swelling front has reached the drug core, possibly followed by extensive dissolution/erosion of the hydrated polymer. The duration of the lag phase is indeed dictated by the physico-chemical properties of the polymer employed, primarily molecular weight and degree of hydrophilicity, and by the thickness of the erodible barrier. The manufacturing technique, which may range from double-compression and spray-coating to hot-processing, can also affect the layer functionality.

In the following sections, oral delivery systems for time-controlled release provided with an erodible polymer barrier are reviewed, and advances in this particular field are illustrated with special emphasis on formulation and performance issues.

Erodible systems manufactured by double-compression

The manufacturing of oral delivery systems provided with erodible coatings dates back to the early 90s. Until then, the use of such polymers in the manufacturing of solid dosage forms was tied to tableted hydrophilic matrices for prolonged release. Indeed, double-compression technique, also known as press-coating, was adopted in all initial attempts. The first one concerned a three-layer tablet system that was proposed for two-pulse release of drugs [15,16]. Such a system was composed of two conventional drug (ibuprofen) layers and a high-viscosity HPMC (Methocel® K4M and Methocel® K15M)

barrier in between. An impermeable ethylcellulose (EC) film covered the lateral area and one of the bases of the assembly so that the outer surface of a single drug layer was allowed to interact with solvent upon first contact with the medium. The former dose fraction was thereby released, whereas the latter was released after a lag phase due to the hydration and erosion of the polymer barrier. The delay between the release pulses depended on the viscosity of the polymers employed, and release of the latter dose fraction was slower. This was ascribed to a less efficient activation of the disintegrant incorporated within the inner drug layer that was progressively exposed to the aqueous fluid. The release behavior observed *in vitro* was reflected in two-peak plasma concentration curves in healthy volunteers. However, because of its multiple-layer configuration and the need for a partial coating, the system would involve serious scalability issues. Therefore, a simpler press-coated formulation was designed, wherein the polymer, a low-viscosity HPMC (Methocel® K100 LV), covered the entire surface of the core [17]. The coated system could yield single-pulse release after a lag phase or, administered in combination with an immediate-release tablet, the repeated release performance attained from the previous device. In the double compression process, positioning of the core tablet in the die represented a critical step. However, by correctly centering it within the polymer powder bed, biconvex tablets with coatings of homogeneous thickness were obtained. As desired, the *in vitro* release was delayed for a reproducible period of time, although leaching of a small percentage of the drug content prior to the quantitative release phase was inferred from the curves. This was ascribed to premature outward diffusion of dissolved drug molecules through the swollen polymer coating.

153 A low- and a high-viscosity HPMC grade (Methocel® K100 and Methocel® K4M)
154 were used, either alone or mixed with each other, as the coating agents of a delivery
155 system containing ibuprofen, aimed at the chronotherapy of rheumatoid arthritis, or
156 pseudoephedrine hydrochloride, a water-soluble model drug [18-20]. Increasing the
157 coating level or the amount of high- vs low-viscosity polymer resulted in longer lag
158 times and slower *in vitro* release as well as decreased absorption rates in healthy
159 volunteers. Sodium alginate, as compared with HPMC, performed as a less effective
160 barrier-forming polymer. Incorporation of a fraction of the drug dose in the coating
161 layer changed the release behavior, generally yielding biphasic kinetics that depended
162 on the composition of the polymeric coat and its drug load.
163 High-viscosity HPMC (Methocel® K4M, Methocel® K15M and Methocel® K100M)
164 was employed to prepare a system intended for colonic delivery of the anti-parasitic
165 drug tinidazole [21]. An enteric coating was applied externally to enable site-selective
166 release. The lag phase duration and the release rate were markedly affected by the
167 viscosity grade of the polymer, while hardness of press-coated tablets in a 40-60 N
168 range did not impact on the relevant performance. Administered to 2 healthy volunteers,
169 the system was shown to disintegrate in the ascending colon. Methocel® K100M was
170 also used to coat, at a compression force of 60-80 N, minitablet cores (3 mm in
171 diameter) intended for immediate or prolonged release of nifedipine [22]. By combining
172 differing core and coated formulations in a gelatin capsule, a variety of release patterns
173 were achieved.
174 Low-viscosity HPMC coatings were applied by an alternative tableting method
175 (One-Step Dry-Coated, OSDRC) based on the use of a specially modified equipment,
176 which was previously set up in order to overcome disadvantages typically encountered

with conventional double-compression technique [23]. These mainly encompass the need for poorly scalable multiple-step processing, the issue of coat thickness homogeneity and difficulties in attaining relatively low coating levels. By the OSDRC method, layers of 0.5-2 mm were obtained, with satisfactory thickness homogeneity and practically unchanged performance within a 100-200 MPa range of compression pressure.

High-viscosity HPMC was mixed with polyvinylpyrrolidone (PVP) at different ratios and applied, by conventional double-compression technique, to minitablet cores containing solid felodipine/PVP dispersions [24,25]. Mixing with PVP at 30-50% resulted in improved mucoadhesion of the HPMC coating. The delays prior to a rapid release of the drug increased in duration with the percentage of HPMC in the formulation. *In vitro* delays of more than 10 h were observed with amounts of HPMC at which mucoadhesive properties were enhanced. The issue of possible inconsistency between duration of the lag phase and gastrointestinal transit was faced by the design of a floating pulsatile delivery system aimed at gastro-retention [26]. For this purpose, a verapamil hydrochloride tablet was first coated with low-viscosity HPMC (Methocel® E5, Methocel® E15 or Methocel® E50), expected to defer the onset of drug release. A blend of a high-viscosity grade of the polymer (Methocel® K4M) and Carbopol® 934P, which also contained sodium bicarbonate to generate effervescence, was subsequently applied to a single face of the unit coated with low-viscosity HPMC. The system was proved able both to delay the onset of release and to float *in vitro*. Lag time depended on the viscosity and amount of HPMC in the coating. A ɣ-scintigraphic evaluation in 6 healthy volunteers highlighted the extended gastric residence of the dosage form and reproducible lag phases before release. In all cases, this occurred in the stomach or

small intestine. Recently, various grades of HPMC were used to coat tablet cores based on drugs with differing solubility values [27]. Poorly soluble carbamazepine was released in a pulsatile fashion after erosion of the coating polymer, and the viscosity characteristics of the latter strongly impacted on the relevant performance. On the other hand, more soluble drugs were released in a sigmoidal mode, which was attributed to their diffusion through the fully hydrated HPMC layer, and a poor influence of the polymer viscosity was noticed. The outward diffusion of the drug prior to its quantitative release could be prevented by inserting an enteric film below the erodible coating. However, this would ultimately impart pH-dependence to the lag phase and possibly hamper a timely release of the drug for chronotherapeutic purposes. The amount of HPMC also affected the time and rate of release.

Although HPMC was most widely utilized as a coating agent intended for delaying dug release, the use of other hydrophilic cellulose derivatives was reported. Particularly, HPC was the component of a compressed shell that was separately prepared and, once perforated, manually assembled with a cylindrical core tablet containing isosorbide-5-nitrate [28]. The upper and lower bases of the resulting system were coated with an impermeable ethylene vinyl acetate copolymer film. Release was deferred until the polymeric shell was completely eroded or detached. Lag time was affected by the thickness of such a shell and by the composition of the core. Indeed, replacing microcrystalline cellulose with lactose shortened the lag phase because of the osmotic effect exerted by the latter filler.

A diltiazem hydrochloride system based on HPC was prepared by conventional press-coating [29,30]. As with HPMC, the lag phase duration was modulated either by increasing/decreasing the amount of coating material applied or by employing HPC, or

mixtures thereof, with differing viscosity values. Prototype formulations having *in vitro* delays of approximately 3 h and 6 h were administered to beagle dogs. A good agreement was found between *in vitro* and *in vivo* data relevant to the former prototype, whereas lag time *in vivo* was shorter than *in vitro* in the latter case. This gap was reduced when a paddle rotation speed of 150 rpm was set instead of 100 rpm during release testing. In order to assess its potential for colon delivery, the system having lag time of 3 h was provided with an enteric HPMCAS film containing a gastric emptying marker (phenylpropanolamine hydrochloride) [30]. The mean difference between the time of first appearance in plasma (TFA) of the drug and of the marker molecule was of about 3 h, which was consistent with the lag time obtained from the pH 6.8 fluid stage of the *in vitro* test. HPC was also used in admixture with EC at a weight ratio of 7:1 [31]. The addition of the insoluble polymer aided a faster release of aceclofenac, intended for the chronotherapy of rheumatic morning pain, after the delay period. The *in vitro* performance of press-coated systems based on this blend was proved independent of various parameters, such as the compression force, paddle rotation speed during release testing and pH of the medium. Provided with an enteric-coating, the formulation was administered to rabbits, showing a clear lag phase as opposed to an immediate-release tablet. However, due to variable residence of solid dosage forms in the stomach, gastroresistance may prevent the anti-inflammatory drug from being released at the time the disease symptoms occur.

Low-substituted HPC (L-HPC), an insoluble swellable hydrophilic cellulose ether that is largely used as a disintegrant, was mixed with glyceryl behenate at differing ratios and subjected to a melt-granulation process [32]. The resulting granules were applied by double-compression to theophylline tablet cores to give the erodible layer.

The press-coated tablet was studied *in vitro* and in beagle dogs, by pharmacokinetic as well as ɣ-scintigraphic techniques. Lag phases were reproducible in duration and increased with the amount of glyceryl behenate in the coating formula up to 75%. No significant differences were found either between *in vitro* and *in vivo* lag times, or between *in vivo* lag and disintegration times, both in the fasted and fed state.

Press-coated tablets for chronotherapeutic purposes were prepared from HEC employed as the erodible barrier-forming material [33]. The onset of release of diltiazem hydrochloride from the core was delayed *in vitro* as a function of the coating level and the viscosity grade of HEC. The particle size of the polymer also affected lag time. Using powders with larger particle dimensions was associated with shorter delay phases, which was ascribed to the positive effect of a greater porosity on the polymer hydration process. The role played by HEC viscosity was studied in healthy volunteers [34]. When this parameter increased, progressively longer lag time (T_{lag}) and lower maximum concentration (C_{max}) values were observed in the plasma concentration vs time curves. However, the area under the curve ($AUC_{0\text{-}24\ h}$) did not change significantly. *In vitro* and *in vivo* lag times were in agreement.

Besides cellulose derivatives, the use of PEO as a hydrophilic erodible coating agent was reported. Blended with PEG 6000 at 1:1, it was applied to tablets containing acetaminophen and differing water soluble excipients, such as PEG 6000, sucrose and lactose [35]. These were added in order to promote erosion of the core in the distal intestine, where the press-coated tablets would be intended to release their drug load, thus possibly counterbalancing the paucity of water of regional fluids. The core erosion was experimentally quantified and expressed by a purposely introduced parameter, i.e. the core erosion ratio. In a pharmacokinetic study conducted with fasted beagle dogs,

greater C_{max} and AUC values were obtained from formulations having a higher core erosion ratio. The amount of PEG 600 vs PEO was raised up to 5:1 in the coating of nifedipine tablets containing sucrose as an erosion enhancer [36]. *In vitro* lag times increased with the percentage of PEO and were aligned with TFA data in beagle dogs. PEO formed the swelling/erodible upper layer of a press-coated system with an impermeable cellulose acetate propionate shell covering one of the bases and the lateral surface [37]. The amount of polymer in the top coating affected both the time and rate of release of drug molecules with different solubility. Visual monitoring of morphological changes undergone by the system during *in vitro* testing highlighted gradual expansion and erosion of the partial PEO coat until final detachment from the underlying unit. Used in place of PEO, sodium alginate and sodium carboxymethylcellulose had less and greater impact on the release performance, respectively, consistent with their observed swelling/erosion behavior. Guar gum having ten-fold higher viscosity than PEO also exerted a tighter control of the onset and rate of release [38]. Increasing the core diameter or adding a soluble filler, such as lactose, to PEO or guar gum top layers resulted in reduced duration of the lag phase and enhanced release rate. Differing PEO grades were employed to coat tablets containing solid dispersions of indomethacin in a novel sucrose fatty acid ester carrier [39]. *In vitro* lag time depended on the viscosity and amount of the coating polymer. In 6 healthy volunteers, press-coated tablet systems with *in vitro* lag phase of approximately 6 h brought about delayed appearance of indomethacin in plasma with respect to an immediate-release commercial product. However, no significant differences were found in the C_{max} and AUC relevant to the two formulations.

Hydrophilic polymers of natural origin were also proposed as press-coating agents for time-controlled delivery systems. For instance, powders composed of sodium alginate and chitosan, forming a polyelectrolyte complex, and of lactose as a filler were obtained by spray-drying, evaluated for flowability and compaction properties and finally applied to acetaminophen tablets [40]. Through progressive erosion of the coating layer, drug release was delayed in pH 6.8 fluid for a time interval that depended on the chitosan content of the composite powder and on the polymer degree of deacetylation. A prompt release phase was eventually observed. In pH 1.2 fluid, acetaminophen was released slowly after longer delays. Prepared for comparison purposes, physical mixtures of chitosan with spray-dried alginate/chitosan particles and spray-dried powders composed of lactose and of pre-formed alginate/chitosan complex failed to provide the desired release pattern.

Blends of the bacterial exopolysaccharide xanthan gum and plant galactomannan locust bean gum were used in the double-compression coating of the SyncroDose™ delivery system according to TIMERx® technology [41]. Differing release modes and lag times were achieved by modifying the concentration and ratio of the two polysaccharides, performing as synergistically interacting heterodisperse polymers.

Erodible delivery systems manufactured by spray-coating

The feasibility of coating techniques other than double-compression was explored for the manufacturing of erodible polymer barriers able to control the onset of drug release. Particularly, the goals were to establish simpler processing modes, with better industrial scale-up prospects, exploit conventional production equipment and broaden the range of viable core formulations (e.g. large tablets, minitablets, granules, pellets, gelatin

capsules) [17]. Furthermore, some performance issues, strictly connected with the structure of press-coatings, their relatively high thickness and the relevant homogeneity limitations, needed to be improved. These primarily involved extended, variable and poorly flexible lag times, incomplete suppression of drug leakage during the delay period and impact on the subsequent release phase. Preliminary spray-coating trials were thus undertaken because such a technique would have allowed continuous and uniform films to be formed rather than layers of pressed powder, and fluid bed as well as rotating pan equipment to be utilized instead of specially devised or modified tableting machines [17,42,43]. In addition, it could in principle be adapted to substrate dosage forms having diverse size, surface and density characteristics, thereby circumventing the dimensional and mechanical constraints associated with double-compression. A limited technical background was available on the use of swellable hydrophilic polymers as film-coating agents, and this mainly concerned application of low-viscosity grades as thin layers with protective, taste-masking or cosmetic function. Nonetheless, HPMC with marked viscosity (Methocel® K4M and Methocel® K15M) appeared potentially suitable for delaying drug release for a time interval on the order of hours without binding to excessively thick coatings. The polymers were suspended in a hydro-alcoholic vehicle in order to counteract the thickening effect they exert upon hydration. The ratio between ethanol and water needed to be adjusted so as to enable nebulization of the coating suspension at reasonable rates and polymer concentrations on the one hand, and adequate coalescence of the solid particles on solvent evaporation on the other. The addition of plasticizing, anti-tacking and binding excipients, such as PEG 400, talc and PVP, was investigated. The coatings applied to tablets and minitablets were provided with consistent thickness and smooth surface. Moreover, they

yielded the desired release pattern. Considering the regulatory issues raised by organic solvents, the feasibility of aqueous spray-coating by fluid bed was then evaluated using HPMC having increasing viscosity, namely Methocel® E5, Methocel® E50 and Methocel® K4M [44-46]. The operating conditions, above all spray rate, inlet air temperature and polymer concentration in the solutions, required an attentive set-up in order to overcome major problems of powdering and nozzle clogging as well as lengthy processing. The viscosity grade of the polymer chiefly affected the process time, nebulization being possible only with diluted solutions that increased the spraying and drying duration. From all of the polymers under investigation, coated units with satisfactory physico-technological characteristics were obtained. The release behavior was studied by paddle dissolution and modified disintegration apparatus. The latter proved indeed better suited to prevent sticking of swollen HPMC to the vessels, thus providing more reliable data. By both testing methods, a prompt release after a lag phase was highlighted, which depended on the coating level and the polymer viscosity. Using Methocel® E50 resulted in acceptable process feasibility, ability to delay drug release and fine-tuning of the lag phase. Moreover, the coating process was shown robust and potentially scalable. In the case of Methocel® K4M, not only the coating operations were strongly impaired by the high viscosity of water solutions, but also a small amount of drug was slowly released from coated units toward the end of the delay period. This was attributed to the formation of a firm, poorly erodible gel structure ultimately rupturing with the aid of the inner tablet disintegration upon water influx [47]. When the Methocel® E50-based coating procedure was applied to hard- and soft-gelatin capsules instead of tablets, the process parameters needed to be adjusted in order to prevent the sticking and shrinking of the shells [48]. In order to streamline

manufacturing of Methocel® E50-coated systems, alternative techniques, such as tangential-spray film-coating and powder-layering carried out by fluid bed rotogranulator, were attempted. Preliminary studies in volunteers demonstrated that, irrespective of the core dosage form, delivery systems coated with Methocel® E50 by aqueous spray-coating were able to defer drug appearance in saliva as a function of the coating level [45,48]. The *in vitro* and *in vivo* lag phases were comparable in duration. Moreover, when provided with a gastroresistant film, labeled formulations were shown to consistently break up in the ascending colon. After low-molecular weight drugs, chosen as models because of their stability characteristics and easy analysis, the possibility of conveying bovine insulin by this delivery system was explored [48-52]. In order to increase the chances of preserving integrity of the protein and promoting its permeation through the intestinal mucosa, enzyme inhibitor and absorption enhancer adjuvant compounds were incorporated in the formulation. Insulin was proved to withstand all manufacturing steps, as inferred by assaying the degradation products mentioned by European Pharmacopoeia, and was released *in vitro* in a pulsatile mode, as previously observed with antipyrine and acetaminophen, along with the adjuvants. The latter were also applied as a separate film enclosed between two Methocel® E50 layers, so that their release would occur earlier than that of the protein drug contained in the core, and less threatening conditions could be established *in vivo* beforehand [53,54].

When erodible coatings were applied to minitablet cores, relatively larger amounts of polymer were found necessary than with single units in order to obtain lag times potentially suitable for chronotherapeutic or colonic release purposes [55-57]. Thus, the thickness of the resulting film coatings would ultimately fail to comply with the size

requirements of multiple-unit dosage forms. Besides, depending on the viscosity grade of the polymer employed, the rate of release at the end of the lag phase would most likely be reduced. With the aim of overcoming this formulation issue, the external application of an insoluble, flexible and increasingly leaky film was proposed. Such a film was mainly intended to slow the uptake of water by the underlying HPMC layer, and consequently the relevant hydration as well erosion processes, without acting as a major mechanical constraint to the polymer expansion. Eudragit® NE 30 D was selected as the film-forming agent, whereas various superdisintegrants, above all Explotab® V17, were added as especially effective non-conventional pore formers. After tuning the composition of the outer film and the ration between HPMC and polymethacrylate coating levels, the desired release performance and dimensional characteristics were obtained from formulations based on this novel two-layer design.

HPMC barriers derived from coalescence of polymer particles were prepared not only by spray-coating but also by dipping, which circumvented the technical difficulties associated with nebulization of highly viscous polymeric solutions [58]. Ethanol/water mixtures were used to disperse the HPMC powder. Immersion steps, each followed by manual hot-air drying, were repeated until the tablets had reached the established weight gain. The latter was related to the lag phase duration. By affecting the structure of the coat layer, parameters such as the ethanol/water volume ratio, the concentration of the polymer and the time during which it was allowed to swell in the hydro-organic vehicle also impacted on the release of nifedipine from the core tablet.

Waxy materials of natural origin, in admixture with a surfactant, were employed as an alternative to swellable hydrophilic polymers in order to attain erodible barriers for time-controlled release [59]. Spraying of water dispersions of such lipophilic coating

agents required that the processing temperature be set at relatively high values (75°C). The resulting delivery system (Time Clock®) proved suitable for deferring salbutamol sulfate release *in vitro* and in healthy volunteers. In both cases, the lag phases were clearly dependent on the coating level. An agreement between *in vitro* and *in vivo* data was achieved when media having increased viscosity were used for release testing, which led to longer *in vitro* delays. The performance of the system in the gastrointestinal tract was demonstrated not to be influenced by food intake in 6 subjects, and $AUC_{0-\infty}$ as well as C_{max} in the fasted state were consistent with those of an immediate-release reference product. The Time Clock® system provided time-based colonic delivery in humans when in gastro-resistant configuration, as highlighted by ɣ-scintigraphy [60]. This was confirmed in 8 fed volunteers through pharmaco-scintigraphic evaluation of a 5-aminosalicylic acid-containing formulation [61].

Erodible delivery systems manufactured by hot-processing techniques

Hot-processing techniques, which enable the production of high-density structures of any desired form from softened/melted thermoplastic material substrates, are raising huge interest in every manufacturing area. However, their exploitation in the pharmaceutical field is still fairly limited despite the enormous potential held [62-65]. It is only recently that drug delivery applications mainly of hot-melt extrusion (HME), injection-molding (IM) and three-dimensional (3D) printing by fused deposition modeling (FDM) have been investigated and reported. Interestingly, the use of such techniques was proposed for the production of void functional capsule shells independent of their core units, with considerable prospective advantages from both the technical and the regulatory point of views [66-68]. In this respect, the feasibility of IM

in fabrication of erodible shells intended to defer release of their contents was explored [66]. HPC of various viscosity grades was selected as the capsule-forming polymer because of the inherent thermoplastic behavior upon heating. A bench-top IM press was employed, and the design of a specially suited mold was required. Through its use, cap and body items were obtained within single automated production cycles. *In vitro* studies pointed out a rapid release of the model drug after lag times that, composition being equal, correlated with the thickness of shells in the 300-900 μm range investigated. By visual inspection of capsule systems immersed in deionized water, it was inferred that release after the delay phase would be connected with rupturing of the hemispherical top and bottom ends of the device that were thinner than the cylindrical region where cap/body portions overlapped. On administration of these prototypes to 3 healthy volunteers, the *in vivo* lag times calculated from salivary concentration curves of acetaminophen were found in linear relationship with the *in vitro* ones [69]. The design of a novel mold for 600 μm thick units and concomitant setting up of proper formulation as well as operating parameters were subsequently undertaken [70]. This allowed faster production cycles to be carried out without adding external or internal lubricants. The shells obtained showed improved mechanical properties, which would aid large-scale filling by the equipment used with conventional gelatin capsules, and less variable thickness that was also closer to the theoretical value. Besides, the issue of thicker body/cap overlap areas was overcome. As a result, more reproducible release profiles were attained. The time to shell opening was demonstrated consistent irrespective of differing types of solid dosage forms conveyed (fine powder, granules, pellets, solid dispersion). These HPC capsules were successfully subjected to enteric coating, with no need for sealing the assembled caps and bodies, and then to final curing

[71]. Such systems fulfilled the requirement of resistance in pH 1.2 medium for 2 h, while maintaining the original pulsatile release curves when tested in pH 6.8 phosphate buffer. Accordingly, they appeared potentially suitable for time-dependent colon delivery, provided that the shell thickness be properly modulated so that duration of the *in vivo* lag phase would match the small intestinal transit time.

Capsule shells composed of HPC were lately replicated by FDM 3D printing, starting from filaments purposely prepared in-house by HME [68]. After assessing the possibility of attaining hollow structures by the use of FDM and developing the needed computer-aided design (CAD) files, bodies and caps of the shells were manufactured. Overall, these exhibited satisfactory physico-technological characteristics and, assembled into a drug-containing device, the typical lag phase before a rapid and quantitative release. Upon contact with deionized water, the behavior of capsule shells fabricated by FDM was comparable with that of analogous molded systems, thus supporting the real-time prototyping potential of this 3D printing technique and its possible exploitation in formulation development studies aimed at IM production.

Based on the expertise gained from the manufacturing of functional capsule shells, cylindrical dosage forms, such as immediate- and prolonged-release polymeric units, were also fabricated by HME and IM [72,73]. The relevant production via hot-processing was found to offer inherent advantages over the established techniques.

Conclusions

Drug delivery systems able to incorporate a lag phase of pre-established duration in their release patterns are a topic of high current interest, primarily in connection with oral chronotherapy and colon targeting.

Among the numerous formulation strategies proposed, those based on erodible polymeric barriers have largely and successfully been exploited. As the main components of such barriers, swellable/erodible polymers of hydrophilic nature, such as HPMC and other cellulose derivatives, have especially been used. Indeed, they easily enable fine-tuning of the release performance in terms of time and also rate through proper selection of the type and amount of polymer, which will affect the thickness and viscosity of the layer upon hydration. Erodible barriers intended for time-controlled release generally consist in coating layers. These may partially or entirely enclose a drug-containing core thus preventing it from immediately being exposed to aqueous fluids on administration of the dosage form. Coatings may be applied by differing techniques and, accordingly, possess diverse structural and functional characteristics.

Apart from coating layers, which are necessarily associated with a specific core formulation, polymeric barriers in the form of erodible shells have recently been manufactured by hot-processing, namely via IM and FDM. Because of the great versatility in terms of design, high innovative content, excellent scale-up prospects and unique benefits related to a separate development as well as production, these capsule shells may open up new ways in the field of time-controlled release and, more broadly, in the oral delivery area.

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