Expert Opinion

Colon drug delivery

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Oral drug delivery to the colon has attracted significant attention during the past 20 years. Colon targeting is recognised to have several therapeutic advantages, such as the oral delivery of drugs that are destroyed by the stomach acid and/or metabolised by pancreatic enzymes. Sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina and arthritis. Local treatment of colonic pathologies, such as ulcerative colitis, colorectal cancer and Crohn's disease, is more effective with the delivery of drugs to the affected area. Likewise, colonic delivery of vermicides and colonic diagnostic agents requires smaller doses. This article aims to provide an insight into the design and manufacturing considerations, and an evaluation of colonic drug delivery systems in order to understand why there are still few delivery technologies that have reached the market, despite intensive research in this field. For this purpose, various approaches to colon-specific drug delivery are discussed.

Keywords: biodegradation, colon drug delivery, colon targeting, controlled release, pH-dependent polymers, prodrugs, time-dependent drug release

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1. Introduction

Targeting of drugs to a specific site in the gastrointestinal (GI) tract has been recognised to have several advantages. A smaller dose is required; therefore, reduced incidence of undesirable systemic adverse reactions can be expected. A number of colonic diseases could be treated more efficiently by delivering the drug locally in the colon, such as Crohn's disease, ulcerative colitis, constipation, colorectal cancer, spastic colon, and irritable bowel syndrome. In addition, colonic drug targeting would be valuable when a delay in absorption is desired from a therapeutic point of view in the treatment of diseases that have peak symptoms in the early morning, such as nocturnal asthma, angina or arthritis. In addition, there has been an increased interest in using the colon as a site for oral peptide drug delivery. At present, the route of administration for this group of therapeutic agents is the parenteral and, more recently, the nasal route. However, both are less convenient than the oral route. Due to negligible activity of brush-border membrane peptidase activity, and much less activity of pancreatic enzymes, the colon has been considered to be more suitable for the delivery of peptides and proteins in comparison to the small intestine [1,2]. However, a substantial amount of research still needs to be conducted in order to find out to what extent these molecules can be absorbed after oral administration.

Colonic delivery can not only be accomplished by oral but also by rectal administration. Rectal delivery forms (suppositories and enemas) lack efficiency as a high variability in the distribution of these forms is observed [3]. Suppositories are only effective in the rectum because of the confined spread, and enema solutions can only offer topical treatment to the sigmoid and descending colon [4,5]. Therefore, oral administration is preferred, but for this purpose many physiological barriers have to be overcome. Absorption or degradation of the active ingredient in the upper part of the GI tract is the major obstacle and must be circumvented for successful colonic drug delivery.

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Table 1. pH values in the human gastrointestinal tract.

Site	Average pH value
Mouth	6.2 – 7.4
Oesophagus	5.0 – 6.0
Stomach	
fasted	1.5 – 2.0
fed	3.0 – 7.0
Duodenum	
fasted	4.9 – 6.5
fed	5.0 – 5.6
Jejunum	
fasted	4.4 – 6.5
fed	5.2 – 6.2
Ileum	
fasted	6.5 – 8.0
fed	6.8 – 8.0

Adapted from [6].

In this review, a brief introduction to the physiology of the GI tract and biopharmaceutical considerations in relation to colon drug delivery will be presented. The main objective of this paper is to review different colonic delivery technologies, which have been presented during the past 20 years. Prodrugs, pH-sensitive polymers, bacterial degradable polymers, hydrogels and matrices, and recently multi-coating time-dependent delivery systems are an array of such targeting systems.

2. Physiology of the gastrointestinal tract and biopharmaceutical considerations relevant to colon targeting

For the purpose of colon targeting there are two important physiological factors to be considered. These are pH and the transit time in the GI tract. The pH of the GI tract is subject to both inter- and intra-subject variations. The absence or presence of food in the stomach determines the gastric pH range, which can vary from values < 3 (interquartile range 1.4 – 2.1) in the fasted state, to ~ 3 – 7 in the fed state [6]. The steepest gradient in the luminal pH of the GI tract is encountered in the proximal part of the duodenum. Beyond the first few centimetres, bile and pancreatic secretions mix with the duodenal content and neutralise the chyme [7]. Passing from the jejunum through the mid-small bowel and the ileum, pH rises slightly from ~ 6.6 – 7.5, but falls to ~ 6.4 in the right colon. The mid and left colon have pH values of ~ 6.6 and 7.0, respectively [8-10]. However, when suitable carbohydrate substrates are present, the pH in the proximal colon may be 2 – 3 pH units lower than in the terminal ileum [6]. Interspecies variability in pH is not only a major concern when developing colon targeting systems, but also when testing of these systems in animals and applying the information to humans is not straightforward. Table 1 gives an overview of pH of the GI tract.

The GI transit time of food and drugs shows great variability and may be another constraint on colonic drug delivery. Factors such as age, disease and drug interactions all contribute to the encountered variability. The arrival of an oral dosage form at the colon is largely determined by the rate of gastric emptying and motility patterns in general. Between meals, mammals exhibit a characteristic cycle of gut motility. In humans, a brief (2 – 10 min) but intense muscle contraction occurs every 90 min, beginning in the stomach and progressing to the distal ileum. This is followed by a period of resting and, later, a period of intermittent milder contractions, after which the cycle restarts. These movements have been designated as Phase I (quiescence), Phase II (irregular activity) and Phase III (intense bursts of contractile activity). However, after food ingestion, the cycle is replaced by irregular activity lasting one to several hours, depending on the type of meal [7]. The stomach does not participate in all the cycles, hence, if a drug is ingested after the phase that involves the stomach, its gastric retention time may be prolonged. Drugs taken before meals usually pass out of the stomach within 1 h but when taken after a meal, the drug can take ≤ 10 h in the stomach [5]. In man, small particles (< 7 mm in diameter) can pass out of the fed stomach regardless of its emptying time [11]. In contrast, the transit time of the small intestine is reasonably constant, ranging from 3 to 4 h [12] regardless of various conditions such as physical state, size of dosage form or presence of food in the stomach [13,14]. More time may be spent at the ileocaecal junction, which acts as a mechanical valve [11,12]. Here, small pellets that may be distributed in the small intestine tend to regroup, and will be redistributed in the ascending colon. Segmentational contractions mix the colonic contents, thus facilitating absorption, whereas peristaltic waves propel the faecal material in the anal direction [15].

The movement of faecal material in the colon is slow compared with the movement of chyme in the small intestine. The transit time of drugs in the large intestine ranges from 20 to 30 h, although transit times of a few hours to > 2 days have been reported [5]. Adkin *et al.* demonstrated that larger tablets (9 – 12 mm) move faster through the proximal and mid-colon than small tablets (3 – 6 mm), but the transit time through the ileocaecal junction is largely unaffected by size [16]. Compared with tablets, pellets move faster through the ascending colon and, therefore, with respect to colonic drug absorption, pellets may be the more favourable [17]. Colonic transit time is only slightly affected by food and, under stress, the transit time may be shorter [18,19]. Drugs that act on the parasympathetic or sympathetic nervous system affect the propulsive motor activity, influencing the transit time accordingly [20]. Finally, transit time can be affected by disease states that result in diarrhoea or constipation, although in most disease conditions transit time appears to remain reasonably constant [21,22].

Table 2. Drug absorption promoting substances.

Agent	Examples
Chelating agents	Na-EDTA; citric acid
NSAIDs	Indomethacin; salicylates
Surfactants	Saponins, polyoxyethylene derivatives; taurocholate
Bile salts Fatty acids	Caprates and caprylates

EDTA: Ethylenediamine tetra-acetic acid; NSAID: Non-steroidal anti-inflammatory drug.

Oral delivery of low-molecular weight peptides and peptide-like drugs is often claimed to be more efficient if these molecules could be targeted to the large intestine. A lot of research remains to be conducted to find out to what extend these molecules can be absorbed after oral administration but in general the colon may not be the best place for drug absorption. The colonic mucosa lacks well-defined villi and this drastically reduces the absorptive surface area, despite the large diameter, which also reduces the exposure of drug molecules to the site of absorption. Moreover, the viscosity of colonic contents is high, especially after the hepatic flexure when chyme is processed into faeces, which makes it even more difficult for a drug to diffuse from the lumen to the site of absorption. Furthermore, there is reduced permeability to polar compounds due to tight junctions between cells [23]. Many factors can impede colonic drug absorption and these were reviewed by Mrsny in an excellent paper on colonic drug absorption [24]. First, specific and nonspecific drug binding can occur in the lumen when drugs interact with dietary components or products released from bacteria. This in turn may result in facilitated enzymatic or environmental degradation by increasing the time that the drug remains in the colon. Second, interaction between the negatively charged mucus layer and drug molecules (e.g., penicillins, cephalosporins and aminoglycosides) can result in either drug–mucus binding or drug–mucus repulsion [25]. Finally, the epithelium, the lipid bilayer of the individual colonocytes, and the occluding junctional complex between these cells provide a physical barrier to the absorption of drugs. Although significantly less than observed in the small intestine, there are enzymatic activities associated with the colonocytes.

As carrier-mediated uptake of drugs across the epithelial cell barrier is not extensive, lipid solubility, the ability of a drug molecule to partition between an aqueous and a lipid environment, the degree of ionisation and the pH at the site of absorption are very important factors. The unstirred water layer between the mucus layer and the epithelial surface area can all produce a diffusional barrier for the absorption of drugs, especially those that are very lipophilic [26]. The positive aspect for drug absorption is the prolonged residence time in the colon, which depends on motility of the colon. Drugs that produce excessive muscular activity of the colon could result in the rapid elimination of drugs, and conversely, the residence time is prolonged for drugs that inhibit muscular activity. In spite of the unfavourable conditions for absorption, a variety of drugs are relatively well absorbed from the colon, such as theophylline, ibuprofen, nifedipine, metoprolol, diclofenac, pseudoephedrine, brompheniramine, isosorbide dinitrate or oxprenolol [27].

Whether or not a peptide drug will benefit from colon targeting should be evaluated in a case-by-case study. The permeability of the epithelium to these molecules can be modified through the use of chemical enhancers, which are compounds that promote absorption. Intestinal absorption of polar drugs has been reported to be promoted by several compounds with widely differing chemical structures: chelating agents; NSAIDs; surfactants and mixed micelles; fatty acids and other substances [24,29-34]. Table 2 lists some of the compounds that possess colonic absorption-enhancing activity. Although many penetration enhancers have been found to improve oral bioavailability, many of them suffer from non-specificity, and the propensity to elicit local irritation and irreversibility in action [35]. A successful approach will be a result of the balance between the efficiency of absorption and the effect of the enhancing agents on cells and tissues.

3. Approaches to colon-specific drug delivery

3.1 Prodrugs

Prodrugs are usually designed to circumvent chemical, physical or physiological problems, and are therapeutic agents that have to undergo biotransformation before exerting a pharmacological action. Prodrug-based systems have been extensively exploited in targeting drugs to the colon. Once in the colon, enzymes produced by colonic-resident bacteria act on the drugs to release the active moiety. The GI tract has a variety of microorganisms that contribute to its physiology and functions, and participate in the metabolism of ingested material. Age, disease state and the presence of antibiotics affect the metabolic capacity of the resident microflora. The upper part (the stomach, duodenum and proximal ileum) only contains a small number of bacteria, mainly Gram-positive facultative bacteria [36,37]. Whereas the stomach and the proximal small bowel have $< 10^4$ colony-forming units (CFU)/ml, the colon contains $10^{11} – 10^{12}$ CFU/ml [38], mostly anaerobic bacteria. *Bacteroides*, *Bifidobacterium* and *Eubacterium* are the predominant species. Also present are the anaerobic Gram-positive cocci as well as *Clostridium*, *Enterococci* and various species of *Enterobacteriaceae* [39], as summarised in Table 3. Hydrolytical and redox reactions are the predominant metabolic conversions triggered by the intestinal microflora. The main hydrolytic enzymes produced by the intestinal bacteria are β-glucuronidase, β-xylosidase, α-L-arabinosidase and β-galactosidase, whereas the reductive enzymes include nitroreductase, azoreductase, deaminase and urea dehydroxylase [40]. Although significantly less important than in the small intestine, proteolysis can also occur in the colon, and this must be

Table 3. Human bacterial population in the lower bowel.

Species	Mean log viable count/g		
	Distal ileum	Caecum	Faeces
Enterobacteria	3.3	6.2	7.4
Enterococci	2.2	3.6	5.6
Clostridia	< 2	3.0	5.4
Lactobacilli	< 2	6.4	6.5
Bacteroides	5.7	7.8	9.8
Gram-positive non-sporing anaerobes	5.8	8.4	10.0

Adapted from [39].

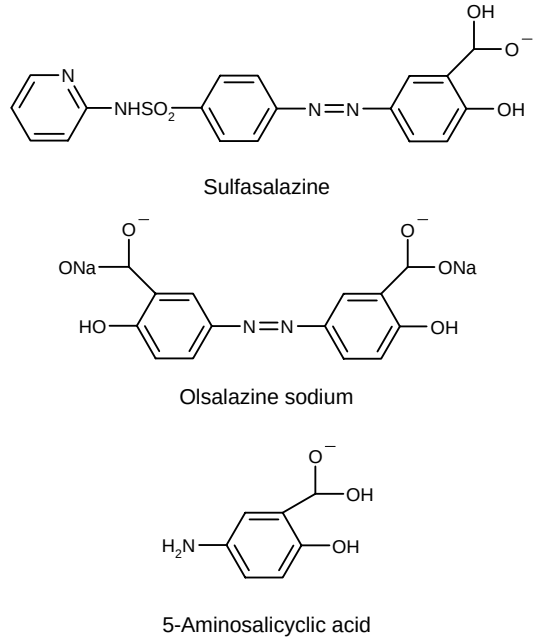


Figure 1. Structures of sulfasalazine, olsalazine sodium and 5-aminosalicylic acid.

kept in mind when targeting peptides and proteins to the large intestine.

Sulfasalazine (SAS), which is used in the treatment of ulcerative colitis, Crohn's disease and rheumatoid arthritis, is a well-known colon-specific prodrug. It consists of 5-aminosalicylic acid (5-ASA) linked via an azo bond to sulfapyridine (SP) (Figure 1). When orally administered, ~ 12% is absorbed in the small intestine but the main part reaches the colon intact, where bacterial azoreductase cleaves the azo bond thereby releasing 5-ASA and SP. It has been demonstrated that 5-ASA is the active moiety, whereas SP is only a carrier that may be responsible for the side effects [41], and therefore, olsalazine (Dipentum®, Pharmacia & Upjohn AB) was developed for the delivery of 5-ASA to the colon, thus avoiding SP. It consists of two molecules of 5-ASA linked by an azo bond (Figure 1) [42]. Olsalazine has been demonstrated to be as effective as 5-ASA in the treatment of ulcerative colitis but did not show a proportionally greater effect, suggesting a maximum effective delivery level of 5-ASA [43].

Other approaches to deliver 5-ASA to the colon resulted in the development of ipsalazide and balsalazide, where 5-ASA is linked to 4-aminobenzoyl glycine and 4-aminobenzoyl β-alanine, respectively [44]. However, only balsalazide has been developed further.

5-ASA has also been azo-linked with polymeric materials [45]. A comparable total release of 5-ASA and metabolites in rats has been reported for SAS and the polymeric prodrug that consists of polysulfonamidoethylene as a carrier molecule (Polyasa) but the latter was more effective in reducing inflammation in the guinea-pig ulcerative colitis model. Schacht and colleagues demonstrated that the release of 5-ASA from polymeric prodrugs was dependent on the structure of the polymeric backbone [46]. When 5-ASA was coupled with glycine or aminocaproic acid as a spacer group to either poly-1-vinyl-2-pyrrolidone-co-maleic anhydride, poly-*N*-(2-hydroxyethyl)-D,L-aspartamide, or dextran, they found that the release of 5-ASA from SAS was initially faster than from the polymeric prodrugs, but after incubation of 5 h in a human colonic fermentation model, release of the parent drug from the dextran derivative was comparable with SAS. The release from the ether polymers was considerably slower, and it was suggested that bacterial degradation of dextran contributed to the higher drug release rate. To compensate for a slow release at the target site, the approach of bioadhesive polymeric prodrugs has been proposed [47,48].

5-ASA polymeric prodrugs containing fucosylamine were prepared (Figure 2), as it was suggested that glucose- and fucose-specific adhesion of bacteria to colonic cells of guinea-pigs resides in the host cells. The rate of azo bond cleavage was comparable to that of low molecular weight compounds. The addition of the redox mediator benzylviologen increased the rate of reduction and of 5-ASA release, which was found to be of a zero order. However, it was later found that hydrophobic binding of the aromatic side chains in the polymeric backbone to the colonic mucosa may have a greater influence than the specific recognition of the fucosylamine groups [49]. The setback of coupling 5-ASA to polymeric materials is the large amount of prodrug that is needed to be taken orally. The dose of 5-ASA ranges from 0.5 to 3 g/day but because the drug can only constitute ~ 20% of the total weight of the prodrug, the total amount would not be acceptable.

Another approach that has been exploited involves prominent bacterial enzymes such as glycosidases and polysaccharidases. Friend and Chang [50,51] developed prodrugs by coupling a hydrophilising promoiety, glucose or galactose, to steroids, such as dexamethasone, prednisolone, hydrocortisone and fludrocortisone, via a β-glycosidic bond. When taken orally, the prodrugs being polar undergo minimal absorption in the small intestine, however, the bacterial glycosidases cleave the polar moiety releasing the steroid.

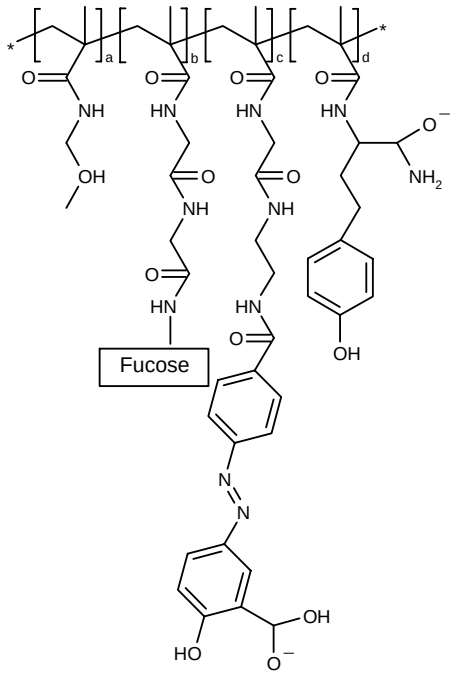
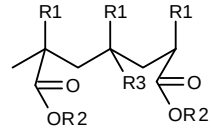


Figure 2. Polymeric prodrug of 5-aminosalicylic acid based on methacrylic copolymers.
a – d: Repeat units.

Such selective delivery of corticosteroids is highly desirable in the treatment of disorders of the large intestine, as side effects can be minimised due to decreased absorption of polar compounds in the small intestine, as well as dose reduction. Although there was no significant difference between drug and prodrug treatment, the results indicated that a lower dose of dexamethasone, given as a prodrug, was equally as effective as the higher dose of the parent drug [52]. This approach has been extended with the development of glycoside prodrugs of budesonide and menthol, and with dexamethasone-poly-L-aspartate [53,54].

A class of macromolecules that has been the focus of increasing interest is one that includes dextran prodrugs. The first attempt was carried out by Harboe and colleagues who conjugated naproxen to dextran by an ester linkage [55]. The release of naproxen was up to 17-fold higher in the caecum and in colon homogenates of the pig than in control medium or homogenates of the small intestine. Furthermore, MacLeod *et al.* and Jung *et al.* reported dextran prodrugs of methylprednisolone or dexamethasone, and 5-ASA, respectively [56,57]. In both cases the results were promising, with most of the drugs being released in the contents of the large intestine, whereas only minor chemical hydrolysis occurred in the upper GI tract. Other developments involve the use of cyclodextrins (CD), which are known to be absorbed only in minor quantities from the small intestine, whereas they are fermented by colonic bacteria. The anti-inflammatory drug biphenyl acetic acid (BPAA) was conjugated to α-, β-, or γ-CD through an ester or amide



R1: CH_3 ; H
R2: CH_3,CH_3CH_2
R3: -COOH (Eudragit L and S)
$-COOCH_2CH_2N^+(CH_3)_3Cl^-$ (Eudragit RL and RS)

Figure 3. Chemical structures of Eudragit® polymers.

linkage [58,59]. The prodrugs were found to be stable in the stomach and small intestine of rats. Interesting results were obtained with the α- and γ-CD derivatives: 3 – 6 h after administration BPAA was released in the colon and caecum and appeared in the systemic circulation. More recently the same research group found that the anti-inflammatory effect of prednisolone hemisuccinate–α-CD conjugate was comparable to that of prednisolone alone, but the systemic side effect of the conjugate was significantly less than that of the parent drug [60]. These promising results highlight CD-based prodrugs as an area for further research.

3.2 Colon delivery systems

3.2.1 pH-sensitive polymers

The pH of the GI tract is low in the stomach but increases when passing to the small and large intestine. For the purpose of targeting drugs to the colon, it is plausible, therefore, to coat tablets, capsules or pellets with a pH-dependent polymer that is insoluble at low pH but soluble at neutral or slightly alkaline pH. This would thus release the drug in the distal part of the small intestine or in the colon. However, problems with this strategy arise from the fact that the intestinal pH is not predictably stable, being influenced by diet, disease and presence of fatty acids, carbon dioxide and other fermentation products. Moreover, the intra- and inter-individual difference in GI-tract pH is considerable and is a major drawback in successful (i.e., reproducible) drug delivery to the large intestine.

Widely used pH-sensitive polymers for the purpose of colon targeting include methacrylic resins, commercially available as Eudragit® (Rohm Pharma), originally described by Lehmann [61]. Different types of Eudragit, whether water insoluble or water soluble, are used for colon targeting (Figure 3). Although Eudragit L is soluble at pH ≥ 6, Eudragit S dissolves at pH ≥ 7 due to a higher amount of esterified groups in relation to carboxylic groups. The former is mostly used for enteric coating, whereas the latter is used for colon targeting. Although Eudragit S showed poor site specificity when its role in colonic drug targeting was investigated [62,63], Khan and colleagues demonstrated that a combination of Eudragit L and S can be successfully used to coat tablets for colon delivery of drugs; the thickness of the coating was found to be a determining factor [64]. Moreover,

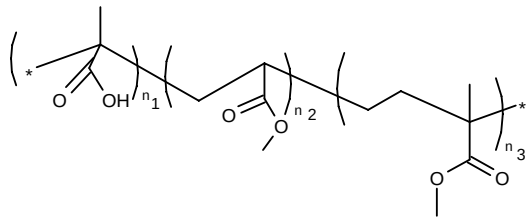


Figure 4. Chemical structure of Eudragit® FS30D.

the formulation can be adjusted to deliver drugs at any other desirable site of the GI tract on the basis of pH variability. Despite the relative unsteadiness of the site where disintegration starts, Eudragit S and L have been widely used, alone or in combination with other polymers to coat tablets [65,66] and microparticles [67-71].

One of the drugs that is commercially available in a colon delivery form is mesalazine™ (Pharmacia & Upjohn AB). It is unstable in the stomach and absorbed in the small intestine, and must be protected against conditions encountered in the upper GI tract. At present, mesalazine is commercially available as an oral dosage form, coated with Eudragit L 100 (Claversal, Mesasal® [Synthelabo] and Colitofalk® [Codali]), or Eudragit S (Asacol®, Giuliani SpA).

A more recently developed member of the Eudragit family is Eudragit FS30D (Figure 4). It is a tercopolymer of methacrylic acid, methyl acrylate and methylmethacrylate. Due to the free carboxylic acid functionality, the polymer dissolves at pH 7 [72,73].

Besides Eudragit, other pH-dependent polymer coatings have been used for the purpose of colonic targeting, such as hydroxypropylmethylcellulose acetate phtalate (commercially available as Aqoat®) [74,75] or cellulose actetate phtalate [76].

3.2.2 *Time-dependent formulations*

The pH-dependence phenomenon has been extended to include a time factor. Time-based positioning of a drug in the colon is designed in such a way to resist the acidic environment of the stomach and to undergo a silent phase of a predetermined time duration, after which release of the drug takes place. The silent phase in this case is the transit time from the mouth to the terminal ileum. One of the first formulations of this type was Pulsincap® (Scherer) [77,78,201]. It consists of a capsule, half of which is enteric coated and the other half is non-disintegrating. The enteric coat dissolves on entering the small intestine revealing a hydrogel plug, which is made up of a crosslinked copolymer of polyethylene oxide and polyurethane, stoppering the non-disintegrating part, which then swells. The swelling is pH-independent, and after a predetermined lag time, which is governed by the length of the hydrogel plug, it is swollen to an extent that it is ejected from the bottom half of the capsule, thereby releasing the drug.

Comparable to the Pulsincap system is the design of an ethylcellulose capsule that is composed of four parts: a drug container, low-substituted hydroxypropyl cellulose, and a capsule body and cap made up of ethylcellulose [79]. As water penetrates through micropores, which are present at the bottom of the capsule, the polymer swells and forces the ethylcellulose cap to disintegrate, thereby releasing the drug. The release time of the drug appears to be ruled by the thickness of the cap. A fair correlation was found between thickness of the cap and the *in vitro* release of fluorescein, as well as with the time of maximal plasma fluorescein concentration in beagle dogs.

The intestinal luminal pressure-controlled colon delivery capsules also uses ethylcellulose as the release-determining polymer [80,81]. Capsules coated with this insoluble polymer release encapsulated drugs, such as caffeine, in the colon due to intestinal pressure as a consequence of peristalsis. Gazzaniga and colleagues developed an oral dosage form consisting of a core coated with two polymeric layers [82,83]. The outer layer dissolves at pH > 5 and serves as enteric coating. The inner layer consists of hydroxypropylmethylcellulose (HPMC) and acts as a retarding agent to give a lag time in order for a drug to be released at a predetermined time. The thickness of the inner layer dictates how long it takes before the drug is released. Preliminary *in vivo* experiments in rats indicated that the tested systems start releasing in the colon between 5 and 10 h, thus confirming the expected release behaviour.

Pozzi and colleagues have developed a pulsed system known as the Time Clock® system [84]. The system is made up of a solid dosage form, coated with a hydrophobic surfactant layer to which a hydrosoluble polymer is added to improve adhesion to the core. The outer layer redisperses in the aqueous environment in a time proportional to the thickness of the film. The core is then available for dispersion. One of the advantages of this system is the fact that it can be manufactured using common technology with excipients known to the pharmaceutical industry. In a study with human volunteers, it was shown that the lag time was independent of gastric residence time, and hydrophobic film redispersion did not appear to be influenced by the presence of intestinal digestive enzymes, nor by the mechanical action of the stomach. Furthermore, pharmacokinetic data indicated that the absorption of salbutamol from the Time Clock system concurred with previous reported data, indicating that the absorption of the drug was not influenced by the *in vivo* behaviour of the this system [85].

Using the same principle as in Time Clock, Ueda and colleagues developed the Time-Controlled Explosion drug delivery system [86]. It has a four layered spherical structure, consisting of a core with the drug, a swelling agent and a water insoluble polymer membrane made up of ethylcellulose. It is characterised by rapid drug release with a programmed lag time. When water penetrates through the polymer membrane, the swelling agent expands, leading to destruction of the membrane with subsequent drug release. An *in vitro* study using metoprolol as a model drug showed that the release was not influenced by the pH but that the lag time was controlled by the thickness of the outer membrane layer. An alternative

approach using a core drug tablet enclosed in a hollow cylindrical polymeric matrix, and coated at the top with a copolymer of ethylene-vinyl acetate has been presented by Vandelli *et al.* [87]. Due to the water-impermeable coating, the drug can only be released after a lag time that is related to the wall thickness of the hollow matrix. Release of isosorbide-5-nitrate, used as a model drug, occurred as a consequence of diffusion through the swollen polymer matrix and polymer erosion, and was related to the polymer:drug ratio and to the exposed surface area. Although this system is inventive, it can encounter difficulties to manufacture. Indeed, incorrect positioning of the hole will produce a nonuniform width of the hollow matrix, decreasing the path length of water penetration and the time needed for polymer erosion. In addition, a nonhomogeneous application of the coating could modify the coating rigidity, leading to nondesirable infiltration of the aqueous medium.

A remark that applies to the majority of the above mentioned time-dependent systems is that only if modification in the design and appropriate manufacturing technology is developed and available, will large-scale manufacturing be possible. In that respect, the system described by Gupta and colleagues is readily scalable to industrial needs [88,89]. This system is simply made up of non-pareils onto which a drug is deposited. This core is subsequently coated with a nonsoluble inner layer made up of Eudragit RL and RS, and a pH-dependent outer layer made up of Eudragit FS30D, a polymer that dissolves around pH 6.8.

3.2.3 Bacterial degradable polymer coatings

The colon is inhabited by a large number and variety of bacteria, which inevitably secrete many enzymes. Of the many metabolic reactions known to be carried out by bacteria, the reduction of the azo bond has been extensively exploited to study colon-specific drug release.

The azo reductase activity is responsible for cleaving the azo bond and is nonspecific [40]. Polymers containing azo bonds have been used to coat drugs to protect them against degradation or absorption in the stomach and the small intestine. On reaching the large intestine, bacterial enzymes act on the azo polymer coat and subsequently release the drug for absorption or local action. The approach of coating a drug with a biodegradable material for colon targeting is advantageous as one can administer a large amount of drugs, and the nature of drug release is unique and selective because the bacterial enzymes, rather than the host's enzymes, are responsible for drug release.

Saffran and colleagues reported the release of insulin and vasopressin in the colon of rats and dogs from oral dosage forms coated with copolymers of styrene and hydroxyethylmethacrylate (HEMA), crosslinked with 4,4′-divinylazobenzene and N,N′-*bis*(*p*-styrene sulfonyl)-4,4′-diaminoazobenzene [90,91]. The coating was degraded in the colon by bacterial azoreductase, with subsequent release of the drug from the capsules. However, problems due to variability in absorption rates were encountered when administering the coated peptide drugs. The variations observed were probably due to intra- and inter-subject differences in microbial degradation of the coating, which may be caused by the fact that the polymer that is applied is insufficiently hydrophilic. An extreme large variation in blood glucose levels was also found by Cheng *et al.* after the administration of insulin with azo polymer-coated capsules to beagle dogs [92]. The difference was also explained in terms of difference in GI transit and microbial digestion in different dogs.

In a number of publications, Van den Mooter and colleagues reported on the relationship between hydrophobicity and biodegradable properties of copolymers of HEMA and methylmethacrylate, and tercolymers of HEMA, methylmethacrylate and methacrylic acid, which were synthesised in the presence of different azo aromatic bifunctional compounds [93-96]. The azo polymers were film forming and used to coat capsules. *In vitro* and *in vivo* release studies in rats confirmed the effectiveness of azo reductase in breaking down the azo bonds to release drugs such as theophylline and ibuprofen. However, only hydrophilic polymers were found to be degraded within an acceptable period of time, but too high a degree of hydrophilicity will lead to premature drug release before the colon is reached. The spacer length of the incorporated azo agent seemed to be of minor importance.

Studies with *Bacteroides fragilis* and *Eubacterium limosum* indicated that the reduction of azo polymers may be influenced by the chemical nature of the azo compound used as a crosslinking agent [97]. The research group of Van den Mooter introduced azo polymers with the incorporation of the azo group in the main chain, and included ethoxy groups to compensate for the presence of hydrophobic C-12 or C-16 chains [98-100]. *In vitro*, the polymers were degraded to a remaining azo concentration of < 60% on average after 48 h in rat caecal content, and the release of ibuprofen from coated capsules showed a significantly higher rate in the reductive medium than in a control medium. However, although these polymers contained a higher azo concentration, the degradation rate was much lower than methacrylic-based azo polymers, stressing the necessity to have hydrophilic, and swellable polymers, which allow better penetration of azo reduction mediators into the polymer network.

It has always been taken for granted that the azo function in azo polymers is reduced in the same way as in small azo aromatic molecules such as azo dyes, and the resulting degradation products were thought to be aromatic amines. However, Kimura and colleagues clearly showed that the azo bonds in segmented polyurethanes were reduced to hydrazo intermediates after incubation with a culture of intestinal flora, as no decrease in the molecular weight was observed. It was then postulated that drug release from pellets coated with these azo polymers was the result of a conformational change and a breakdown of the film structure [101,102]. In this respect, interesting observations were made by Schacht *et al.* with azo-containing polyamides [46]. The polymers were reduced in relation to their hydrophobicity to the hydrazo intermediates or to amines.

As the toxicity of azo polymers is still an issue of debate, some biodegradable materials of natural origin have been studied [103]. Poor film-forming properties or the water solubility of these natural products are often encountered and, therefore, may be mixed with other synthetic polymers in order to obtain a polymer film, or they have to be derivatised to decrease the aqueous solubility.

The ability of the microflora to degrade substances of natural origin was exploited by Lehmann and Dreher [104], who described a suspension of polygalactomannans in polymethacrylate solutions to form biodegradable coatings. The polygalactomannans can form a swellable layer around a drug core, thus delaying the release of the active substance in the small intestine, but they are digested in the colon followed by drug release.

It is known that inulin can resist degradation in the small bowel but in the colon it is fermented by *Bifidobacteria* and *Bacteroides* spp. Taking this into account, Vervoort and Kinget incorporated the oligosaccharide in Eudragit films and observed a significant increase in the permeability of isolated films of these materials after incubation in human faecal degradation medium, indicating that inulin was still fermentable after incorporation into the polymer films [105]. Similarly, in order to overcome manufacturing problems when using high methoxy pectin as a biodegradable excipient, film coatings consisting of pectin–chitosan, pectin–HPMC, pectin–chitosan–HPMC or ethylcellulose–pectin were investigated [106-109]. *In vitro* degradation studies indicated that the release was controlled by the amount of pectin.

Although galactomannan, inulin and pectin, and recently β-CD in Eudragit type films, were incorporated and somehow coated with a water-insoluble polymer, the oligo- and polysaccharides clearly retained their susceptibility to be degraded by bacterial glycosidase [110]. At first sight, this may look surprising as it may be expected that the physical structure of the polysaccharides is altered by the manufacturing process. A clear example of altered physical structure leading to different hydrolytical susceptibility was described for amylose. Indeed, amylase, when prepared under appropriate conditions, is not only able to produce films, it was also found that the microstructure of the film is resistant to the action of pancreatic α-amylase but is digested by the colonic flora [111]. This was later confirmed by Milojevic *et al.* [112]. However, the incorporation of ethylcellulose was necessary to control swelling in order to prevent premature drug release through simple diffusion. *In vitro* release of 5-ASA from pellets coated with a mixture of amylase–ethylcellulose (ratio 1:4) was complete after 4 h in a colonic fermenter, although it took > 24 h to release only 20% of the drug in conditions mimicking the stomach and the small intestine. A more recent study confirmed the relationship between the extent of digestion of the films and the amylose concentration [113].

Poor film-forming properties or high-water solubility of natural substances, such as guar gum or locust bean gum, was overcome by applying the polysaccharides as compression coatings onto solid dosage forms [114-116]. A colonic drug delivery system based on pectin, which has been 70% methoxylated on the acid groups was investigated by Ashford and colleagues [117]. *In vitro* experiments demonstrated that this high methoxy pectin, when applied as a compression coat, proved capable of protecting a core tablet during conditions mimicking mouth-to-colon transit and was susceptible to enzymatic attack. *In vivo* γ-scintigraphic studies confirmed the *in vitro* findings. As expected, pectins with a low degree of methoxylation were more susceptible to degradation, and it was assumed that the presence of calcium increased the susceptibility to enzymatic attack [118]. Some polymers such as chitosan or crosslinked dextran have also been investigated as materials to manufacture colon-specific capsules [119-121].

In some cases, however, it is possible to derivate natural polymers without compromising their biodegradable properties. By synthesising block copolymers of polyurethanes with ethylated or acetylated galactomannan segments, materials were obtained that were film forming and water insoluble. A significant change in the mechanical properties of these films was observed when they were incubated in a suspension of human faeces and pig caecal content, indicating that the derivatised polysaccharides were still fermentable. Interesting observations were also made with lauroyl dextran esters [122]. Esters based on dextran with a molecular weight of ~ 250 kD and a degree of substitution ranging from 0.11 to 0.3 were found to be film forming and stable between pH 1 and 7.4. Tablet cores with theophylline were coated using conventional equipment with a dispersion of 4% lauroyl dextran to theoretical polymer weights of 4 – 17 mg/cm^2 [123]. Theophylline dissolution was monitored for 4 h in a buffer of pH 5.5, after which the passage to the caecum was simulated by the addition of dextranase. Almost linear dissolution was observed during the first 4 h. The release rate was inversely proportional to the amount of ester applied on the coatings. After the addition of dextranase, the coatings were degraded, leading to complete release of the drug in < 2 h after the addition of the enzyme. These results are very promising, not only because the degradation is fast but also because the polymers are film forming, and as they are based on natural products that are derivatised by conventional methods using acceptable reactants, they are expected to have an acceptable toxicological profile.

3.2.4 Bacterial degradable matrix and hydrogel systems

An alternative approach to the manufacture of a colon-specific dosage form involves the compression of blends of active agent, a degradable polymer and additives to form a monolithic or multiparticulate solid dosage form; the drug is embedded in the matrix core of the degradable polymer. Bioerodible matrix systems of crosslinked chondroitin sulfate with different levels of crosslinking were developed by Rubinstein and colleagues for the delivery of indomethacin [124,125]. When the matrix was incubated in PBS and inoculated with rat caecal content, a significant difference in release of the drug was observed after 14 h, as compared with release in PBS alone. Furthermore, a linear relationship was found between

the degree of crosslinking of the polymer and the amount of drug released in rat caecal content. A more promising matrix system was developed by the same research group by mixing pectic salt with indomethacin, which was compressed into matrices [126]. The difference between the indomethacin levels measured in the rat caecal medium and in the control medium was significant at each time point of the experiment.

A drawback of every monolithic or single-unit controlled release system is that they may exhibit a delay at the ileocaecal junction, leading to drug loss prior to entry into the colon. This may be avoided when using a multiparticulate dosage form that passes freely through the ileocaecal junction. Such a multiparticulate system based on amidated pectin, a low methoxyl pectin in which some of the carboxylic groups are amidated, has been investigated [127]. Coating of the amidated pectin beads with chitosan significantly reduced the release of sulfamethoxazole and indomethacin in simulated gastric and intestinal juice as compared with non-coated beads. The cationic polymer chitosan forms a polyelectrolyte complex around the bead, thereby altering the properties of the amidated pectin beads. In simulated colonic medium, both drugs were released within ~ 2 h. Several other studies have also demonstrated that chitosan seems to be a promising material in the manufacture of colon-degradable multiparticulates. Significant increase in the release of small organic drugs, such as 5-ASA or diclofenac, or macromolecules, such as BSA, was observed after incubation of the chitosan-based matrices [119,120].

Recently, formulations containing the disaccharide lactulose were evaluated as colon-targeting systems [128]. Lactulose is not absorbed in the upper part of the GI tract but degraded, mainly to organic acids in the colon. A novel colon-targeted delivery system (CODES®, DDS Research) comprising of a lactulose–drug core, an inner acid soluble material (Eudragit E100) and an enteric coating layer (Eudragit L100) was effective in targeting 5-ASA to the colon of dogs.

An interesting approach was introduced by the research group of Kopecek. Several types of hydrogels based on N-substituted (meth)acrylamides, N-tert-butylacryl amide and acrylic acid were synthesised in the presence of different azo crosslinking agents (crosslinking polymerisation) [129,130]. Due to the incorporation of acidic monomers, the hydrogels showed a pH-dependent degree of swelling, which was highest in the colonic environment. *In vitro* and *in vivo* biodegradation studies in rat caecal contents and rats, respectively, showed that the degree of degradation was related to the equilibrium degree of swelling of the hydrogels, the degradability being inversely proportional to the crosslinking density. It also appeared that hydrogels with a larger azo crosslinking agent, but, with the same crosslinking density, were degraded faster. However, the enzymatic degradation of the azo crosslinks occurred over a period of a few days. Alternatively, azo polymeric hydrogels were prepared by the crosslinking of polymeric precursors, or by polymer–polymer reactions [131-133]. By manipulation of the stoechiometry of the monomers, a variety of copolymer compositions was achieved and, although biodegradation of the gels *in vivo* was consistent with the *in vitro* data, the degradation rate was faster *in vivo.* A comparative study was performed to differentiate between the degradation rate of the azo functionality present in methyl orange, a linear, soluble azo polymer, and a hydrogel that was synthesised from the linear azo polymer. The azo dye was completely reduced in 1 h, whereas the soluble polymer was reduced ≤ 70%. The degradation rates were 23.76 and 17.55 µmol/g·h for the azo dye and the polymer, respectively. The difference was attributed to reduced azo accessibility due to the presence of bulky polymer chains, and to inter- and intra-molecular aggregates formed by the hydrophobic side chains. As expected, the reduction rate decreased dramatically for the hydrogel; the degradation rate was 0.14 µmol/g·h, or 125-fold lower than for the soluble azo polymer. It was also found that hydrogels prepared by crosslinking polymerisation, but having the same polymer composition and crosslink structure, followed predominantly a bulk degradation-like process. Hydrogels prepared by the crosslinking of polymeric precursors, or by a polymer–polymer reaction, followed predominantly a surface erosion process when having a low degree of crosslinking, and a bulk degradation-like process when the degree of crosslinking increased.

Similar systems were reported by Kakoulides *et al.* with azo networks based on acrylic acid and crosslinked with 4,4′-divinylazobenzene [134,135]. These materials showed an optimal crosslinking density that allowed for particles to reach the colon. However, within the colonic environment, the azo network degrades and a structure capable of developing mucoadhesive interactions with the colonic mucosa is produced. This will effectively lead to increased residence time in the large intestine.

Instead of incorporating the azo aromatic functionality in the crosslinks, Shanta *et al.* prepared hydrogels by copolymerisation of 2-hydroxyethyl methacrylate with 4-methacryloyl-oxyazobenzene [136]. *In vitro* release of 5-fluorouracil from the hydrogels was faster in human faecal medium compared with the release in simulated gastric and intestinal fluids, and followed zero-order release for up to 4 h. During this period ~ 80% of the drug was released. Although the degradable azo bonds were not located in crosslinks, cleavage of them seems to cause loosening of the polymeric matrix, leading to the release of 5-fluorouracil. A serious drawback of this system is that microbial degradation of the hydrogel will result in the release of the toxic substance aniline.

Hydrogels based on natural products are considered to be more acceptable with respect to toxicity, and are, therefore, more preferable than azo polymeric materials. However, care must be taken when derivatisation is carried out, as chemical modifications of natural, biodegradable products may possibly lead to products that are less prone to degradation. Indeed, altering chemical structure or configuration may lead to sites that are no longer recognisable to the enzyme system responsible for biodegradation. It is also preferable that the enzymes can penetrate the polymer network, leading to bulk

degradation instead of surface degradation, and consequently a faster release of the entrapped drug. Hovgaard and Brondsted formed hydrogels of dextran using diisocyanate as the crosslinking agent [137]. The gels were still biodegradable but from a study by Simonsen *et al.* it was shown that, although the gels were fermented completely to short-chain fatty acids in a human colonic fermentation model, it took > 24 h before the gels started to degrade [138]. Clearly, such delivery systems are only capable to release a drug in the distal part of the colon, where the conditions for absorption are dramatically reduced. On the other hand, it was found that the release of hydrocortisone from dextran hydrogels was successfully triggered after the addition of dextranase; in < 2 h, 100% of the hydrophobic drug was released.

Rubinstein and Gliko-Kabir reported on the biodegradable properties of guar gum crosslinked with borax [139]. *In vitro* degradation of the modified guar gum showed that the rate of degradation by galactomannase from *Aspergillus niger* was the same as for noncrosslinked guar gum. The molecular weight decreased with more than a factor of 10 after only 45 min of incubation. Taking into consideration the time required for hydrogel degradation, this system seems to be able to release drugs in the proximal colon. In order to confirm these promising findings, the experiments should be performed with bacterial enzymes, or a comparison should be made between the activity of the fungal enzyme and the enzymes present in the human microflora. Besides its application in compression coating, guar gum has been mainly investigated in the form of matrix tablets. Its potential in colon drug delivery has been further demonstrated *in vitro* and *in vivo* [140-142]. Crosslinked derivatives of this natural polysaccharide have been synthesised in order to reduce its swelling properties while maintaining the biodegradable properties [143,144].

By introducing methacrylic groups on the backbone of inulin, biodegradable three-dimensional structures were prepared [145,146]. It was shown that the release of proteins, such as BSA or lysozyme, was influenced by factors such as the drug-loading procedure as well as the molecular weight and loading concentration of the proteins. However, the degree of substitution and the monomer feed composition seems to be crucial in controlling the extent and rate of release. Protein release was clearly influenced by the presence of inulinase [147]. The conservation of the biodegradable properties of the derivatised inulin prompted these investigators to combine azo bonds with hydrolytically cleavable inulin hydrogels [148]. Surprisingly, the azo function in the methacrylated inulin hydrogels was not degradable anymore [149]. This was attributed to increased hydrophobicity and increased network density.

Although it seems to be possible to design crosslinked systems with reduced aqueous solubility with unaltered biodegradable properties, the matrices and hydrogel systems have the disadvantage that only a limited amount of drug can be incorporated. Thus, when a large amount of drug is required at the target site, as in the case of 5-ASA, this may not be the best vehicle. A specific problem for hydrogels is the drug-loading procedure. A high drug yield can be obtained if the hydrogel is loaded during the polymerisation step but then residual monomers or initiator molecules may attain intolerable levels. If, on the other hand, drugs are loaded after hydrogel formation, the level of drug may be too low. New drug-loading procedures must be investigated and in this respect physical hydrogels (crosslinking due to electrostatic interaction or hydrogen bonding) using water as the solvent may be more promising than covalent networks.

4. Expert opinion

During the past 20 years, a considerable amount of work has been carried out in order to design several delivery systems for targeting drugs specifically to the large intestine. In spite of this, reliable systems that deliver drugs reproducibly to specific sites in the large intestine still do not exist. The large inter- and intra-subject variation in GI pH makes the approach of delivery systems based on pH-dependent polymers less suitable. Nevertheless, marketed products of 5-ASA rely on the use of Eudragit. As a matter of fact, the preferred industrial approach today is the use of pH-dependent polymer coatings because of the availability of the necessary equipment and the familiarity with the manufacturing process.

Despite the fairly constant small intestinal transit time, the possible 'hold-up' time at the ileocaecal valve is a serious drawback in the use of delivery systems that release drugs after a predetermined lag time. Undoubtedly, the preferred systems are those that rely on conditions that are only encountered in the colon, as these systems will give true site-specific delivery. In this respect, systems that can be degraded by colonic bacteria are very attractive and promising. However, this is only true if the degradation of the dosage form and subsequent drug release can be completed in < 3 h if absorption is desired, or if the release can be sufficiently prolonged when local action over an extended part of the colon is wanted.

A question that still remains to be fully addressed is the level of reproducibility (inter- and intra-subject variability) of bacterial degradation of dosage forms. Azo polymers have been demonstrated to be degradable in the human colonic environment. However, for the moment, no conclusive data are available to assign the same toxicological profile to azo polymeric delivery systems as to azo dyes, which are known to be potential carcinogenic/mutagenic agents. These polymers have no acceptable status today and can thus not be used in commercial products.

Although every new excipient has to undergo a whole series of safety assessment tests, delivery systems based on natural polymers, such as dextran, pectin, galactomannan, inulin and so on, are more favourable with respect to safety. However, the disadvantage of most naturally-occurring polymers is the inherent water solubility, which has to be decreased by chemical derivatisation but which can lead to a decreased biodegradability. With respect to large-scale pharmaceutical production, coated dosage forms (pellets, tablets) and matrix systems are preferable.

Local therapy of pathologies of the large intestine and reduced drug availability due to degradation by digestive or mucosal enzymes can benefit from colon delivery. Still, a substantial amount of research remains to be conducted in order to find out to what extent drugs, and more specifically peptides and proteins, can be absorbed, as it has often been claimed that colon targeting is one of the best alternatives for the oral administration of peptides and proteins. In this respect, the use of so-called homing devices to target specific sites has been considered. The use of lectins to attach to sugars at the mucosal surface and using sugars to attach to lectins at the mucosal surface have been proposed to target the intestine. However, the use of lectins as targeting agents has been questioned due to adverse biological effects. The interested reader is referred to an excellent and comprehensive review regarding the colon as a possible targeting site for the oral administration of peptides and proteins [150].

A major problem in comparing different delivery systems is the fact that reported drug-release studies are often performed under different conditions, which do not always reflect the *in vivo* situation (e.g., chemical *in vitro* degradation tests instead of bacterial enzymatic degradation *in vivo*). In this respect, the use of the simulated human intestinal microbial system, originally described by Molly *et al.*, may offer the possibility to establish standardised *in vitro* drug-release studies mimicking the colonic environment and will permit the results to be correlated with *in vivo* situations [151].

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• This paper describes an *in vitro* system that simulates the gastrointestinal tract.

Patent

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