Expert Opinion

Time-controlled oral delivery systems for colon targeting

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In recent years, many research efforts have been spent in the achievement of selective delivery of drugs into the colon following oral administration. Indeed, colonic release is regarded as a beneficial approach to the pharmacological treatment or prevention of widespread large bowel pathologies, such as inflammatory bowel disease and adenocarcinoma. In addition, it is extensively explored as a potential means of enhancing the oral bioavailability of peptides, proteins and other biotechnological molecules, which are known to be less prone to enzymatic degradation in the large, rather than in the small, intestine. Based on these premises, several formulation strategies have been attempted in pursuit of colonic release, chiefly including microflora-, pH-, pressure- and time-dependent delivery technologies. In particular, this review is focused on the main design features and release performances of time-controlled devices, which rely on the relative constancy that is observed in the small intestinal transit time of dosage forms.

Keywords: capsular device, colon delivery, erodible coating, lag phase, rupturable film, small intestinal transit time

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1. Introduction

Over the past two decades, increasing research efforts have been spent in the accomplishment of colon drug delivery [1-12]. Local, as well as systemic, therapeutic goals are stimulating the interest in colonic release. Local goals are primarily connected with the need for high efficacy and tolerability tools intended for the pharmacological treatment or prevention of widespread large bowel pathologies, especially inflammatory bowel disease (IBD) and colorectal cancer [13-21]. In these instances, colon targeting would indeed hinder the drug from being extensively absorbed or metabolised in the stomach and small intestine, thus affording improved therapeutic outcome and a limited incidence of side effects. Moreover, the potential benefits from colonic release of β-lactamases, which is meant to control the spread of antibiotic-resistant bacterial strains, have recently been highlighted [22]. On the other hand, systemic goals are closely related to the pursuit of enhanced bioavailability for peptides, proteins, oligonucleotides and nucleic acids from the gastrointestinal tract [23-28]. The impressive applications that are likely to be associated with such drugs, which have become available on a large scale and in a wide variety due to biotechnology advances, are strongly constrained by well-known stability, biodegradability and permeability issues. In this respect, because of the inherent lower abundance of luminal and brush-border lytic enzymes, the colon has been recognised as a hypothetically less threatening environment than upper gastrointestinal districts. Furthermore, an extended contact with the mucosal surface (enabled by the physiologically long transit), the presence of lymphoid tissue follicles that are possibly responsible for macromolecule uptake, and the higher effectiveness of permeation enhancers, which may reach elevated local concentrations due to the limited fluid volume and slow progression of the contents, could all promote absorption into the systemic circulation. However, despite encouraging premises, evidence for the actual potential of colonic release for oral peptide delivery

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is still lacking, as human data in support of such a hypothesis have not yet been reported.

Although the distal colon can also be targeted via the rectal route, oral administration is needed when reliable delivery into the caecum and ascending and transverse colon is sought [1,5,9,11]. Oral colonic release involves the design of systems that are able to remain intact during gastric residence and small intestinal transit, and release the active ingredient only after entering the large bowel, in response to opportune inherent or extrinsic triggers. For this purpose, a variety of approaches have been attempted, each exploiting characteristic gastrointestinal variation patterns of one or more physiological parameters, such as microflora distribution, pH, intraluminal pressure and, finally, residence/transit time. Chemical–microbiological and technological–physiological formulation strategies have basically been distinguished [1]. Chemical–microbiological strategies take advantage of the selective presence in the colon of bacterial species catalysing peculiar enzymatic reactions on substrates that are not significantly dissolved, metabolised or absorbed in proximal gastrointestinal regions [29-31]. Accordingly, prodrugs or, alternatively, natural or synthetic polymeric excipients are used, which are subject to colonic activation or degradation, respectively. The main criticism addressed to such a formulation approach, that has become quite popular in the field of colon targeting since the early research stages, concerns the high variability in the composition of the gut microflora. In addition, prodrugs or synthetic polymeric adjuvants proposed for enzymatically activated colonic release would potentially entail the regulatory burden that has to be faced when dealing with any new chemical entity. On the other hand, natural polymers used as such often exhibit hydrophilicity and, to some extent, solubility properties. Therefore, they may be unsuitable for effectively preventing drug release during transit in the upper gastrointestinal tract. In contrast, technological–physiological strategies envisage pH-, intraluminal pressure- or time-controlled delivery technologies. pH-based systems, some of which have been granted marketing authorisation for IBD therapy, are typically devised as drug reservoirs coated with pH-dependent solubility materials [32-34]. In particular, polymers that are soluble > pH 7 have been used to match the hypothesis of a progressive pH increase from the stomach to the distal colon. However, due to short-chain fatty acid accumulation resulting from local anaerobic enzyme activity, the pH profile actually points out weakly acidic values in the caecum and ascending colon [35]. Even markedly acidic pH data have been recorded in the right colon of IBD patients [36]. Therefore, in more innovative instances of pH-based devices, acid-soluble coating polymers have been employed so as to exploit the acidic environment of the inflamed proximal colon [37,38]. With respect to the pressure-controlled delivery strategy, a single prototype has been described in the literature [39-41]. Such a system is liable to mechanical disruption due to the enhanced intraluminal pressure that is built up in the colon as a result of a spasmodic, more intense peristaltic motility. Finally, the time-based formulation approach relies on the reasonably predictable time lapse that dosage forms take to transit along the small bowel, from the pylorus down to the ileo–caecal valve. Indeed, small intestinal transit time (SITT) has been shown to last 3 ± 1 h (mean ± standard deviation) despite different unit characteristics and fasting or fed states of the subjects [42,43]. Notwithstanding these findings, it has to be noted that some criticisms have been directed to a reliable exploitation of relative SITT consistency. According to the time-dependent strategy, oral single-unit colon delivery systems are expected to remain intact while retained in the stomach on account of highly variable and unpredictable gastric residence time. After emptying into the duodenum, they would be triggered to start a lag phase, during which the drug should not be significantly released. Provided that the lag time is properly modulated so as to roughly correspond to, or otherwise exceed, the average SITT, drug delivery may eventually take place when the dosage form is located within the colon. The triggering signal, which causes the lag time to be initiated in the duodenum, generally relies on the sharp pH gradient between the stomach and intestine environments. Hence, such a trigger is simply achieved through the application of an outer enteric coating onto the delivery system. On the other hand, the lag phase can be attained as a result of solvent activation of different release-controlling formulation items. Whatever their working mechanism, those items have to delay drug liberation for a programmable, reproducible and possibly pH-independent time period, without involving complicated or poorly scalable manufacturing processes. In this respect, the use of plugs or layers with physical–chemical properties in a broad range, intended to seal drug-containing capsule bodies or coat inner drug reservoirs, has been proposed in pursuit of consistent lag phases for time-based colon delivery. In particular, swellable/erodible hydrophilic polymers have been widely employed both as coating agents and as the main plug matrix components. Alternatively, release-controlling coats have also been prepared with dispersible surface-activated wax mixtures, water-insoluble film-forming materials, enteric polymers applied in sufficiently thick layers and, finally, with an acid-soluble coating resin combined with organic acid contents. In principle, any device that is capable of imparting a predetermined delay phase to drug release is potentially eligible for time-based colon targeting. Notably, most time-dependent colon delivery formulations have originally been proposed to attain pulsatile release performances for chronopharmaceutical applications [44,45]. Likewise, systems for time-controlled colon targeting can conveniently be distinguished in reservoir, capsular and osmotic devices, according to the relevant design features. Reservoir systems are in turn differentiated based on the functional characteristics of their coating layer, which may work as a rupturable, erodible or diffusive barrier.

The aim of this review is to survey the most prominent examples that have been described in the primary literature of

oral colon delivery systems complying with time-dependent design requirements. In particular, key formulation details, along with *in vitro* and, where applicable, *in vivo* release performances referring to each above-mentioned device typology are addressed in the article.

2. Reservoir systems with rupturable polymeric coats

Many single- and multiple-unit systems for time-dependent colon targeting are devised as inner drug cores coated by a water-insoluble, but moderately permeable, polymeric film liable to mechanical disruption following contact with aqueous fluids. The breakage of the coating membrane is due to an expansion of the core formulation, which may result from osmotic or highly water-swellable excipient-induced massive water uptake, or alternatively from gas development brought about by effervescent additives.

An early example of rupturable dosage form with possible applications as a colon delivery system was proposed in the form of an isoniazid-containing press-coated tablet [46]. A large amount of calcium carboxymethylcellulose was used as the core disintegrant, whereas mixtures of co-melted hydrogenated castor oil and PEG_{6000} in different percent ratios were employed for the coating layer. When immersed in aqueous media, the system experienced a slow water penetration that caused the hydrophilic polymer to swell, finally leading to a collapse of the outer barrier. The so-called pulsatile release tablet yielded a fast and quantitative drug liberation following lag phases, which could be programmed by varying the thickness or the PEG 6000 content of the shell. The *in vivo* evaluation of diltiazem hydrochloride pulsatile release tablet systems on beagle dogs indicated pulsatile release performances characterised by an ample inter-individual variability in the fasting state and more reproducible behaviour in fed conditions [47].

Another diltiazem hydrochloride-containing press-coated rupturable device was based on crosslinked polyvinylpyrrolidone as the hydrophilic swellable polymer and a 1:2 mixture of ethylcellulose (EC) and the enteric acrylic resin Eudragit® L (methacrylic acid copolymer; Röhm GmbH & Co. KG) as the rupturable membrane [48]. The system was proven to withstand the acidic pH that is typical of gastric fluid and to give rise, after an additional lag time depending on the coating level, to a rapid liberation of the active ingredient in pH 6.8 medium. A key step in the release process was identified in the pH-dependent dissolution of Eudragit L. In fact, this resulted in the formation of pores within the EC membrane and consequent water penetration into the core, which caused crosslinked polyvinylpyrrolidone to swell until the system disintegrated. The system performances were also explored in a human pharmacokinetic study versus an immediate-release formulation. No significant differences were found in the AUC and C_{max} parameters, thus indicating that neither the rate of release nor that of absorption was changed. On the other hand, the appearance of detectable drug quantities in the plasma was clearly delayed by the delivery device. Lag time, as well as T_{max} values, were in agreement with *in vitro* data.

Recently, press-coating was employed to prepare a further colon delivery system based on swelling-induced disruption [49]. It consisted of a cylindrical indometacin and superdisintegrant sodium croscaramellose (Ac-Di-Sol®; FMC BioPolymer)-containing inner tablet that was completely covered by a waxy behenic acid shell, except for one face, which was coated with behenic acid and lactose blends in different percent ratios. Lactose dissolution was responsible for the formation of a pore net, which allowed water to penetrate into the core and interact with the superdisintegrant, finally leading to the breakage of the porous coating region. Delayed-release patterns were achieved, with lag phases shortening as a function of the amount of lactose in the outer shell. In particular, only when lactose content was included in the 60 – 70% range was the relationship with lag time found to be linear. Moreover, no pH dependence was observed for the modified release performances of such formulations.

The preparation of rupturable films for time-controlled colon delivery devices was also accomplished by spray-coating. A dibutyl sebacate-plasticised EC membrane was applied by this technique onto core tablets containing an effervescent citric acid and sodium bicarbonate mixture [50]. In this instance, disruption of the outer coating was induced by carbon dioxide developing within the core as a consequence of water influx. A fast liberation of chlorphenamine 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 instead of EC, floating dosage forms were attained due to higher permeability and flexibility characteristics of the films, which allowed water to diffuse into the inner tablet with no delay and were not subject to disruption caused by the subsequent gas development.

A rupturable system, provided with an EC membrane comprising diethyl phthalate as a plasticiser and PEG_{400} as a pore-former, was prepared by spray-coating from sodium diclofenac tablet cores containing sodium carboxymethyl starch and sodium chloride as swelling and osmotic excipients, respectively [51]. *In vitro* lag time was increased by raising the coating level. The mean *in vivo* lag time obtained by a pharmacokinetic study on fasted dogs was consistent with the corresponding *in vitro* result. Moreover, absorption and cumulative release versus time curves showed similar patterns, as confirmed by a good correlation coefficient.

Different rupturable devices were achieved starting from hard-gelatin capsule cores, which were coated with EC on their whole inner surface [52]. The gelatin lining was then dissolved from the capsule body, and a few micropores were drilled in its bottom to enable water influx. After inserting a drug container along with highly swellable low-substituted hydroxypropylcellulose (L-HPC), the body was sealed with the cap by means of EC glue. Drug liberation was enabled when the swelling pressure that developed inside the capsule was sufficient to induce cap failure. Accordingly, both the time

to complete *in vitro* release and the T_{max} of fluorescein observed in a dog pharmacokinetic study correlated with the cap thickness. Fluorescein-containing time-controlled colon delivery capsule prototypes were also evaluated on fasting, as well as fed, beagle dogs to assess the effect of food intake [53]. Owing to the lack of an enteric coating, premature release in the upper gastrointestinal tract could not be prevented, as demonstrated by substantially unchanged marker pharmacokinetic profiles. In a subsequent study focused on the role played by drug dissolution properties on the outcome of colon targeting, the *in vivo* behaviour of time-controlled colon delivery capsules based on carbamazepine as a hydrophobic model molecule was explored on fasting beagle dogs [54]. Higher bioavailability was achieved when the drug was formulated in oily suspension, rather than in physical mixture, with lactose within the capsule system.

Recently, hard- and soft-gelatin capsules were used as cores for pulsatile release devices that were provided with inner highly swellable and outer rupturable layers, which were both applied by spray-coating onto the external capsule surface [55-57]. In-depth investigations into the mechanical and swelling properties of films obtained from different materials were undertaken in order to select suitable candidates for the preparation of both coating barriers [58,59]. In particular, an EC blend with hydroxypropyl methylcellulose (HPMC) as a pore-former in 60:40 ratio and hydrophilic plasticiser triethyl citrate (TEC) was shown as a promising formulation by means of a specially developed test procedure [58]. With respect to the expanding layer, Ac-Di-Sol was proven to be superior to other swelling agents because it was effective in promoting a complete breakage of the outer film, thus leading to a rapid drug release at the end of the lag phase [59]. From both properly formulated hard- and soft-gelatin capsule systems, pulsatile delivery patterns were achieved, with the lag time increasing as a function of the outer coating level, and decreasing when the relevant HPMC percent amount or the thickness of the underlying Ac-Di-Sol layer were raised [55,57]. Shorter lag phases were obtained from coated soft-gelatin capsules compared with hard-gelatin capsules. This result was explained by the complete liquid filling of soft-gelatin units, which caused the whole swelling pressure to be discharged outwards, thereby inducing an earlier breakup of the external release-controlling membrane. When tablet cores were used in place of gelatin capsules, prolonged delay phases were unexpectedly observed by increasing the swelling coating level. In this respect, it was hypothesised that Ac-Di-Sol may delay the core disintegration by enhancing the overall hardness characteristics and hindering further water penetration when in the hydrated state [60].

The time-controlled explosion system (TES) is a notable example of a rupturable delivery system presented in multiple-unit form [61]. It was composed of central sucrose seeds covered by an inner drug layer, an intermediate L-HPC swellable coating (both applied by powder-layering) and an outer EC film [62]. The film underwent time-controlled disruption as a consequence of water uptake-induced expansion of the L-HPC layer. To attain pulsatile release, the application of an at least 180 µm-thick swelling layer was necessary. Otherwise, a diffusion-controlled slow drug liberation was observed. The release behaviour was shown to be unaffected by solubility and amount of the active ingredient, pH of the medium and particle size of TES subunits. The duration of the delay was strictly dependent on the thickness of the EC membrane [63]. The addition of talc into the composition of this film yielded shortened lag phases. An investigation carried out on volunteers pointed out consistent *in vitro* and *in vivo* performances of TES containing a vasodilator and antiplatelet drug [64]. Moreover, no significant differences in terms of AUC were found between fasting and fed regimens of administration, nor between the intake of TES or of an immediate-release tablet with the same drug dose in the fasting state. TES formulations containing sodium diclofenac, selected as the model drug in view of the consistent absorption throughout the intestine, with *in vitro* lag times of 3 and 6 h were studied on fasting gastrointestinal physiology-regulated beagle dogs, in order to gain indirect information on the system behaviour in human subjects [65]. The pharmacokinetic profiles of sodium diclofenac were related to the gastrointestinal performances of TES by estimating the dosage form location through a double marker method, which allowed gastric emptying and small intestinal transit times to be determined. Again, an agreement was found between *in vitro* and *in vivo* delays. However, the 6-h delay formulation showed markedly decreased AUC, which was ascribed to incomplete drug dissolution in the colonic environment due to the poor inherent water content.

A multiple-unit rupturable device for time-controlled release consisting of pellets that were film-coated with TEC-plasticised cellulose acetate was described in [66]. The core expansion responsible for the formation of micrometric fissures in the semipermeable membrane was due to the presence of sodium chloride in the pellet formulation, which promoted an osmotically driven influx of water. In order to obtain delayed release of the model drug acetaminophen, a minimum 2 mg/cm^2 coating level was required. Beyond such a value, a linear correlation was found between the lag time and coating level itself. The addition of less hydrophilic plasticisers (tributyl citrate or diethyl phthalate) into the film composition led to decreased water permeability as a function of the excipient lipophilicity, finally resulting in extended lag phases and lowered release rates [67]. On the other hand, mechanical properties of the films, evaluated by means of a tensile testing apparatus, were more affected by the quantity rather than the type of plasticisers. Finally, unchanged mechanical characteristics of the membrane, but longer lag times, were noticed when micronised talc was added into the coating formula.

Rupturable microcapsules for colon delivery of high molecular weight hydrophilic molecules were prepared by applying (spray-coating) self-synthesised colloidal methacrylic

terpolymers onto crystalline lactose particles loaded with fluorescein-labelled dextran [68]. Through the proper selection of the terpolymer molar ratio, satisfactory film-forming properties, even at temperatures < 40°C, and delayed release performances were obtained. In particular, prolonged silent phases were observed by raising the coating level beyond 40%. The disruption-based delivery mechanism was elucidated by measuring the progressive expansion undergone by microcapsules in the aqueous release medium using photomicrographs taken at subsequent time points.

3. Reservoir systems with erodible polymeric coats

Erodible release-controlling layers intended for time-dependent colon delivery are mainly obtained by exploiting swellable hydrophilic polymeric materials. In particular, cellulose ethers, such as HPMC, hydroxypropylcellulose (HPC) and hydroxyethylcellulose (HEC), are widely employed especially because of their consolidated safety profile, availability in several grades and affordability. When exposed to aqueous biological fluids, such polymers typically undergo combined swelling, dissolution and mechanical erosion phenomena, which account for a delayed onset of drug release from the core formulation. The application of hydrophilic swellable materials is accomplished by press-coating or, in more innovative instances, spray-coating and powder-layering techniques. Alternatively, erodible coatings have been prepared with surface-activated wax mixtures subject to dispersion in the intestinal fluid, or with an acid-soluble acrylic resin dissolving as a consequence of the pH decrease caused by time-dependent ionisation of an organic acid within an underlying formulation compartment. Finally, enteric polymers that are soluble at pH values > 6.8 – 7.0 have been applied in relatively thick layers, rather than in thin films, so that the dosage form could be protected not only during gastric residence, but also while transiting along the small intestine until complete pH-dependent dissolution of the coating had occured. By relying on a combination of pH- and time-formulation principles, such delivery devices have presumably been designed in an attempt to overcome the inherent limitations of the merely pH-based strategy. However, besides being affected by unpredictable pH fluctuations often associated with IBD, their gastrointestinal performances are likely to be impaired by the intrinsic physiological variability of both pH and time parameters.

Among the devices provided with swellable/erodible hydrophilic polymeric coats, the Chronotopic™ (Polichem SA) system was proposed for pulsatile and time-based colonic release by Gazzaniga *et al.* [69-74]. It consisted of a drug core, a HPMC barrier and, when colon delivery was sought, an outer gastric-resistant Eudragit L film. *In vitro* performances characterised by a lag time, which could be programmed based on the grade and amount of the coating agent, and a subsequent rapid and quantitative delivery phase were obtained. Such behaviour was well reflected in the salivary concentration profiles of an opportune marker drug, achieved through a pharmacokinetic study carried out on fasted volunteers [73]. In particular, *in vitro* and *in vivo* delays of the same rank order were observed. Moreover, the ability of the system to selectively deliver drugs into the proximal colon was demonstrated by scintigraphic investigations [73,75]. Throughout the technology development, the application of the HPMC release-controlling layer has represented a critical step. Press-coating and hydro-alcoholic spray-coating were initially attempted [69-71]. However, double compression was soon abandoned because of a number of practical drawbacks, such as the difficulties in having the core positioned in the die centre, with possible repercussions for the coat homogeneity and thus for lag time reproducibility, and the need for special equipment and time-consuming multiple-step processes, which are likely to be associated with poor scale-up prospects. Furthermore, the large polymer amount required by press-coating led to remarkable versatility constraints, particularly in terms of core candidates and achievable lag-phase periods. On the other hand, hydro-alcoholic spray-coating was ceased on account of the environmental and safety-related issues involved by organic solvents. The feasibility of aqueous spray-coating processes based on different HPMC grades was then explored [72-74]. Methocel® E50 (HPMC; Dow Chemical Co.) offered the best balance among various key items (i.e., reasonable process time, effectiveness in delaying drug release, flexibility in the modulation of lag time and lack of impact on the release rate). Subsequently, the possibility of preparing the Chronotopic system starting from gelatin capsules was assessed [76]. Indeed, the use of capsule cores could enable colon delivery of multiparticulate or dispersed formulations, which were described as potentially beneficial to the gastrointestinal stability and absorption chances of peptides and proteins [77-79]. More recently, studies aimed at improving the overall yield and time of the coating process preliminarily indicated the suitability of innovative techniques such as tangential spray-coating in a rotary fluid bed and powder-layering, which are undergoing further in-depth investigations [80,81].

In analogous delivery systems, high-viscosity HMPC was applied onto drug-containing tablet cores by press-coating or dipping methods [82,83]. Press-coated devices showed lag times increasing as a function of their hardness and the viscosity grade of HPMC [82]. In a preliminary γ-scintigraphic study, they were demonstrated to disintegrate in the ascending colon. On the other hand, lag times obtained from systems that were prepared by dipping turned out to be affected by the coating level and by some different coating conditions, which were supposed to impact on barrier properties of the HPMC layer [83]. Namely, when the ethanol/water ratio was raised or the polymer concentration diminished in the coating dispersion, longer delays were observed. By extending the time period during which HPMC was allowed to swell in the hydro-organic mixture prior to dipping operations, drug release was slowed.

A diltiazem hydrochloride-containing press-coated tablet for pulsatile delivery, based on HPC as the swelling coating

material, was described in [84]. The system was shown to afford lag times increasing as a function of viscosity and amount of the applied swellable polymer, without impacting on the rate of release. An evaluation carried out in fasting beagle dogs pointed out an agreement between *in vitro* and *in vivo* lag phases for 3-h *in vitro* delay prototypes, whereas the 6-h *in vitro* delay was shorter *in vivo*. In a gastric-resistant HPMC acetate succinate (HPMCAS) film-coated configuration, the system was also proposed for colon targeting [85]. Colon delivery devices provided with an additional gastric emptying marker (phenylpropanolamine hydrochloride) layer under the enteric film were administered to fasting beagle dogs. By comparing the times at which the marker and model drugs first appeared in the bloodstream, *in vivo* lag times consistent with *in vitro* data could be estimated. Moreover, because only slight differences were found in C_{max} values yielded by the delivery system and an immediate release tablet, it was concluded that the model drug absorption was not hindered in distal intestinal regions. In an attempt to simplify the overall coating procedure by avoiding the film-coating step, HPMCAS press-coated tablets were prepared [86]. Potential benefits in terms of gastric and mechanical resistance arose from the addition of water-soluble plasticisers, such as TEC, into the enteric coating composition [87]. Interesting effects were produced by magnesium stearate and calcium stearate, which afforded markedly prolonged release suppression in pH 1.2 and extended lag time in pH 6.8 fluids, respectively. The mechanism of such effects was elucidated through *in vitro* release, porosity and Fourier-transformed infrared spectroscopy studies [88].

HPC was also used to prepare a composite delivery system, which was manually assembled by inserting a cylindrical tablet core into a hollow swellable matrix, and provided with impermeable ethylene vinyl acetate copolymer coatings on either bases [89]. Drug release could take place after complete radial erosion or detachment of the HPC shell. *In vitro* delays were dependent on the thickness of the shell and on the core formulation. The use of lactose instead of microcrystalline cellulose, for instance, led to a faster water uptake, thereby shortening the lag time. When HPC was employed as the core-forming material as well, drug release was prolonged following programmable lag phases.

Pulsatile release tablet systems, in which HEC was used as the press-coating agent, were described in [90]. The induction phases preceding *in vitro* delivery of model drug diltiazem hydrochloride depended on the coating level and, to a lesser extent, on the polymer particle size. In fact, larger particles were associated with a higher barrier porosity, which may initially aid the hydration process. *In vivo* lag times obtained from a human pharmacokinetic study were consistent with *in vitro* data, and both were affected by the viscosity grade of HEC [91]. Although AUC did not significantly vary, C_{max} showed a progressive decrease with lag time prolongation.

In order to overcome the issue of a possible bioavailability reduction following delivery of drugs into distal intestinal regions with limited water content, a press-coated system composed of an outer macrogol 6000/polyethylene oxide (PEO) erodible hydrophilic layer and a highly water-soluble excipient-containing tablet core was devised [92]. *In vitro* tests were performed to screen various formulations differing in the core and/or coating composition. On the basis of the residual mass, measured after standardised immersion in pH 6.8 fluid and drying phases, and of the original core weight, a special parameter (named core erosion ratio) was introduced to describe the inherent tendency of the core to erode. Higher values of core erosion ratio were related to enhanced acetaminophen bioavailability results from a pharmacokinetic study carried out in fasting beagle dogs.

Finally, swellable/erodible coatings were obtained from sodium alginate/chitosan complex-containing composite lactose particles prepared by spray-drying, and applied onto acetaminophen tablet cores by press-coating [93]. These layers were demonstrated to withstand acidic pH and undergo, in pH 6.8 fluid, hydration and erosion phenomena, which were effective in delaying drug release according to the coating level and deacetylation degree of chitosan.

In addition, hydrophobic mixtures of natural waxes (carnauba and white beeswax) and surfactant (polyoxyethylene sorbitan monooleate) in water dispersion were sprayed at elevated temperatures onto tablet cores to prepare the release-controlling layer of the TimeClock® system [94]. When in contact with aqueous fluids, the hydrophobic barrier was subject to a progressive redispersion, thereby delaying the release onset for a time period correlated with its original thickness. Pharmacokinetic and γ-scintigraphic studies involving volunteers with different digestive conditions indicated the ability of the system to give rise to reproducible lag times, regardless of food intake. Notably, AUC and C_{max} values relevant to the model drug salbutamol sulfate were not diminished, compared with those afforded by a corresponding immediate-release product. An agreement between *in vitro* and *in vivo* delays could be found when *in vitro* tests were carried out in 120 cps viscous media, whereas lag times obtained in common release fluids were far shorter than *in vivo*. The suitability of placebo and 5-aminosalicylic acid (5-ASA)-containing enteric-coated devices for selective colon targeting was subsequently highlighted on fed volunteers through γ-scintigraphic and pharmacoscintigraphic investigations, respectively [95,96]. In addition, the screening of prototypes with different coating levels helped to identify a possible formulation candidate for further developmental studies [96].

The colon-targeted delivery capsule is a reservoir system for time-controlled colonic release with a particular design concept [97]. It was based on a hard-gelatin capsule core containing the active ingredient and organic acid blends. The external capsule surface was completely covered by an inner acid-soluble Eudragit E and an outer enteric HPMCAS polymeric coat. The inner and outer coats were separated by an intermediate hydrophilic HPMC layer. All of the coating agents were applied by a conventional spray-coating technique. After fast dissolution of the enteric and HPMC films in the duodenum, a lag phase

was provided by progressive water penetration into the capsule, ionisation of the organic acid and consequent dissolution of the Eudragit E release-controlling layer. By adjusting the thickness of this layer, programmable lag phases were achieved. Proof-of-concept data were obtained by a γ-scintigraphic investigation performed on volunteers under fasting and fed conditions, although a higher variability was observed in the fasting state [98]. Further evidence for the pursued *in vivo* behaviour was gained from dog pharmacokinetic studies carried out on colon-targeted delivery capsule units with gastric emptying (theophylline or acetaminophen) and/or colon arrival (sulfasalazine) marker drugs in the HPMC layer and capsule body, respectively [99,100].

Claiming a combined pH- and time-dependent design strategy, Eudragit S that is soluble > pH 7 was used to prepare (by the dipping method) a coated matrix system, which was considered suitable for sustained delivery of drugs throughout the colon, on the basis of *in vitro* release data obtained under a pH gradient [101]. By coupling gastric-resistant coatings with underlying organic acid layers that were meant to slow down the enteric polymer dissolution in intestinal fluids, diltiazem hydrochloride pellet formulations were devised, which provided *in vivo* lag times that were compatible with positioned drug release into different colonic regions [102]. Formaldehyde-crosslinked gelatin minicapsules containing the polypeptide hormone vasopressin were dip-coated with a 3:7 mixture of Eudragit S and water-insoluble, but permeable, Eudragit NE, and coated externally with cellulose acetate phthalate for gastric-resistance purposes [24]. *In vitro* vasopressin release was both delayed and prolonged according to the Eudragit S/Eudragit NE coating level. Most importantly, a significant and relatively persistent decrease in urine output was observed when the coated minicapsules were administered to hormone-deficient rats. Recently, Eudragit S was also employed as a spray-coating agent for alginate beads entrapping bee venom peptide-loaded liposomes, which were proposed as a further multiple-unit colon delivery system exploiting both pH and time functions [103]. Colonic release of the model peptide was highlighted by a preliminary γ-scintigraphic investigation on volunteers. In addition, a pellet formulation comprised of inert nonpareils and three overlapping coats respectively based on 5-ASA, Eudragit RS and RL mixtures, and Eudragit FS that is soluble > pH 6.8, was prepared, statistically optimised and evaluated *in vitro*, as well as *in vivo* (human pharmacokinetic study) [104-107]. Relying on the conventional involved techniques (i.e., powder-layering for 5-ASA and aqueous spray-coating for methacrylic copolymers) and on the achieved performance results, the authors regarded the device as easily scalable and potentially advantageous for the therapy of ulcerative colitis.

4. Reservoir systems with diffusive polymeric coats

A few examples of time-dependent colon delivery systems presented in the form of drug reservoirs with diffusive release-controlling barriers are described in the literature. These systems would afford sustained release throughout the gut after an induction phase, coinciding with the time lapse required for full water penetration through the diffusive layer, which should prevent drug liberation during transit in upper gastrointestinal regions. On the other hand, a fast delivery of drugs following lag time could hardly be accomplished. However, in view of the difficulties in matching the lag phase of these formulations with SITT, the prolongation of release may yield improved chances of having the active ingredient at least partly delivered to the colon.

A device based on a drug-containing central unit and an external layer composed of Eudragit RS mixed with opportune channelling agents was prepared by press-coating, and evaluated *in vitro* [108-110]. Drug release was delayed until the channelling agent was entirely dissolved and a pore network was formed within the external barrier, thus allowing water influx and outward drug diffusion to be accomplished. Both the lag time and release rate were affected by the type and particle size of the channelling agent, which impacted on the time necessary for pore formation, and by the applied amount of release-controlling polymer, which was related to the length of the diffusion pathway connecting the drug core and the outer medium. The core composition also influenced the release kinetics [110]. When the model drug sodium diclofenac was formulated in PEG_{4000} solid dispersion, the rate of delivery was higher. The overall *in vitro* release performances were considered potentially adequate to yield prolonged delivery of drugs into the colon district.

A peculiar multiple-unit formulation comprising drug/succinic acid mixtures loaded on nonpareil seeds and an outermost Eudragit RS film applied by spray-coating was described by Narisawa *et al.* [111]. After the characteristic *in vitro* release profiles, it was named sigmoidal release system. Due to the organic acid-induced permeability increase of the external membrane, a fairly rapid delivery of drugs could be achieved following lag times that were dependent on the Eudragit RS coating level. *In vivo* delays afforded by a pharmacokinetic study performed in fasted beagle dogs almost matched *in vitro* data. The gastrointestinal performances of sigmoidal release systems based on model drugs with different water solubility (i.e., theophylline and propranolol hydrochloride) were then investigated [112]. For this purpose, standard product amounts lodged inside small polyester-net bags were administered to fasting dogs at predetermined time intervals and assayed for residual drug content after recovery. The *in vivo* release data of propranolol hydrochloride were in good agreement with *in vitro* results, whereas theophylline was not completely delivered from the formulation, even though *in vitro* and *in vivo* lag times appeared to be similar. Incomplete release of the less-soluble drug was explained by a possible influence of the limited fluid volume available for dissolution in the distal intestine. Through dissolution, ion exchange and glass transition temperature experiments, it was elucidated that both the ionised and non-ionised forms of organic acids contributed to

improve the outer Eudragit RS membrane permeability by ionic interaction with positively charged quaternary ammonium groups of the polymer and partitioning into its hydrophobic segments, respectively [113]. Furthermore, as lag times were prolonged and the release rate diminished when the medium osmotic pressure was raised by adding a non-ionisable excipient, an osmotic pumping effect was hypothesised to be involved in the overall delivery [114].

Finally, a multiple-unit device with a more typical diffusive barrier was obtained by spray-coating application of TEC-plasticised Eudragit RS onto diltiazem hydrochloride-loaded nonpareil seeds [115]. Delayed release profiles were observed, with *in vitro* lag times increasing as a function of the coat thickness and of curing time. After the lag phase, a faster delivery could be achieved when highly water-soluble drugs and limited coating levels were handled.

5. Capsular systems with release-controlling polymeric plugs

A number of pulsatile delivery systems potentially suitable for colon targeting are designed in the form of capsules provided with a release-controlling polymeric plug inserted in their body opening.

The leading example is that of Pulsincap™ (Scherer DDS Ltd), which consists of a water-soluble cap and a rigid, insoluble and impermeable body filled with the drug formulation and sealed with a hydrogel plug based on crosslinked PEG_{8000} [116]. On contact with aqueous fluids, the cap was rapidly dissolved and the plug started swelling until ejection from the body, thus enabling drug release into the medium. The time to release depended on the size and position of the plug within the capsule body. Reproducible *in vivo* lag times were obtained, as highlighted by a human γ-scintigraphic study. However, concerns were raised beacuse of the apparently complicated manufacturing and use of non-approved crosslinked hydrogel. In this respect, the tolerability and patient compliance that were related to a treatment envisaging repeated placebo Pulsincap administrations over a relatively extended time period (28 days) were assessed [117]. The system, proposed in a gastric-resistant configuration for colon delivery, was evaluated by γ-scintigraphy and showed selective plug ejection in the caecum or ascending colon [118]. Through combined imaging and pharmacokinetic techniques, Pulsincap devices containing opportune marker drugs were advantageously exploited to carry out non-invasive permeability studies in the large bowel [119-121]. In an attempt to simplify the original technology, the use of erodible plugs based on low-viscosity HPMC and lactose blends in place of hydrogel matrices was successfully investigated [122]. Longer delay phases were obtained with plugs prepared by wet granulation rather than by direct compression [123]. The effect of wet granulation on plug performances was elucidated with the aid of microwave dielectric analysis. Moreover, the reasons for the different behaviour of capsules on which the outer EC film was applied by aqueous or organic spray-coating were explored through NMR studies [124]. The poorly reliable performances of aqueous spray-coated systems were attributed to a looser plug seal, which was not effective in preventing water influx into the body prior to the ejection step. Finally, superior integrity characteristics were found in the case of organic spray-coated capsules subjected to a specially set up crush test following exposure to high moisture levels [125].

Further capsular devices based on a polypropylene impermeable body, a swellable/erodible plug and effervescent excipients to promote a fast drug release after the lag phase were proposed by Krögel and Bodmeier [126]. Materials with different physical–chemical properties, such as various HPMC viscosity grades, polyvinyl alcohol and PEO, were evaluated as the plug-forming agents. Delayed delivery of the model drugs chlorphenamine maleate and ibuprofen was attained, with lag phases depending on the type and amount of the employed polymer. Alternatively, the use of plugs composed of pectin and pectinase mixtures was investigated [127]. When in contact with aqueous fluids, pectin underwent progressive enzymatic degradation. The lag time could be programmed by varying the polymeric substrate/enzyme ratio or total weight of the tablet plug. The addition of an appropriate buffer was necessary to maintain the pH value in the immediate proximity of the plug within the 4 – 8 range required for pectinase activity, and could even prevent the enzyme degradation via pepsin catalysis in acidic medium.

In 2002, analogous systems were assembled from high-viscosity HPMC or guar gum-based tableted plugs and insoluble/impermeable formaldehyde-crosslinked gelatin capsule bodies [128].

In contrast, the Programmable Oral Release Technologies (PORT™; TSRL Inc.) system was comprised of a hard-gelatin capsule provided with a semipermeable cellulose acetate coating on the body surface, an insoluble lipid plug and an inner osmotic charge/drug formulation [129]. Following osmotically driven water influx through the semipermeable capsule wall, the internal pressure was increased until time-controlled expulsion of the lipid plug. Delay phases with different duration could be achieved by modifying the cellulose acetate membrane thickness, plug length and/or osmotic charge. A γ-scintigraphic study carried out on volunteers under fasted and fed conditions indicated that the time to release was reproducible and not markedly affected by food intake [130]. Furthermore, a good agreement was found between *in vitro* and *in vivo* release data.

Finally, design similarities to capsular devices are envisaged by the Egalet® (Egalet a/s) technology, which was proposed for sustained or pulsatile delivery of drugs, including salmon calcitonin [131,132]. When intended for pulsatile release, the system was based on an impermeable cylindrical shell, in which a central drug core and two plugs sealing each open end were encased. The release-controlling plugs, prepared with high molecular weight PEG or PEO and PEG

monostearate, and the drug-containing unit were embedded in the shell by injection-moulding. On contact with the aqueous medium, the plugs were subject to gradual surface erosion until drug release from the inner formulation was enabled. By opportunely modifying the dimensions or composition of the plug and core components, the time and rate of delivery could be controlled. γ-Scintigraphic studies carried out on fasting volunteers highlighted the attainment of pursued *in vivo* release performances.

6. Osmotic systems

Gastrointestinal therapeutic systems, also referred to as osmotic pumps, are oral devices based on osmotic pumping as the inherent working principle. Their primary aim was to provide zero-order release kinetics over an extended time period. However, the need for an activation phase, which could be adjusted according to the thickness and diffusion properties of a semipermeable membrane irrespective of pH and hydrodynamics of the medium, has also been exploited to achieve delayed delivery for chronopharmaceutical purposes and time-controlled colon targeting [133-135].

The first osmotic system proposed for colonic release was the Osmet pump [134]. It consisted of an enteric-coated semipermeable, rigid cylindrical shell, which embodied an osmotic layer along with a central impermeable and collapsible reservoir filled with solutions or suspensions of drugs or other tracer substances. The interior of this compartment was connected with the external environment through a delivery orifice located at one end. After dissolution of the gastric-resistant film, water was allowed to penetrate through the semipermeable barrier, thus raising the pressure inside the device. As a result, the inner reservoir shrank and the drug formulation was pumped out at a constant rate via the shell opening. In spite of satisfactory *in vivo* performances highlighted in fasted as well as fed volunteers by γ-scintigraphy, the possible application of Osmet systems was chiefly confined to research because of the relatively large size, limited capacity and need for faecal recovery. These practical constraints were partially overcome throughout the subsequent evolution of the original technology.

Another osmotic colon delivery system was later proposed in the form of a tableted core, in which metoprolol fumarate was contained as the model drug, covered by an inner placebo compression coating based on swellable HEC and highly soluble dextrates, an intermediate cellulose acetate semipermeable membrane provided with a 1.0 mm-diameter orifice and an external enteric film [135]. The placebo lining separating the semipermeable membrane from the drug reservoir was the main difference between this system and the previously described elementary osmotic pump [136]. Following dissolution of the outermost acrylic layer, osmotic water influx across the cellulosic film caused the underlying coat to hydrate and dissolve, thus further delaying the onset of release. When water reached the tablet core, the active ingredient was solubilised and the internal pressure increased. Consequently, the drug was dispensed in solution at a constant rate through the membrane orifice. The *in vivo* behaviour of the system was evaluated in fasted beagle dogs. In an attempt to compare *in vitro* and *in vivo* data, the pharmacokinetic study was performed against colonic model drug infusion at a rate approximately corresponding to that observed for *in vitro* delivery, after assessing parallel *in vitro* release and postinfusion absorption profiles. It was thereby established that, following administration of the osmotic pump, the average lag time and residual drug content at 24 h were consistent with *in vitro* results, whereas the rate of absorption was markedly reduced, possibly due to the presence of faecal material in the colon lumen, even after fasting for 16 h.

Recently, a prevailing osmotic release mechanism was invoked with reference to a tablet system containing bronchodilator terbutaline sulfate, chosen as the model drug in view of its chronotherapeutic potential for nocturnal asthma, and sodium chloride as an osmotic agent [137]. The device contained a swellable low-viscosity HPMC layer and outer insoluble, but moderately permeable, film composed of Eudragit RS/Eudragit RL mixtures, which were prepared by spray-coating. When sodium chloride and HPMC were both included in the formulation, *in vitro* pulsatile delivery was obtained after delay times that depended on the external membrane thickness, and were unaffected by pH or hydrodynamic test conditions. A composite working principle was highlighted through release studies carried out in different osmolality fluids, scanning electron microscope-aided analysis of the outer membrane structure before and after exposure to aqueous media and measurements of water uptake-induced unit expansion performed by a profile projector method. In particular, it was elucidated that the lag phase was due to the time needed for water penetration across the Eudragit RS/Eudragit RL film and consequent enlargement of the underlying compartments, until delivery was enabled by micrometric fissures formed within the acrylic layer. Diffusion, as well as osmotic pumping phenomena, was demonstrated to be involved in driving drug liberation, although the latter were identified as the key mechanism of release.

7. Expert opinion and conclusion

Colon delivery, which has been drawing considerable research interest because of highly appealing potential applications, is currently pursued through a variety of formulation strategies. These include microflora- and pH-dependent technologies, which are the only ones available as drug products on the marketplace, as well as pressure- and time-controlled release platforms. In particular, the latter rely on a relatively consistent transit time of dosage forms along the small intestine. The possible exploitation of this feature has been first highlighted by Davis [42]. In the paper that has been recognised as the mainstay of time-based colon delivery approaches, enteric-coated formulations that are able to provide a lag phase commencing on gastric emptying and roughly corresponding to SITT have

been identified as a potential means of targeting the colon through oral administration. Since then, several modified-release dosage forms have been designed to seize that opportunity, in spite of criticisms addressed to the concept of SITT reproducibility. In addition, a number of pulsatile delivery systems originally proposed with the aim of meeting chronopharmaceutical needs have later been adapted for colon targeting. In general, the delay time responsible for preventing drug release in the upper intestine has been accomplished by programmable disruption, swelling/erosion, dispersion, pH-induced dissolution or water permeation of polymeric coats with different physical–chemical properties. Otherwise, the lag phase has also been obtained through a timed ejection or a progressive erosion or biodegradation of matrix plugs sealing capsular devices. Thereafter, a fast or prolonged liberation of drugs into the large bowel has been achieved, depending on formulation characteristics that impact the rate of release.

With possible exceptions for multiple-unit systems, which are less affected by unpredictable gastric residence, any colon delivery device that is expected to fulfil time-based design principles requires gastric protection in order to overcome the influence of stomach residence. In effect, delay times would hardly be related to the intestinal location of dosage forms, as it could not *a priori* be estalished how long these might be retained in the stomach. On the other hand, for the purpose of colon targeting, the selection of a proper release-controlling mechanism is also necessary, which may allow lag periods to be programmed according to the average SITT. When this is not possible, no selective site targeting is attainable. For example, this may be the case of systems provided with relatively thick enteric coatings, for which a combined pH- and time-based approach is claimed. However, in view of the considerable intra- and inter-subject variability in intestinal pH values, an opportunely time-programmed dissolution of these coats could barely be achieved. As a result, the position of dosage forms after the lag time would also be affected by pH variability issues. Furthermore, when dealing with prolonged-release devices requiring an activation time for full water permeation through a diffusive barrier, colon delivery is presumably pursued on the basis of the initial activation step, which may prevent release in upper gastrointestinal regions, and a subsequent extended drug liberation that is likely to partially occur within the large bowel. However, such a strategy is far from affording a temporal control on the release site.

When appropriately designed to overcome unpredictable gastric residence and exploit a fairly consistent SITT, time-based delivery platforms may yield improved chances of targeting the colon as compared with different available formulation strategies. Indeed, the variability of small intestinal transit seems to be less threatening than that relevant to other biological parameters, which have been relied on in pursuit of colonic release. For example, it is well known that gastrointestinal pH may display ample physiological fluctuations and is also affected by drug intake or disease conditions, for the therapy of which site-selective formulations are often indicated. On the other hand, microflora is liable to imbalances, which can be simply caused by diet or habit changes, whereas the exploitation of intraluminal pressure is constrained by inherent limitations connected to the particular motility pattern of the colon. In addition, time-dependent technologies would not necessarily imply the use of new pharmaceutical excipients, which could hinder approval procedures by raising the regulatory burden.

Major issues in the development of time-based colon delivery devices may arise from performance evaluation steps. In fact, as generally experienced when handling systems for colonic release, difficulties may be encountered in setting up biorelevant *in vitro* tests due to the many involved determinants, such as pH, ionic strength, surfactants, enzymes, microorganisms, viscosity, gas, intraluminal pressure and slow progression, which in combination with reduced water content may impair sink conditions [138]. Hence, *in vivo* testing has emerged to be of the utmost importance from early developmental stages. Available animal models have unfortunately proved poorly suitable for the human gastrointestinal transit [139]. Accordingly, studies on volunteers are required in order to assess the performance of devices *in vivo*. The use of opportune marker drugs embedded in specific formulation compartments has sometimes allowed pharmacokinetic investigations to be carried out in place of imaging studies. However, reliable assessments of the potential of a given time-controlled colon delivery technology could only be expected from human scintigraphic evaluations. Their costs and limited accessibility may pose primary obstacles to a rapid advancement of these devices, which, in turn, could probably account for (together with the relative novelty of the underlying approach) the lack of commercially available drug products. In fact, although several time-based systems for colon targeting have been described, and some have also undergone mainly animal *in vivo* pharmacokinetic studies, a limited number of relevant imaging investigations have been reported in the literature. However, it is impressive that, besides highlighting the outcome of individual delivery platforms (which were generally successful yet dependent on the inherent release-controlling mechanism), scintigraphic studies conducted in fasted and fed administration regimen have provided an overall confirmation for SITT reproducibility, thereby further supporting the time-based strategy for oral colon targeting.

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