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Advances in Colonic Drug Delivery

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Abstract

Targeting drugs and delivery systems to the colonic region of the gastrointestinal tract has received considerable interest in recent years. Scientific endeavour in this area has been driven by the need to better treat local disorders of the colon such as inflammatory bowel disease (ulcerative colitis and Crohn's disease), irritable bowel syndrome and carcinoma. The colon is also receiving significant attention as a portal for the entry of drugs into the systemic circulation. A variety of delivery strategies and systems have been proposed for colonic targeting. These generally rely on the exploitation of one or more of the following gastrointestinal features for their functionality: pH, transit time, pressure or microflora. Coated systems that utilise the pH differential in the gastrointestinal tract and prodrugs that rely on colonic bacteria for release have been commercialised. Both approaches have their own inherent limitations. Many systems in development have progressed no further than the bench, while others are expensive or complex to manufacture, or lack the desired site-specificity. The universal polysaccharide systems appear to be the most promising because of their practicality and exploitation of the most distinctive property of the colon, abundant microflora.

1. Rationale for Targeting Drugs to the Colon

The challenge of targeting drugs to the colonic region of the gastrointestinal tract is one that has been embraced by scientists over the past two decades.[1-6] Work in this area has been driven primarily by the need to improve the treatment of pathologies of the colon. These disease states range in severity from constipation and diarrhoea, to irritable bowel syndrome and inflammatory bowel disease (ulcerative colitis and Crohn's disease), through to infection and colon carcinoma. While some of these disorders are fairly innocuous, the majority are debilitating and life threatening. For example,

colorectal cancer is the third most common cause of cancer-related death in both men and women.[7] Current pharmacotherapy for colonic disorders is generally inefficient, requiring the need for surgical intervention in some patients. While the introduction of new therapeutic agents would no doubt improve therapy, there is much that can be done from the perspective of drug delivery. The targeting of drugs specifically to the colon using new and improved delivery strategies would provide significant clinical benefits. This would ensure direct treatment at the disease site, and a possible reduction in the administered dose and associated systemic adverse effects.

Additional interest in targeting the colon has stemmed from the potential of this region as a site for the entry of drugs into the systemic circulation. Compared with the stomach and small intestine, the colon is believed to contain lower levels of luminal and mucosal digestive enzymes.[8,9] Molecules that are degraded and/or poorly absorbed in the upper gut, such as peptides and proteins, could therefore be bioavailable via the colon.[10] Moreover, drug delivery to the colon could be beneficial when an intentional time delay in absorption is required for the treatment of diseases that are sensitive to circadian rhythms (chronotherapy), such as asthma, angina pectoris and arthritis.[11]

2. Colonic Anatomy and Physiology, and Implications for Drug Delivery

The gastrointestinal tract is essentially a hollow muscular tube, which functions to take in nutrients and eliminate waste by such physiological processes as secretion, motility, digestion, absorption and excretion. On the basis of function and morphology, the gastrointestinal tract is divided into the mouth, pharynx, oesophagus, stomach, small intestine and large intestine. The large intestine is approximately 1.5m in length and extends from the ileocaecal junction to the anus. It is divided into four sections: caecum, colon, rectum and anal canal. The colon is further subdivided into ascending, transverse, descending and sigmoid regions. The colon is involved in the fermentation of polysaccharides and proteins, absorption of water and electrolytes, and the formation, storage and elimination of faecal material.[12]

As a consequence of the functions of the colon, the colonic environment is generally viscous in nature. This could impact on the performance of drugs and delivery systems in this region of the gut. Rapid water absorption in the ascending colon results in the distal colonic contents being more viscous. It has been estimated that the human colon contains only 220g of wet contents.[13] Further studies suggest that the volume of the contents in the ascending colon is 50–150mL.[14,15] The human colon also contains 200–300mL of gas, in the form of nitrogen, carbon dioxide, methane and hydrogen, confined to the ascending and transverse colon.[16] In addition, the colon has a near neutral pH[17] and is home to a viable microflora.[18] These bacteria are involved in the fermentation of polysaccharides and proteins that have escaped digestion in the upper gut. The main consequences of bacterial fermentation are faecal bulking, increased transit of the colonic contents, increased nitrogen utilisation in the gut, and the formation of short chain fatty acids, which provide a useful energy supply.[19] Moreover, the resident bacteria can also metabolise drugs.[20,21] The protein-based drugs insulin and calcitonin are rapidly degraded in simulated colonic contents,[22] suggesting that while the proteolytic activity in the colon may be lower than the upper gut, it is not insignificant. The colon has a significantly smaller surface area ($1.3m^2$) than the small intestine ($200m^2$),[23] and displays a 'tighter' paracellular pathway[24,25] and elevated levels of the efflux transporter P-glycoprotein,[26] potentially limiting drug transport across the epithelium.

These perceived limitations have given rise to the assumption that the colon is a poor site for drug delivery and absorption. However, the longer residence time in the colon, often in excess of 24 hours[27,28] and the lower activity of the cytochrome P450 3A class of drug-metabolising enzymes present in the mucosa of the distal bowel[29] may overcome some of the potential constraints of this region of the gut. In fact, the colon is a favourable site for

the absorption of a number of drugs from a variety of different therapeutic classes.[30-32]

3. Strategies for Targeting Drugs to the Colon

As the colon represents the most distal segment of the gastrointestinal tract, targeting this region of the gut can be problematic. Although the rectal route can be used to gain access to the colon via the administration of suppositories and enemas, such formulations rarely succeed in spreading beyond the descending colon, with little or no drug reaching the proximal colon.[33,34] Also, the rectal route is not convenient or acceptable for most patients. The oral route is therefore the preferred mode of administration.

Orally administered drugs are generally administered in the form of immediate-release or modified-release formulations.[35] While the former are intended to release the drug in the stomach, so providing rapid absorption, modified-release systems are designed to extend or delay the release of the drug in the gastrointestinal tract. Modified-release systems are further subdivided into single-unit or multiple-unit dosage forms. Single-unit systems, such as tablets and capsules, usually move through the gut intact, whereas multiple-unit dosage forms, such as pellets, granules or mini-tablets, exist as discrete entities in the gastrointestinal tract. Traditionally, single-unit systems have proven to be more popular than multi-unit preparations because of their ease and cost of manufacture. However, the fundamental distinction in design between the two systems gives rise to their differing *in vivo* behaviour. The small size and divided nature of multiple-unit systems permit more uniform gastrointestinal transit – particularly gastric emptying and colonic transit – and drug release characteristics than with single-unit systems. The chances of dose dumping, and conversely incomplete drug release, are also less likely with multiple-unit dosage forms. Specific details of the gastrointestinal handling of the two types of systems can be found elsewhere.[36,37] On balance, the multiple-unit design provides the more reliable platform on which to base the development of oral colonic release drug delivery systems.

Colon-specific drug delivery via the oral route is a simple concept. The formulation must retard drug release in the stomach and small intestine but allow release in the colon. However, this is difficult to achieve in practice because the formulation will be exposed to a range of conditions and environments on passage down the gut, including pH, enzymes, electrolytes, transit time and pressure. Moreover, these parameters are subject to considerable inter- and intraindividual variation and are also affected by disease, which makes colonic delivery via the oral route a challenging proposition.[38-42]

The concept of drug targeting is based on the identification and exploitation of a characteristic that is unique to the target organ. In the context of colonic targeting, the exploitable gastrointestinal features have included pH, transit time, pressure and microflora. On the basis of these features, a range of approaches have been proposed and systems developed, but the majority of these have never progressed beyond the bench, with very few reaching the stage of clinical evaluation. This article therefore focuses on the systems that have been commercialised and the newer targeting systems that have been investigated in humans, as these have the greatest potential for future clinical use.

3.1 Means of Effecting Drug Release

3.1.1 Gastrointestinal pH

It is well known that gastrointestinal pH increases from the stomach to the small intestine (figure 1). This rise in pH has traditionally been utilised to deliver drugs to the small intestine by way of pH-sensitive enteric coatings.[43] These enteric polymer coatings are insensitive to the acidic conditions of the stomach but ionise and dissolve at the more neutral pH of 5–6 found in the upper small intestine. This concept has since been adapted and attempted for colonic delivery purposes, using polymers that have a threshold pH for dissolution higher than those used in conventional enteric coating.[44,45]

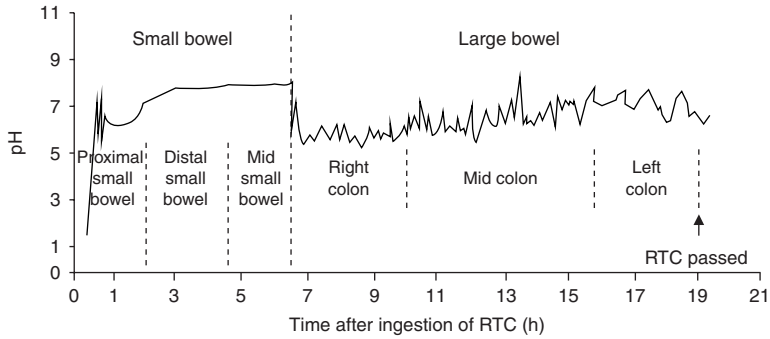

Fig. 1. Gastrointestinal pH profile from a healthy individual (reproduced from Evans et al.,[17] with permission from the BMJ Publishing Group). **RTC** = radiotelemetry capsule.

Acrylic polymers from the Eudragit® [1] range that dissolve above pH 6 have been commonly used for this purpose. This concept is based on the assumption that gastrointestinal pH continues to increase on passing from the small intestine to the colon.

A number of preparations that rely on this concept for drug release in the distal gut are commercially available. These are primarily used in the treatment of inflammatory bowel disease (table I). Inflammatory bowel disease is an umbrella term for two conditions: ulcerative colitis and Crohn's disease, both of unknown aetiology.[46] Ulcerative colitis is an inflammatory disease of the colonic mucosa, which in all patients affects the rectum and possibly more proximal regions of the colon. Crohn's disease is a transmural inflammatory disease that can affect the small intestine only (30%), the colon only (27%) or the ileocolonic region (40%). The anorectal region is only affected in 3% of patients.[47] The principle of treatment in inflammatory bowel disease is to induce remission of disease (acute treatment) and maintain remission (maintenance therapy), primarily through the use of anti-inflammatory agents. Targeted drug delivery should provide high intraluminal concentrations of drug at the affected sites, while minimising systemic availability and the potential for adverse effects.[48]

Dew et al.[49] were the first to utilise gastrointestinal pH as a trigger for drug release in the distal gut by applying the enteric polymer Eudragit®S to capsule dosage forms. Eudragit®S is a copolymer of methacrylic acid and methyl methacrylate that dissolves above pH 7. The transit and disintegration of the coated capsule dosage form was investigated in a group of convalescent patients using x-ray imaging. In most patients, capsule disintegration and drug release was observed in the distal gut. A subsequent study involving Eudragit®S-coated tablets was conducted in patients with ulcerative colitis.[50] The results from these studies provided the basis for the development and subsequent commercialisation of the Asacol® MR preparation, a Eudragit®S-coated tablet formulation containing the anti-inflammatory agent mesalazine (mesalamine or 5-aminosalicylic acid). A number of other modified-release mesalazine-containing products have since appeared in the marketplace (table I).[51] Mesren® MR, Ipocol® and Salofalk® rely on gastrointestinal pH to initiate drug release. However, these products cannot be considered interchangeable because of their different *in vitro* release characteristics.[51,52] The other coated mesalazine product in this class, Pentasa®, works independent of pH. Drug release occurs via diffusion through a water-insoluble ethylcellulose film coat and hence release occurs throughout the gastrointestinal tract.[53] More recently, a combination of pH and diffusion mechanisms has been used to control the release of the corticosteroid budesonide in the gastrointestinal tract (Entocort®).[54] This product comprises pellets of budesonide in the form of an ethylcellulose matrix.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

This is overcoated with an enteric polymer (Eudragit® L100-55, pH >5.5) to prevent drug release in the stomach. The budesonide is slowly released as it passes through the small intestine and colon, with 69% of the drug being delivered to the ileo-colonic region.[55] A further modified-release budesonide product is also commercially available (Budenofalk®). This consists of pellets of budesonide overcoated with a Eudragit®L/S polymers to target the distal gut.[45] In theory, this product should deposit more drug in the distal segments of the gastrointestinal tract compared with the Entocort® product. It is interesting to note that the early modified-release formulations in this therapeutic class were based on the principle of single units (e.g. Asacol® MR), while the more recent preparations utilise the multiple-unit design (e.g. Entocort®).

In contrast to the aforementioned assumptions about gastrointestinal pH, Evans et al.[17] reported in 1988 that the pH in the colon is lower than that in the distal small intestine (figure 1). The mean pH in the distal small intestine and caecum was 7.5 ± 0.4 and 6.4 ± 0.4, respectively. This drop in pH is attributed to the presence of short chain fatty acids produced as a result of bacterial fermentation of polysaccharides. The pH then progressively rises to a final value of 7.0 ± 0.7 in the distal colon. Moreover, the colonic pH in ulcerative colitis and Crohn's disease patients is considerably lower than in healthy individuals.[41] These findings have major ramifications for the *in vivo* efficacy of pH-dependent formulations.

Gamma scintigraphy has been used to assess the performance of Eudragit®S-coated formulations.[56] Gamma scintigraphy is a nuclear medicine technique that is used to visualise the *in vivo* behaviour of pharmaceutical dosage forms in a non-invasive manner.[57,58] The dosage form is radiolabelled with a radionuclide (e.g. technetium-99m, indium-111) and its activity is monitored using a gamma camera. This imaging modality is now the method of choice for investigating the fate (gastrointestinal transit and disintegration) of orally administered formulations under normal physiological conditions.[59,60] In a study involving seven healthy volunteers, the performance of Eudragit®S-coated tablets was assessed using gamma scintigraphy.[56] The position of the Eudragit®S-coated formulation in the gastrointestinal tract at the time of fragmentation was highly variable, extending from the ileum in the small intestine to the splenic flexure in the distal colon.

Table I. Oral preparations for the treatment of inflammatory bowel disease (ulcerative colitis [UC] and Crohn's disease [CD]) in the UK

Drug	Trade name	Delivery system	Site of release	Indication
Mesalazine (mesalamine)	Asacol® MR	Eudragit®S-coated tablet (release at pH >7)	Distal small intestine and colon	UC acute/maintenance CD ileocolitis maintenance
	Mesren® MR	Eudragit®S-coated tablet (release at pH >7)	Distal small intestine and colon	UC acute/maintenance
	Ipocol®	Eudragit®S-coated tablet (release at pH >7)	Distal small intestine and colon	UC acute/maintenance
	Salofalk®	Eudragit®L-coated tablet (release at pH >6)	Mid to distal small intestine and colon	UC acute/maintenance
	Pentasa®	Ethylcellulose-coated granules in tablet or sachet form (slow release of drug through membrane)	Stomach to colon	UC acute/maintenance
Budesonide	Entocort®	Eudragit® L100-55-coated ethylcellulose granules (slow release at pH >5.5)	Proximal small intestine to colon	CD acute
	Budenofalk®	Eudragit®L/S-coated granules (slow release at pH >6.4)	Distal small intestine to colon	CD acute
Sulfasalazine	Salazopyrin®	Sulfa moiety linked to mesalazine (mesalamine); azo bond cleaved by colonic bacteria	Colon	UC acute/maintenance CD acute
Olsalazine	Dipentum®	Two mesalazine molecules linked together; azo bond cleaved by colonic bacteria	Colon	UC acute/maintenance
Balsalazide	Colazide®	Inert carrier linked to mesalazine; azo bond cleaved by colonic bacteria	Colon	UC acute/maintenance

Equally variable was the time of tablet disintegration, ranging from 5 hours to >15 hours. Variability in product performance has also been noted with the commercial Asacol® MR and Ipocol® preparations,[61,62] with the site of disintegration ranging from the small intestine to the descending colon, although in some cases the preparation did not break up on passage through the gut. This explains the occasional appearance of intact Asacol® MR tablets in the stools of ulcerative colitis patients,[42,63] which can be attributed to colonic pH being significantly lower in patients with ulcerative colitis than in healthy volunteers.[41] The threshold pH for polymer dissolution is probably never reached in the gastrointestinal tract of these patients, thereby preventing drug release. This is possibly an oversimplification and other factors such as differences in gastrointestinal transit times could also play a role.[42,64] There is also recent evidence to suggest that there is considerable inter- and intra-batch variability in the dissolution characteristics of Asacol® MR tablets,[65,66] which could further add to the variability observed *in vivo*.

The variability in the performance of enteric-coated dosage forms has led to the conclusion that gastrointestinal pH is not a reliable mechanism for colonic specific drug release.[56] In an attempt to improve the colon specificity of this approach, a number of alternative strategies have been proposed, including the chemical modification of established enteric polymers,[67] utilisation of new formulations[68] or development of new polymers.[69] For example, starch capsules have been coated with a mixture of Eudragit®L and S polymers to provide a targeting technology (TARGIT™).[70] Eudragit®L dissolves at pH 6, a lower pH than Eudragit®S. The nature of the mixed film coating is such that it begins to dissolve on entering the small intestine, although the thickness of the coating prevents complete dissolution of the film and breakdown of the capsule until further down the gut. Scintigraphic evaluation of the system in healthy volunteers has revealed a colonic targeting success rate of 90%.[70]

A new copolymer of methacrylic acid, methyl methacrylate and methyl acrylate (Eudragit®FS), has been recently described.[69,71,72] This polymer has a slightly lower dissolution threshold pH of 6.8, but dissolves in a slower and more controlled manner than Eudragit®S. We have conducted a gamma scintigraphic study in eight fasted male volunteers to investigate the potential of this polymer coated onto tablet cores compared with the established Eudragit®S polymer.[73] The coated tablets were separately radiolabelled with a different radioisotope, indium-111 or technetium-99m, and simultaneously administered. As expected, variable release positions were observed with the Eudragit®S coated tablets, with no disintegration detected in three of the eight participants. In contrast, Eudragit®FS-coated tablets disintegrated in all subjects and in a more consistent manner, with disintegration positions focused on the ileocaecal junction and ascending colon. In a separate study involving Eudragit®FS-coated hydroxypropyl methylcellulose (HPMC) capsules, rupture was observed in the distal small bowel.[74] This polymer forms the basis of a new proprietary coating technology for drug delivery to the distal gut (EUDRACOL™).[75] The delivery system consists of drug-loaded pellets that are coated with a blend of two pH-independent water-insoluble polymers, Eudragit®RL and RS, and then overcoated with the pH-dependent polymer Eudragit®FS. After dissolution of the outer coat in the distal gut, the inner coat should provide slow diffusion and release of drug on passage through the colon. A study in healthy volunteers using caffeine as a model drug indicated that the combined pH independent and dependent system was superior to a simple Eudragit®FS-coated system in terms of extending release over the timescale of colonic transit.[75]

Although the use of enteric coatings is an established method of delivering drugs to the small intestine, their success in targeting drugs to the colon is mixed. *In vivo*, these systems behave in an erratic manner, ranging from premature release in the small intestine to little or no release throughout the gut. Nevertheless, simplicity is the key attraction of this approach, with a number of commercial pH-sensitive modified-release products on the market. How-

ever, given our current knowledge about gastrointestinal pH, one can only speculate whether some of these products would have reached the market had this information been available in the early 1980s.

3.1.2 Gastrointestinal Transit Times

The rate of transit of solid oral dosage forms through the gastrointestinal tract is largely unpredictable, in part because of the variability in gastric emptying. Depending on the size, shape and density of the dosage form and the feed status of the individual, residence time in the stomach can range from a few seconds to a number of hours.[76-78] In contrast, small intestinal transit time is reported to be more consistent at 3–4 hours, irrespective of formulation and dietary factors.[79] The total gastrointestinal transit time (mouth to rectum) averages out at 24 hours,[80] although there is considerable variation around this figure.[81,82] The reported relatively constant small intestinal transit time provides a feature that has been exploited for colonic delivery purposes.

Time-dependent formulations are designed to release their drug load after a predetermined lag time. A nominal lag time of 5 or 6 hours is usually incorporated into the system on the assumption that this is the time required for the dosage form to reach the colon. A number of systems have been developed on this principle, with one of the earliest being the Pulsincap™ device.[83] Somewhat complex in design, the device consists of an impermeable capsule sealed at one end with a hydrogel plug. On contact with gastrointestinal fluids, the plug hydrates and swells and, after a pre-set lag time, ejects from the capsule body, enabling drug release to occur. The size and composition of the plug control the lag time from the device. The performance of two different Pulsincap™ devices, preprogrammed with 5- and 6-hour time delays, was investigated in fasted human volunteers using gamma scintigraphy.[84] The position of the device at the time of release varied considerably; in some individuals the device remained in the stomach, while in others the capsule had advanced to the descending colon (table II). This demonstrates the problems associated with using large single-unit systems for modified-release applications. Subsequent studies also revealed that the emptying properties of the capsule were poor in the distal bowel, probably because of the lack of fluid in these regions.[37] This lack of fluid in the distal gut is also likely to hamper drug release from other time-release systems that operate on a similar principle.[85,86]

Table II. Site of release of the Pulsincap™ delivery systems (5-hour [5h] and 6-hour [6h] release configurations) in healthy volunteers[84]

Site of release	5h Pulsincap™ (n = 23)	6h Pulsincap™ (n = 16)
Stomach	2	
Small intestine	5	5
Ascending colon	11	5
Transverse colon	4	6
Descending colon	1	

To minimise the impact of gastric emptying on the eventual position of time-dependent systems at the time of release, the application of an enteric coat has been proposed.[87,88] This multi-barrier concept now forms the basis for most of these systems. The outer enteric coat dissolves on entering the small intestine to reveal an inner polymeric layer that swells, erodes or dissolves over a period of time sufficient to delay drug release from the core of the formulation.

The recently described colon-targeted delivery capsule combines both pH and time-based mechanisms for delivery.[89] A mixture of drug and organic acid is encapsulated in a conventional hard gelatin capsule. The capsule is then coated with a three-layered film consisting of an acid-soluble layer, a hydrophilic layer and an outer enteric layer. On ingestion, the outer enteric layer remains intact until gastric emptying of the capsule. The enteric film then dissolves followed by the intermediate hydrophilic layer. The inner acid-soluble layer (soluble below pH 5) remains intact in the small intestine but allows the ingress of fluid into the core of the capsule. When the pH inside the capsule decreases by the dissolution of the organic acid, the acid-soluble layer dissolves and the drug is released. The thickness of the acid-soluble layer, therefore, controls drug release from the system. The performance

of the dosage form was evaluated in a crossover study involving fed and fasted volunteers.[89] The site of disintegration of the coated capsule was more consistent in the fasted state (ranging between the ileocaecal junction and the descending colon). In the fed state, gastric emptying and colonic arrival of the capsule was significantly retarded. No capsule disintegration was noted in some volunteers and premature disintegration was observed in the small intestine in some of the others. This variability is partly the result of the large size of the capsule and provides further evidence for the inherent problems associated with using single-unit systems as a platform for modified-release dosage forms. Similar multi-layer coatings have also been applied to tablet dosage forms for colonic delivery purposes.[90,91] Zhang et al.[91] proposed a variation on this concept by incorporating mesalazine into a triple-layer coated tablet. Mesalazine serves two functions in this system: apart from being the pharmacological agent, mesalazine also acts as the acid-regulating agent in the system because it is acidic in nature.

The fundamental premise for the functionality of timed-release system is that gastrointestinal transit is a consistent parameter. However, not withstanding the influence of disease, transit is prone to considerable intra- and inter-individual variability in healthy individuals.[92] Moreover, gastrointestinal transit is subject to diurnal variations, with transit being appreciably slower in the evening compared with the morning.[93,94] The basic fact that such systems are unable to sense and adapt to an individual's transit time and merely release their drug load after a pre-set lag time, irrespective of whether the formulation is in the colon or not, clearly limits their practical utility.

3.1.3 Gastrointestinal Pressure

The use of gastrointestinal pressure has been proposed as a method of targeting release in the distal gut.[95] This pressure, which is generated via muscular contractions of the intestinal wall for grinding and propulsion of luminal contents, varies in intensity and duration throughout the gastrointestinal tract. The colon is believed to exert a higher effective luminal pressure via the action of haustral contractions coupled with a viscous environment. Takaya and co-workers[95] have developed a novel capsule that is sensitive to this raised pressure. This pressure-controlled colon delivery capsule (PCDC) is composed of drug, dispersed in a suppository base, coated with the water-insoluble polymer ethylcellulose. Once swallowed, the temperature of the body causes the suppository base to melt and increase in volume, and the system resembles a liquid filled ethylcellulose balloon. The system is able to withstand the luminal pressures of the stomach and small intestine resulting from muscular contraction of the gut wall, since there is sufficient fluid present in the lumen to dissipate this pressure. In the distal gut, reabsorption of water increases the viscosity of luminal contents. As such, the capsule will be directly affected when subjected to the pressure of the intense haustral contractions of the colon and hence will rupture. The PCDC can be manufactured using a number of different methods, by coating the inner surface of a gelatin capsule with an organic ethylcellulose solution,[95] by coating capsule-shaped pieces of suppository base at low temperature[96] or by a dipping method.[97]

These systems have been assessed for their ability to deliver model drugs *in vivo* in beagle dogs[97] and humans.[96] Most of these investigations have involved conventional pharmacokinetic evaluation, with the authors correlating parameters such as the time for first appearance of drug in the plasma with literature values for colon arrival times in dogs and in humans. As gastric and small intestinal transit times are known to be variable, these studies did not conclusively show that the capsules had disintegrated in the colon. More recently, the same group used the biomagnetic measurement system, a non-radioactive alternative to gamma scintigraphy, to determine the time and site of capsule disintegration.[98] In a small study, caffeine-containing PCDCs were administered to two volunteers. Caffeine was first noted in the saliva at 6 and 5 hours, respectively. These times coincide with capsule presence in the colon, implying that the PCDCs disintegrated in the colon.

The use of gastrointestinal pressure provides an innovative approach to targeting drugs to the gut. However, there are limited data on the luminal pressures of different regions of the gastrointestinal tract, and whether these are subject to the inter- and intra-individual variation as is pH and intestinal transit time. Therefore, it remains to be seen whether the PCDC represents a viable means of colon-specific delivery.

3.1.4 Gastrointestinal Bacteria

Much of the recent interest in colonic delivery has focused on the use of gastrointestinal microflora as a mechanism for drug release.[99-101] Although bacteria are distributed throughout the gastrointestinal tract, the vast majority are present in the distal gut (figure 2). The bacterial count has been estimated to be 10^{11} per gram in the colon, compared with 10^4 per gram in the proximal small intestine.[18,102,103] Moreover, over 400 different species are present.[18] Colonic bacteria are predominantly anaerobic in nature and secrete enzymes that are capable of metabolising endogenous and exogenous substrates, such as carbohydrates and proteins, which escape digestion in the upper gastrointestinal tract.[103] Such materials that are susceptible to bacterial fermentation in the colon, while remaining recalcitrant to the conditions in the stomach and small intestine, could therefore be utilised as carriers for drug delivery to the colon.

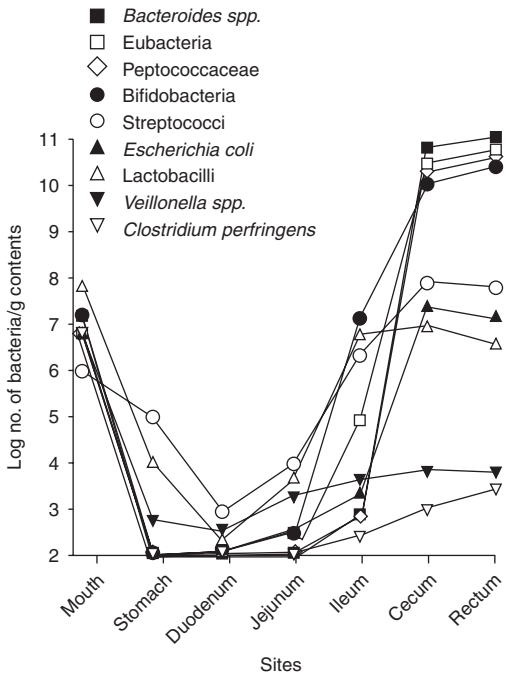

Fig. 2. Distribution of selected bacteria in the gastrointestinal tract (reproduced from Abu Shamat,[102] with permission from Elsevier).

The first bacteria-sensitive system developed for colonic delivery was sulfasalazine, a prodrug consisting of the active ingredient mesalazine linked by an azo bond to a carrier molecule, sulfapyridine (table I).[104-106] Mesalazine is rapidly absorbed from the small intestine,[107] but when administered as a prodrug is not absorbed until it reaches the colon where the azo bond is cleaved by colonic bacteria to liberate the active ingredient at the site of inflammation. Non-enzymatic mechanisms for cleavage and drug release from these systems have also been proposed.[108] Although the majority of patients with mild to moderate ulcerative colitis achieve complete remission when treated with sulfasalazine, the total incidence of adverse effects or allergic reactions is high (occurring in up to 50% of recipients).[109] These adverse effects are related to the sulfapyridine component.[110] To overcome this, mesalazine has been azo bonded to another mesalazine molecule (olsalazine)[111] or an inert carrier (balsalazide)[112] to provide alternative prodrugs for use in inflammatory bowel disease (table I). The concept of prodrug delivery has also been investigated using non-azo-bonded molecules for colon delivery.[113]

In contrast to the above, a universal system would be more useful in terms of transporting any drug molecule to the colon, and as a further advantage would not be subject to the same stringent regulation as prodrugs (new chemical entities). Saffran et al.[10] expanded on the azo bond principle by fabricating synthetic polymers cross-linked with azo-aromatic groups suitable for use as a coating. Coated insulin and vasopressin loaded pellets were delivered to the rat colon.[10] However, in humans there is evidence to suggest that azo-reductase enzyme activity is reduced in active Crohn's disease.[114] More significantly, the fact that azo-aro-

matic compounds are potential carcinogens casts a shadow over the safety and toxicity of synthetic azo-polymers.[115] This has prevented the investigation of azo-polymer-based systems in humans and clearly limits the usefulness of this approach.

The use of natural polysaccharides offers an alternative substrate for the bacterial enzymes present in the colon. Many of these polymers are already used as pharmaceutical excipients in formulations or are constituents of the human diet. Issues with regard to safety, toxicity and availability are therefore much simplified. Although specifically degraded in the colon, many of these polymers are hydrophilic in nature and swell under exposure to upper gastrointestinal conditions, which would result in premature drug release. To overcome this problem the natural polysaccharides are either chemically modified or mixed with hydrophobic, water insoluble polymers. This has the effect of limiting the swelling in the upper gastrointestinal tract, but still permitting a partial solubilisation of the matrix or coating in the colon due to bacterial degradation, resulting in drug release.

Ashford et al.[116] investigated the ability of a direct compression coat of pectin to achieve colon delivery. Tablets were manufactured by directly compressing a high methoxy grade of pectin around a core tablet. A minimum of 700mg pectin was needed to prevent release of a model drug, fluorescein, in simulated mouth to colon conditions. When tested in humans, the coated tablets all disintegrated in the colon, in regions varying from the caecum to the splenic flexure after a time of between 5.5 and 8.8 hours. Although the system was successful *in vivo*, the method of manufacture is not conducive for scale-up, and patient acceptability would be poor because of the cumbersome nature of the tablets; a proportionally large amount of pectin (700mg) is needed to control release from a core tablet weighing only 120mg.

A more practical system was produced by the same group, consisting of a film composed of a mixture of pectin, chitosan and hydroxypropylmethylcellulose coated onto placebo tablets.[117,118] The film coating process provides a more expeditious method of manufacture than compression coating. The chitosan component of this coat offers an additional substrate for the colonic bacteria. An overcoat of enteric polymer was also applied to the tablets prior to administration. The tablets were radiolabelled with technetium-99m and administered to healthy volunteers. By using scintigraphy the tablets were observed to pass through the stomach and small intestine intact, and then break in the colon.

Pectin in the form of its water-insoluble calcium salt, calcium pectinate, has also been evaluated as a colonic carrier. This material has been investigated in the form of a matrix formulation[119] and compression coat.[120] A scintigraphic study was subsequently conducted to investigate the performance of two different calcium pectinate-based placebo matrix tablets.[121] The first formulation contained calcium pectinate and pectin, while the second preparation consisted of calcium pectinate and guar gum. Contrary to the authors' previous work *in vitro*, an outer enteric coat was deemed necessary for application to both formulations prior to administration. Both formulations started to break in the small intestine. Complete disintegration occurred in the colon, with the mixed calcium pectinate and pectin formulation breaking at a faster rate.

Pectin has also been investigated in combination with an additional biodegradable polysaccharide, galactomannan, in the form of a coating on tablets and soft gelatin capsules.[122] The two polysaccharides form a complex in aqueous solution above pH 7. The resultant film is insoluble in gastric and small intestinal fluids, but remains susceptible to bacterial degradation. On assessing their performance *in vivo* it was found that in the majority of cases the site of initial disintegration of the formulation was the colon, irrespective of whether the tablet or soft gelatin capsule was administered.

The potential of guar gum has been investigated in the form of a matrix and compression coat by a number of groups.[123-131] Owing to its high viscosity, this polymer should be usable as a matrix material to carry certain drugs to the large intestine without appreciable release in the stomach or small intestine. Once in the large intestine, the guar gum matrix

should be degraded by specific enzymes produced by the microflora to initiate drug release. Kenyon and co-workers[123] investigated the *in vivo* performance of three guar gum-based matrix formulations containing dexamethasone using a combined scintigraphic and pharmacokinetic approach. The results of the study provided a rank order for the three formulations on the basis of their disintegration positions and drug release characteristics in the gut. More than 70% of the drug load was delivered to the colon, but an appreciable quantity of drug was released in the small intestine (20–30%). This is a common limitation associated with matrix formulations. The relatively open structure of matrix formulations renders them liable to premature drug release, particularly when the drug is freely soluble. A coating, on the other hand, should provide a more resistant barrier to diffusion and minimise early drug release in the gut. To this end, Krishnaiah et al.[126] investigated the utility of guar gum in the form of a compression coat on placebo tablets. A gamma scintigraphic investigation indicated that the tablets disintegrated in the vicinity of the colon. Guar gum-coated drug-loaded tablets have subsequently been assessed by the same group in a number of pharmacokinetic studies.[127-130] One such study involved the pharmacokinetic evaluation of guar gum-based systems for colonic delivery of ornidazole, a drug used in the treatment of amoebiasis of the colon.[128] A guar gum-based compression coat (400mg) applied to tablet cores (300mg) containing 250mg of ornidazole was found to significantly delay the onset of drug release and absorption, and suppress the peak plasma concentration compared with the uncoated core. However, the area under the drug plasma concentration-time curve was 2-fold higher for the colonic-targeted formulation than the uncoated preparation, suggesting that the drug is preferentially absorbed, albeit at a slower rate, from the colon.

A combination of locust bean gum and chitosan has been evaluated *in vitro* and *in vivo* as a vehicle for colonic delivery.[132] These polysaccharides were mixed in different ratios and applied to tablet cores. A direct correlation was found between the quantity of locust bean gum in the coat and the rate of degradation. A coat composition of four parts locust bean gum and one part chitosan was more extensively fermented in the presence of rat caecal contents. This also translated into a high bioavailability of mesalazine from this formulation in humans.

A new single-unit technology named CODES™ requires the presence of a polysaccharide in its core to activate drug release.[133-136] The system consists of a core tablet containing the active agent and a biodegradable polysaccharide such as lactulose. The tablet is coated with three separate film layers: (i) an inner acid-soluble layer; (ii) an intermediate hydrophilic polymer; and (iii) an outer enteric coat. On passage down the gut the outer enteric layer is insoluble in the stomach but dissolves in the small intestine. This is followed by the dissolution of the hydrophilic polymer. The acid-soluble layer (pH <5) remains intact, although it is slightly permeable to water. On arrival in the colon, the lactulose inside the core will dissolve and diffuse through the coat. The local bacteria will degrade the polysaccharide into organic acid, which will lower the local pH sufficiently to initiate dissolution of the coating and drug release. Scintigraphic studies in healthy volunteers have validated the design concept of this technology, with disintegration occurring in the colon.[136] The thickness of the acid-soluble layer and the concentration of lactulose in the core are the main factors that affect its performance. This system therefore works on the principle of pH, time and bacteria for release. Conceptually, this technology is very similar to the colon-targeted delivery capsule described earlier (section 3.1.2).[89]

The polysaccharide amylose has been exploited as a colonic carrier.[137] Amylose is one of the two major components of starch, the other being amylopectin, accounting for 15–25% of the total weight.[138] Although it has long been thought that starch is broken down by pancreatic enzymes in the small intestine, in 1982 a fraction which resisted digestion *in vitro* was identified.[139] Subsequently, a number of forms of starch were shown to survive passage through the human small intestine.[140] These are classified as forms of resistant

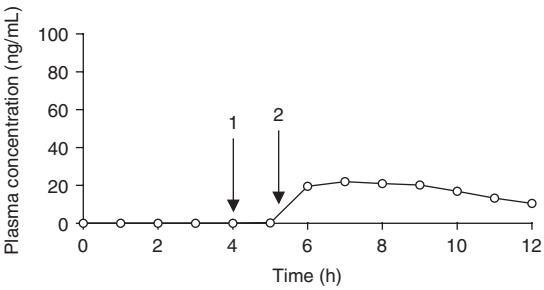

Fig. 3. Correlation between the colonic arrival of amylose-coated pellets and the appearance of ranitidine in the blood in one of ten healthy volunteers, which is representative of the group.[153] **1** First entry of pellets into the colon. **2** Complete entry of pellets into the colon.

starch.[140,141] Resistant starch can be further subdivided into four types: (i) physically inaccessible starch; (ii) resistant starch granules; (iii) retrograded starch; and (iv) chemically modified starch.[142] *In vivo,* all four types of resistant starch totally resist digestion in the small intestine and become available for fermentation in the large intestine. The glassy amorphous form of amylose, a type of retrograded starch, is resistant to pancreatic enzymes and can be formed into films that are biodegradable by colonic bacteria.[143-145] Amylose is fermented by a broad range of colonic bacteria,[146,147] with more than 50% of the bacterial population showing a tendency to digest amylose.[148] Amylose films swell in aqueous media and, therefore, require the addition of a water-insoluble polymer, ethylcellulose, to act as a structuring agent.[143-145] These mixed coatings can be applied directly to solid dosage forms by conventional coating methods with equipment that is widely available and so is amenable to industrial scale up. The film coating remains intact in the stomach and small intestine. On arrival in the colon, the amylose component of the film is digested, producing pores through which the drug is released.[143,149,150] The ratio of amylose to ethylcellulose in the film and the thickness of the coat control the drug release rate. A number of phase I studies involving scintigraphic and pharmacokinetic evaluation have provided confirmatory evidence for the targeting performance of the amylose delivery system.[82,151-153] A representative example is shown in figure 3.

Table III. Summary of the different oral colonic drug delivery approaches

Approach	Concept	Comments
pH-based systems	Application of polymers with pH-dependent solubility properties that dissolve in the elevated pH conditions of the distal gut	pH is higher in the distal small intestine than in the colon, hence potential for premature drug release. Colonic pH is significantly lower in patients with inflammatory bowel disease, hence potential for incomplete drug release. Unreliable mechanism of release; however, products for the treatment of inflammatory bowel disease are commercially available
Time-based systems	Drug release is initiated after a predetermined lag time, which is assumed to be equivalent to the colonic arrival time	The variability in gastric emptying and small intestinal transit times in healthy volunteers and patients with gastrointestinal disease limits the usefulness of this approach. Transit is also influenced by circadian rhythms
Pressure-based systems	Rupture of dosage forms in response to the raised luminal pressure in the distal gut	Limited data on luminal pressures in different regions of the human gastrointestinal tract. Influence of gastrointestinal disease on product performance yet to be established. Potential issues with the ease and cost of manufacture of the systems
Microflora-based systems	The distal gut is populated with substantial numbers of bacteria that secrete a diverse array of enzymes. Two concepts have been proposed: *Prodrugs:* enzymatic cleavage of the bond between the drug and the carrier moiety *Universal systems:* fermentation of starch and non-starch polysaccharides in the form of a film coating or matrix	The prodrug approach provides site specificity. Marketed products for the treatment of inflammatory bowel disease are commercially available. However, a prodrug is considered a new chemical entity from a regulatory perspective. The universal approach extends the utility of the prodrug concept by 'carrying' any drug to the colon. Some polysaccharides take considerable time to ferment, and there are potential issues with the impact of diet and disease on the microflora population

Significantly, the amylose system (COLAL™) has also been assessed in phase II clinical trials.[154] As far as the author is aware this is the only universal polysaccharide-based formulation to have progressed beyond the phase I stage. The corticosteroid prednisolone metasulfobenzoate sodium, a more polar and less well absorbed analogue of prednisolone,[155] was incorporated into the COLAL™ system to provide a new oral treatment for ulcerative colitis (COLAL-PRED™). Patients were treated at six UK centres in randomised, double-blind parallel groups for 4 weeks, followed by dose tapering. One group received the equivalent of prednisolone 60mg, the other the equivalent of prednisolone 40mg. The study results revealed dose-dependent improvement in the disease activity index and physician's global assessment (measures of disease severity) in mild to moderate ulcerative colitis patients, with clinical remission at 60mg daily. These beneficial effects were not associated with typical corticosteroid adverse effects or depression of adrenal function, because systemic exposure to prednisolone was very low. In addition to achieving remission in ulcerative colitis, this treatment offers the potential for maintenance therapy. Phase III clinical evaluation of COLAL-PRED™ is scheduled to begin in the near future.

4. Conclusions

The colonic region of the gastrointestinal tract is an attractive organ for targeting purposes. Targeting the colon via the oral route offers substantial therapeutic rewards, both in terms of local therapy and systemic treatment. Delivery systems that rely on pH, transit time, pressure or microflora to initiate release in the colon have been proposed (table III). While some of these systems have reached the market, most lack the basic attribute of site-specificity. Many of the systems currently in development are either complex or expensive to manufacture, thereby limiting their future commercial potential. Oral formulations based on polysaccharides that are susceptible to digestion in the presence of colonic bacteria show particular promise, although no such preparation is commercially available. In summary, while some advances have been made in this area, much remains to be done to fully realise the clinical potential of colonic drug delivery.

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