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Colonic Drug Delivery

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INTRODUCTION

Within recent years, there has been considerable research activity within the field of colonic drug delivery. This interest has been stimulated by a number of factors: i) The development of new therapeutic agents for the treatment of colonic diseases has required colon-specific delivery systems to maximize the effectiveness of these drugs; ii) The desire to produce oral delivery systems for therapeutic peptides and proteins; iii) The introduction of once-a-day sustained release formulations has required a better understanding of the transit of dosage forms through the colon, and of the colonic absorption of the drugs contained within them.

This article provides a review of colon function, physiology, and drug absorption characteristics relevant to pharmaceutical scientists and of the technologies available for colon-specific drug delivery.

STRUCTURE AND FUNCTION OF THE COLON

The colon forms the lower part of the gastrointestinal tract and extends from the ileocecal junction to the anus (Fig. 1). A summary of some of the anatomical and physiological features of the small intestine and colon are provided in Table 1 (1,2).

The function of the colon differs significantly from the small intestine. The primary role of the small intestine is to digest foods and absorb nutrients. Efficient absorption is assisted by the very high surface area, a result of the folds, villi, and microvilli present there. In contrast to the small intestine, the surface area of the colon is low, although it is increased 10–15 times compared to that of a cylinder of the same dimensions by the presence of folds and microvilli on the epithelial cells (2). The major function of the colon is the consolidation of the intestinal contents into feces by the absorption of water and electrolytes and to store the feces until excretion. The absorptive capacity is very high; each day up to 2000 ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed. Fluid and salt absorption is assisted by the segmenting movements which circulate the chyme across the colonic mucosa. In the healthy human colon, sodium and chloride ions are usually absorbed and potassium and bicarbonate ions are usually secreted (3). The progressive absorption of fluid as material passes along the colon results in a gradually solidifying mass. Whereas the contents of the cecum and ascending colon are fluid and semisolid, in the transverse colon solidification commences and in the descending colon solid feces have formed.

The amount of material in the human colon is surprisingly small. On average, it has been estimated that the

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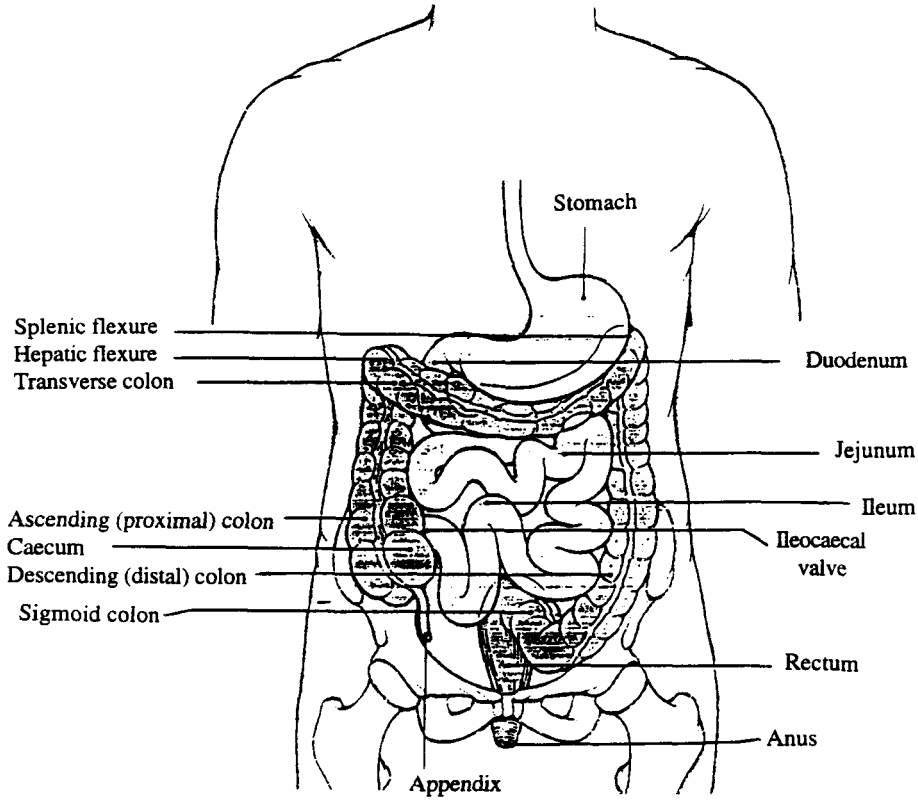


Figure 1. Anatomy of the human gastrointestinal tract (picture taken from *Human Anatomy and Physiology*, D. van Wynsberghe, C. R. Noback, and R. Carola, 3rd ed., McGraw-Hill, 1995. With permission. Additional test added).

colon contains only about 220 g of wet material, equivalent to just 35 g of dry matter (4). The majority of this dry matter is bacteria.

Activity in the colon can be divided into segmenting and propulsive movements. Segmenting movements, caused by circular muscle and causing the appearance of the sac-like haustra (Fig. 1), predominate and result in mixing of the lumenal contents. Significant propulsive activity, associated with defecation and effected by longitudinal muscles, is less common and occurs an average of three or four times daily (2). Retrograde movements are common in the proximal portions of the colon and serve to increase the retention of material in the ascending colon and cecum. In the middle section of the colon, segmenting movements result in a slow progression of feces towards the rectum, whereas propulsive activity predominates in the distal portions of the colon.

Colonic Microflora

The slow movement of material through the colon allows a large microbial population to thrive there. Over 400 species of bacteria are found, predominantly anaerobes, and a small number of fungi. The rate of microbial growth is greatest in the proximal areas of the colon, since this is where the concentration of energy sources is highest. The principal source of nutrition for the colonic microorganisms are carbohydrates arriving in intestinal chyme. These include starch, non-starch polysaccharides (dietary fiber) such as cellulose, hemicellulose, guar, pectins and ispaghula, and sugars and oligosaccharides such as lactose, sorbitol, and xylitol. The carbohydrates are degraded by the action of polysaccharidase and glycosidase enzymes and the ultimate products of fermentation are short chain fatty acids, carbon dioxide, hydrogen, methane, and hydrogen sulphide. There is also significant protein digestion within the colon, although the protease activity of feces is 20–60 times less than in ileal effluent. It is estimated that approximately 12 g of proteinaceous material enters the colon each day from the small intestine, partly dietary in origin, but also including pancreatic and small intestinal enzymes. From within the colon there are sloughed colonic epithelial cells and proteins and peptides released

Table 1

Summary of Anatomical and Physiological Features of the Small Intestine and Colon

Region of the Gastroinestinal Tract		Characteristic
		Length (cm)
Entire gastrointestinal tract		500–700
Small intestine	Duodenum	20–30
	Jejunum	150–250
	Ileum	200–350
Large intestine	Cecum	6–7
	Ascending colon	20
	Transverse colon	45
	Descending colon	30
	Sigmoid colon	40
	Rectum	12
	Anal canal	3
		Internal diameter (cm)
Small intestine		3–4
Large intestine		6
		pH
Stomach	Fasted	1.5–3
	Fed	2–5
Small intestine	Duodenum (fasted state)	≈ 6.1
	Duodenum (fed state)	≈ 5.4
	Ileum	≈ 7–8
Large intestine[a]	Cecum and colon	5.5–7
	Rectum	≈ 7

[a]Also see Section 5.

from bacteria. Products from metabolism of proteinaceous materials include organic acids, hydrogen, carbon dioxide, methane, ammonia, amines, phenols, and indoles. In the proximal regions of the colon, carbohydrate fermentation predominates and results in a relatively low pH. The low pH tends to inhibit the action of proteolytic enzymes. In the distal regions, there is little carbohydrate fermentation, resulting in a higher pH, but increased levels of protein digestion. The bacteria within the colon are predominantly anaerobic and there is a low redox potential (reducing environment) (5).

It is evident that the colonic bacterial population will have a significant impact, both positive and negative, on colonic drug delivery. The ability to selectively metabolize certain carbohydrates and the anaerobic environment has been exploited in the development of delivery systems. On the other hand, significant proteolytic activity has implications for the delivery of peptide and protein drugs. These issues will be discussed later in this review.

pH in the Colon

Radiotelemetry has been used to measure the gastrointestinal pH in healthy human subjects. The highest pH levels (7.5 ± 0.5) were found in the terminal ileum. On entry into the colon, the pH dropped to 6.4 ± 0.6. The pH in the mid-colon was measured at 6.6 ± 0.8 and in the left colon, 7.0 ± 0.7 (6).

As mentioned in the previous section, the fall in pH on entry into the colon is due to the presence of short chain fatty acids arising from the bacterial fermentation of polysaccharides. Consequently, polysaccharide drugs and diet can affect the colonic pH. For example, lactulose, a semisynthetic disaccharide used as a laxative, is fermented by the colonic bacteria to produce large amounts of lactic acid. This results in further acidifica-

tion of the colon contents with the pH dropping to about 5.0 (7). The in vitro fermentation of two other pharmaceutical polysaccharides, ispaghula and guar gum, in the presence of fecal bacteria also resulted in a fall in pH (8). A diet high in dietary fiber will have the same effect, producing a high colonic concentration of unmetabolized polysaccharides.

Colonic pH has been shown to be reduced in disease. In a group of 7 patients with untreated ulcerative colitis the mean pH in the proximal colon was 4.7 ± 0.7, whereas in a group of 5 patients receiving treatment it was 5.5 ± 0.4 (9).

TRANSIT OF MATERIALS INTO AND THROUGH THE COLON

Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. In one study, the emptying of nondisintegrating single unit dosage forms varied from 15 min to more than 3 hr (10). The presence of food generally increases gastric residence and, in some cases, with regular feeding, dosage forms have been shown to reside in the stomach for periods in excess of 12 hr (11,12).

Small intestinal transit is surprisingly constant at 3–4 hr and appears to be independent of the type of dosage form and whether the subject is in the fasted or fed state (13). Therefore, a dosage form could take from as little as 4 hr to longer than 12 hr to arrive at the colon following oral administration.

Compared to other regions of the gastrointestinal tract, movement of materials through the colon is slow. The total time for transit tends to be highly variable and influenced by a number of factors such as diet, in particular dietary fiber content, mobility, stress, disease, and drugs (14).

Colonic Transit Under Normal Conditions

Using a radiopaque marker technique, the transit times in a group of 73 healthy adults has been estimated. The mean mouth-to-anus transit time was 53.3 hr. The mean total colonic transit time was 35 hr with mean segmental transit times of 11.3 hr, 11.4 hr, and 12.4 hr for the right (ascending + portion of transverse), left (descending + portion of transverse), and rectosigmoid colon, respectively. Total colon transit was significantly shorter in the male subjects than in females (15). However, other studies have shown no difference between male and female transit rates (16,17).

The technique of gamma scintigraphy has been widely used to measure the movement of pharmaceutical dosage forms through the colon. In a scintigraphic study, 5 × 5 mm, nondisintegrating radiolabelled tablets were administered to each of 6 healthy subjects on 3 consecutive days. The tablets became widely dispersed on passage through the colon. Transit rates varied markedly, with the mouth-to-anus transit time for a group of 5 tablets varying from 18 hr to 72 hr. The mouth to colon component of total transit was between 2 hr and >11 hr (18).

The gastrointestinal transit of a radiolabelled nondisintegrating osmotic tablet formulation was measured in 6 subjects using gamma scintigraphy. The tablets emptied from the stomach in a mean time of 0.8 hr. The mean transit time through the small intestine was 3 hr. Colonic transit was highly variable with a median transit time of 20.9 hr. In one subject the tablet moved through the colon in just 2.5 hr, giving a whole gut transit time of only 6 hr (19).

There have been a number of studies investigating the effect of the size of a dosage form on the rate that it moves through the colon. The colonic transit rate of 0.5–1.8-mm indium-labelled beads, delivered into the colon in an enteric-coated gelatin capsule, has been compared to a radiolabelled liquid phase (20). When the capsule containing the beads arrived at the colon, 10 ml of ^{99m}Tc-DTPA solution was delivered into the colon through an orocecal tube. The solid and liquid phases travelled at the same rate through the colon. In a related study, the transit rate of 0.5–1.8-mm radiolabelled beads was compared to the transit of 6-mm diameter pieces of radiopaque tubing. The mean transit times were 9.9 ± 3.8 hr and 11.9 ± 2.0 hr for the radiopaque marker and beads, respectively. This difference was statistically significant (21).

The effect of capsule size and density on colonic transit has been investigated. Capsules with a density of 1.1 g/cm^3 and a volume of 0.3, 0.8, and 1.8 cm^3 and capsules with a volume of 0.8 cm^3 and a density of 0.7 and 1.5 g/cm^3 were tested. Capsule transit through the ascending colon was not affected by density, and although there was a tendency for the transit rate to increase with volume, this effect was not significant (22).

The transit rates of a radiotelemetry capsule (25-mm length × 9 mm-diameter) and 0.5–1.8-mm ion-exchange resin beads were compared in healthy subjects. Although the beads and capsule entered the colon si-

multaneously, the capsule moved through the ascending colon more rapidly, reaching the hepatic flexure ahead of 86% of the beads. Whole colon transit of the capsule ranged from 13 hr to 68 hr (23).

The simultaneous colonic transit rate of 0.2-mm ^{111}In-labelled ion-exchange resin particles and ^{99m}Tc-labelled 5-mm or 8.4-mm nondisintegrating tablets has been measured. Under normal conditions there was no difference in ascending colon transit of 0.2-mm particles versus 5-mm tablets or 0.2-mm particles versus 8.4 mm-tablets. When the subjects were administered the laxative, lactulose, to produce a hypermotile colon, and simulate the transit conditions that may be found in inflammatory bowel diseases, the ascending colon residence of the 0.2-mm resin was significantly shorter than for the 5-mm tablets, although the magnitude of the effect was small (24).

Some dependency of dosage form dimensions on colonic transit was also demonstrated in a study which compared the colonic transit of 3-mm, 6-mm, 9-mm, and 12-mm tablets. In 2 out of 8 subjects, 6-mm tablets moved ahead of 3 mm-tablets and in all subjects 9-mm tablets moved ahead of 6-mm tablets. However, 12-mm tablets moved ahead of 6-mm tablets in only 3 of the subjects. The lower degree of separation between 6 mm and 12 mm compared to 6 mm and 9 mm was explained by the fact that while the 9-mm tablet had a larger thickness and diameter compared to the 6 mm, only the diameter of the 12-mm tablet was changed, which perhaps suggested that rate of colonic transit of the tablets was volume-dependent (25).

The results from these studies would suggest that smaller units travel through the colon more slowly than larger ones. Hence, additional retention of a dosage form within the colon could perhaps be achieved by the use a multiparticulate formulation, rather than a large single unit. Consequently, there may be advantages in formulating a controlled-release dosage form as a multiparticulate rather than as a single unit to ensure that it does not pass too rapidly through the colon and be excreted before all of the drug has been released.

Effect of Diet on Colonic Transit

The principal dietary component which can affect colonic motility is dietary fiber. It is generally considered that dietary fiber supplementation increases fecal weight, partly by retention of water and partly by increasing bacterial mass, and reduces colonic transit times. For example, addition of 20 g/day of bran to the diet of group of healthy subjects increased stool weight by 127% and reduced whole gut transit by 73 ± 24 hr to 43 ± 7 hr (26).

However, a more recent study investigated the effects of two levels of fiber intake on the gastrointestinal transit of radiolabelled dosage forms. Four vegetarian and 4 omnivore volunteers received diets containing 15 or 40 g/day of dietary fiber for 6 days prior to the scintigraphic investigation. For the omnivores, dosage form residence time in the colon was similar at both fiber levels with mean ascending colon residence times of 267 and 246 min for the low- and high-fiber diets, respectively. Surprisingly, transit was slower in the vegetarians, with mean ascending colon residence times of 405 and 627 min for the high- and low-fiber diets, respectively. It was suggested that the fiber may exert a normalizing effect on colonic transit, increasing it in individuals with slow transit and decreasing it in individuals with rapid transit (27).

The ingestion of food is known to stimulate colonic activity in what is termed the "gastrocolonic response." The effect of eating a meal on the colonic transit of radiolabelled tablets has been investigated. Each of 8 volunteers received 5 × 6-mm radiolabelled tablets. When the tablets reached the ileocecal region, each subject received a high-fat meal on one occasion or a high protein meal on a second occasion. Ingestion of food appeared to be followed by an acceleration of tablet movement through the ileocecal junction into the colon, although the phenomenon was not influenced by which of the meals was eaten (28).

Effect of Disease on Colonic Transit

Diseases affecting colonic transit have important implications for drug delivery; diarrhea will result in an increase in colonic motility and constipation in a decrease in colonic motility. Diarrhea has been defined as an abnormal frequency and liquidity of fecal discharge. Irrespective of the precise cause, diarrhea will result from an imbalance between electrolyte and water absorption and secretion. If fluid absorption within the small and large intestines is decreased and/or secretion is increased, then diarrhea will result (29). A direct stimulation of secretion or inhibition of absorption can be produced by a number of substances, including certain drugs such as stimulant laxatives (e.g., senna, bisacodyl) and bacterial toxins. Poorly absorbed substances retain excessive fluid within the intestinal lumen and this is the mechanism by which substances such as magnesium salts, sorbitol, and polyethylene glycols can cause diarrhea (30).

Diarrhea is also a major feature of Crohn's disease and ulcerative colitis, also known as the inflammatory bowel diseases (IBD). These are serious, debilitating conditions, the causes of which are not yet fully understood. Ulcerative colitis affects the lower colon and rectum and is characterized by mucosal inflammation and ulceration resulting in chronic diarrhea and abdominal pain. In contrast, Crohn's disease can affect any part of the gastrointestinal tract, although in most patients there is disease in the colon and terminal ileum. In Crohn's disease, the inflammation extends through all layers of the intestinal wall which can lead to the formation of fissures and fistulae. Both diseases are characterized by periods of remission interspersed with relapses. Antiinflammatory agents are used in IBD with the aim of increasing the length of remission and reducing the intensity and frequency of relapse (31).

Irritable bowel syndrome (IBS), as the term "syndrome" might suggest, is an ill-defined disorder affecting the small and large intestine and appears to describe a range of conditions, associated with symptoms such as abdominal pain and distention and altered transit. In some patients IBS is associated with diarrhea, and in others, with constipation. The causes are unknown, although it is thought that physical stress on the gut and/or mental stress may have an important role to play. Since the possible causes and symptoms are variable, the treatment approaches differ accordingly (32).

There is an obvious difficulty in measuring colon transit in diseased patients since many conditions are extremely debilitating and patients will be unwilling in such circumstances to participate in clinical investigations. However, a scintigraphic study of colonic transit in ulcerative colitis patients has been reported. A group of 6 patients was used, 2 with active disease at the time of the study. The residence time of individual tablets in the ascending colon varied from as little as 0.8 hr to greater than 20 hr. Combined residence times in the ascending and transverse colon were about 7 hr in the 2 subjects with active disease, and in excess of 17 hr in the remainder (33).

To overcome the problems of studies in patients, healthy subjects have been used who have been administered materials which alter colon transit. To produce a high motility rate, lactulose was administered to healthy volunteers and the transit rate of radiolabelled dosage forms through the colon was measured (34). In a related study, volunteers were pretreated with lactulose, to stimulate a hypermotile colon, and also received codeine, to try to understand the effects of this antidiarrheal drug on gastrointestinal motility and whether it affected the differential transit of different sized particles (35). In lactulose-treated subjects, the mean transit times of 50% of the administered quantity of 0.2-mm particles and 5-mm tablets through the ascending colon were 5.3 ± 2.5 hr and 4.7 ± 3.4 hr, respectively. For the lactulose + codeine treatment, mean transit times were 7.4 ± 2.5 hr and 10.4 ± 7.7 hr for the 0.2-mm particles and 5-mm tablets, respectively. Hence codeine slowed down ascending colon transit, but there was no significant difference between the transit rate of the particles and tablets.

ABSORPTION OF DRUGS FROM THE COLON

Conventional Drugs

The primary routes by which drugs are absorbed from the gastrointestinal tract are illustrated in Fig. 2.

The vast majority of drugs are absorbed by passive diffusion. There are, however, some exceptions. A few drugs have chemical structures which allow them to be carried across the small intestinal wall by the di- and tripeptide active transport mechanism, the means by which dietary di- and tripeptides, generated from protein digestion, are absorbed from the small intestine. Such drugs include angiotensin converting enzyme (ACE) inhibitors and β-lactam antibiotics (36). Some drugs with very high lipophilicity may be incorporated into chylomicrons inside the intestinal epithelial cells and absorbed into the systemic circulation via the lymphatic system (37).

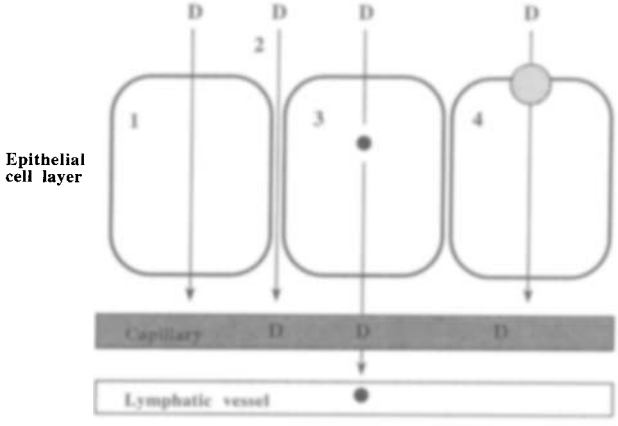


Figure 2. Illustration of the main pathways of intestinal drug absorption: (1) Transcellular absorption; (2) paracellular absorption; (3) transcellular absorption followed by incorporation into chylomicron and transport into lymphatic system; (4) Active transport.

Drugs are absorbed passively by paracellular or transcellular routes. Transcellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs will take, whereas paracellular absorption involves the transport of the drug through the tight junctions between cells and is the route most hydrophilic drugs will take. Studies in the rat have indicated that paracellular absorption is constant throughout the small and large intestine, but transcellular absorption appears to be confined to the small intestine, with negligible colonic absorption by this route (38). The poor paracellular absorption of many drugs in the colon is due to the fact that epithelial cell junctions are very tight (39). In addition, compared to the small intestine, the colon has a much lower surface area, although this is compensated for in part by the slow rate of transit which means that drugs stay in contact with the mucosa for a longer period than in the small intestine.

Because of the smaller extent of paracellular transport, the colon is a more selective site for drug absorption than the small intestine. Drugs shown to be well absorbed include glibenclamide (40), diclofenac (41), theophylline (42), ibuprofen (12), metoprolol (43), and oxprenolol (19,44). Drugs whose absorption from the colon is reduced by comparison to other parts of the gastrointestinal tract include furosemide (45), piretanide (46), buflomedil (47), atenolol, cimetidine and hydrochlorothiazide (48), and lithium, which is not absorbed at all (49). The majority of drugs with poor colonic absorption are those that are primarily absorbed by the paracellular route.

The progressive absorption of water means that the further one travels through the colon, the more viscous the contents will become. This will theoretically reduce the dissolution rate of particulate drug and slow the diffusion of dissolved drug to the mucosa. The bioavailability of diclofenac was found to be the same whether distilled into the colon at the cecum or at the splenic flexure, but since the colon was cleansed by enema prior to drug administration, the study merely demonstrated that the permeability of the mucosa to the drug was the same at both locations (41). A capsule containing ciprofloxacin was remotely triggered to release its contents into different portions of the gastrointestinal tract. Colonic absorption was poor compared to the small intestine. However, within the colon, drug absorption from the descending colon was reduced by comparison to the ascending colon (50).

A study with an osmotic tablet formulation containing oxprenolol demonstrated the importance of the colon in determining drug bioavailability from sustained release dosages forms. In a subject in which the tablet was resident in the colon for just 2.5 hr, the absolute bioavailability of oxprenolol was 13.8%, with 79% of the dose remaining in the excreted tablet. On the other hand, in a subject where the tablet took 27.5 hr to pass through the colon, the bioavailability was 54.3% with only 14.3% of the dose remaining in the excreted tablet (19). Therefore, in cases of abnormally rapid gastrointestinal transit, drug therapy could be compromised by using a once-a-day sustained-release formulation.

Since it is now apparent that many sustained-release dosage forms rely on a degree of colonic absorption to remain therapeutically effective (12,19), it is an essential part of the development of long acting oral dosage forms (12- or 24-hr release) to establish the extent of colonic drug absorption. Inadequate colonic absorption has prevented and will continue to hinder the development of sustained-release dosage forms for many drugs. Knowledge of colonic absorption may also be of importance when developing enteric-coated dosage forms. Poor bioavailability from a erythromycin tablet was thought to be a result of its enteric coat resisting dissolution until pH 6.5. This probably resulted in tablet disintegration beyond the proximal small intestine, the main absorption site for erythromycin (51).

Peptides and Proteins

A more elusive goal is to use the colon as a site for the oral absorption of therapeutic peptides and proteins. Although it is recognized that peptides and proteins can be absorbed intact from the gastrointestinal tract (52), the bioavailability of therapeutic peptides and proteins administered by this route is invariably extremely low. As discussed earlier, there are exceptions, such as di- and tripeptide analogues. Another exception is cyclosporin. This cyclic peptide (MW 1203) is lipophilic and normally administered in an oil-based vehicle or as a microemulsion and the bioavailability of the drug in such formulations is approximately 30% (53) which may, in part, be due to lymphatic absorption (36). In the case of the peptide desmopressin (MW 1089), a tablet formulation is available and although the oral absorption is less than 0.5%, this is sufficient for therapeutic efficacy (53).

However, for the majority of peptide and protein drugs, oral absorption is limited by the following factors:

- Degradation in the acidic environment of the stomach.
- Enzymatic degradation in in the small and large intestine.

Low mucosal permeability.
Rapid small intestinal transit.
Extensive first pass metabolism by the absorbing membrane and the liver.

One of the attractive properties of the colon as a site for peptide/protein delivery is often considered to be its relative lack of degradative enzymes compared to the stomach and small intestine. However, as discussed earlier, there is significant protease and peptidase enzyme activity within the colon, arising from the microflora. Consequently, the stability of peptide and protein drugs within the colon is likely to be poor, and the opportunities for absorption, although better than in the small intestine, are still relatively limited.

Although there are numerous examples in animal models (e.g., 54–59), there are few published studies of the colonic absorption of therapeutic macromolecules in man. The colonic absorption of human calcitonin (hCT, MW 3527) has been reported. The peptide was directly instilled into the distal colon using a colonoscope following administration of an enema to clear fecal matter (60). In 5 out of 8 subjects, the enema was effective in clearing fecal material from the distal colon. However, in the other 3 subjects some fecal matter remained. This appeared to affect bioavailability; the mean bioavailability (relative to intravenous) in the group of 5 subjects was $0.118 \pm 0.63\%$ and in the group of 3 subjects it was $0.007 \pm 0.002\%$. Overall, the mean bioavailability was $0.076 \pm 0.075\%$. In another study, increasing the colonic dose of hCT increased the absolute bioavailability, whereas coadministration of the protease inhibitor, aprotinin, resulted in a significant reduction in hCT absorption (61). The reduction in bioavailability was probable due to an interaction between aprotinin and hCT. The absorption of hCT from the transverse colon of stoma patients has also been investigated (62). The mean bioavailability was higher than in the earlier study (60) at $0.22 \pm 0.06\%$. Although there may be differences in the lumenal environment between normal individuals and stoma patients, it was concluded that the transverse colon is a better absorption site for hCT than the distal colon.

Another attractive feature of the colon, because of the low level of motility, is the ability to generate high local concentrations of absorption enhancers (63).The use of penetration enhancers to increase mucosal permeability and improve bioavailability has been extensively reviewed (64,65). In the case of hCT, the absorption from the rat colon was enhanced 9-fold in the presence of a mixture of 40-mM monolein and 40-mM sodium taurocholate (66).

In man, the use of absorption enhancers to improve intestinal drug absorption is already established. A suppository formulation containing the antibiotic ampicillin, and the sodium salt of capric acid (C_{10} fatty acid) as an absorption enhancer is currently marketed in countries including Sweden (67).

The use of an absorption enhancer to improve oral insulin absorption in man has been reported (68). Enteric-coated capsules were prepared containing insulin and a bile salt, to act as an absorption enhancer. Increases in plasma insulin were measured in the 3 experimental subjects, although no estimates of bioavailability were made.

There are many companies developing formulations for the oral delivery of peptides, proteins, and other macromolecules, although information within the public domain tends to be limited for commercial reasons. For example, at least three companies were reported to have delivery systems for 3 macromolecules (insulin, calcitonin, and low molecular weight heparin) in clinical testing during 1996 (69). These technologies probably rely on drug absorption from the small intestine. In contrast, we are developing an oral delivery system in which the colon is used as the absorption site. The technology uses an absorption enhancer system based on GRAS (generally regarded as safe) excipients that modify the paracellular pathway and has been shown to improve the absorption of a variety of macromolecules, including insulin, calcitonin, and low molecular weight heparin, from the large intestine of the pig (59). An illustration of the glucose-lowering effect in pigs of a formulation comprising this enhancer system and insulin is shown in Fig. 3. Formulations in which the enhancer system and a peptide are encapsulated in a colon-targeted enteric-coated starch capsule were in phase I clinical testing during 1996.

METHODS FOR TARGETING DRUGS INTO THE COLON

The most direct route for delivery of drugs into the colon is by rectal administration. A 60-ml radiolabelled enema remained mainly confined to the rectum in healthy volunteers, although it spread as far as the ascending colon in subjects who had been predosed with an evacuation enema (70). In another study, 50-ml enemas were retained within the rectum and sigmoid colon while with a 200-ml volume there was spread into the transverse colon. It was concluded that the optimum enema volume is probably 100 ml (71). The spread of a 5-ml volume of radiolabelled foam enema was generally confined to the sigmoid colon in a group of IBD

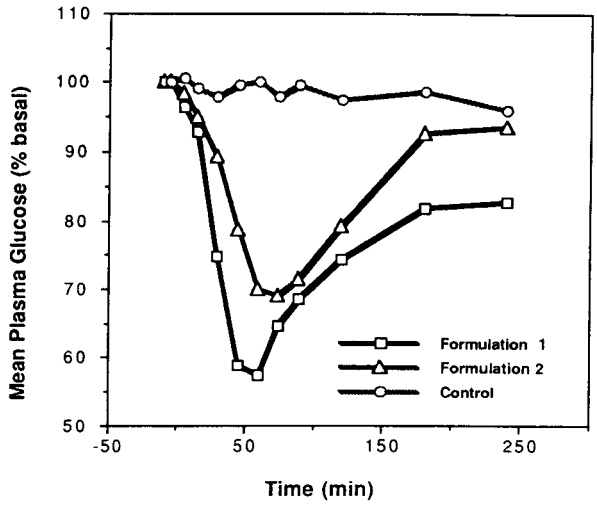


Figure 3. Change in plasma glucose following administration of 20 units/kg of insulin to pigs inside capsules. Formulations 1 and 2 contain absorption enhancers. (From ref. 59. With permission)

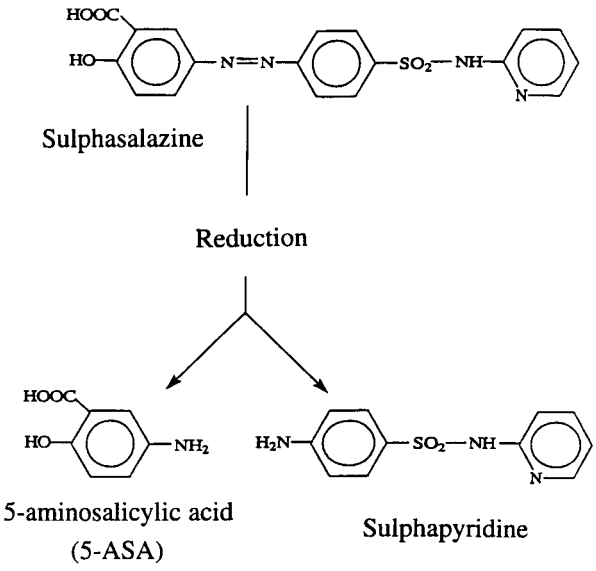


Figure 4. Pathway of colonic reduction of sulphasalazine.

patients and was not significantly altered by increasing the enema volume to 50 ml (72). The spread of enemas is probably greater in active colitis (73).

Since there are problems in both patient acceptability and accessing the proximal colon using rectally administered dosage forms, orally administered colon-specific delivery systems have been developed. There are three practical mechanisms by which a delivery system can be targeted into the colon following oral administration.

Activation by colonic bacterial enzymes or by the reducing environment created by the microflora
pH-dependent coating
Time-dependent coating

Bacterially Triggered Delivery Systems

Both prodrugs and dosage forms from which the release of drug is triggered by the action of colonic bacterial enzymes have been devised.

Azo-prodrugs

For many years, sulphasalazine has been a mainstay of treatment for IBD. This drug was originally developed for treating rheumatoid arthritis, combining a sulphonamide antibiotic, sulphapyridine, and a salicylate, 5-aminosalicylic acid (5-ASA), with the two molecules linked by an azo bond (-N = N-) (Fig. 4). In the treatment of IBD, sulphasalazine is acting as a 5-ASA prodrug. At least 85% of an oral dose of sulphasalazine passes unabsorbed into the colon (74) where it is reduced by the anaerobic environment into its two constituent molecules, 5-ASA and sulphapyridine (Fig. 4). The involvement of a specific enzyme, "azoreductase", in the reduction of azo compounds is often mentioned. However, it has been suggested that azo reduction is mediated through low molecular weight electron carriers such as NADPH rather than through a specific enzyme (75). 5-ASA is largely unabsorbed from the colon where it is thought to exert topical antiinflammatory activity. In contrast, sulphapyridine is well absorbed giving rise to side-effects, and as many as 30% of patients are unable to tolerate treatment with sulphasalazine (76).

Because of the toxicity of sulphapyridine, there was an interest in using 5-ASA alone as a treatment for IBD. However, since 5-ASA is well absorbed from the small intestine (77), it is not available for topical action in the colon if administered in a conventional oral dosage form. Hence dosage forms for colon-specific delivery of 5-ASA have been developed and these are described later in this review. New-generation prodrugs with fewer side-effects than sulphasalazine have also been developed.

To date, the only new-generation prodrug of 5-ASA to be introduced into clinical use is olsalazine (Fig. 5), a dimer of 5-ASA (78). This drug is as effective as

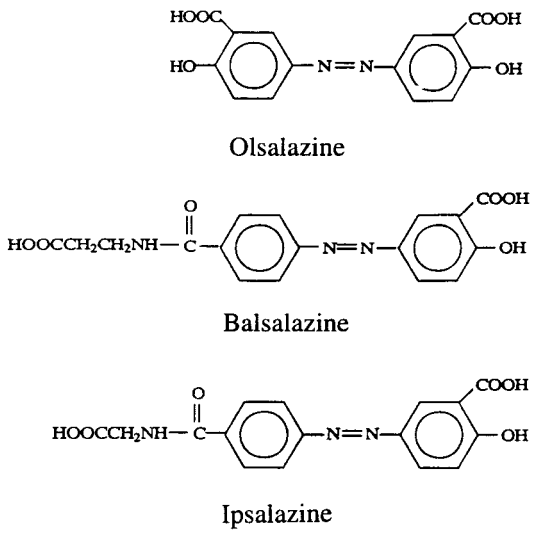


Figure 5. Structure of new-generation prodrugs of 5-ASA.

sulphasalazine in maintaining remission in ulcerative colitis (79) and in treating mild forms of the disease (80). Other 5-ASA prodrugs described include balsalazine and ipsalazine in which 5-ASA is azo-linked to 4-aminobenzoylglycine and *p*-aminohippurate, respectively (81) (Fig. 5).

Prodrugs have also been prepared by azo-linkage of 5-ASA to polymers (82–84).

Azo-Polymers

The first work in this field was published in 1986 by Saffran and described the synthesis of polymers of polystyrene and hydroxyethyl methacrylate cross-linked with divinylazobenzene (85). Insulin and vasopressin were administered to rats inside polymer-coated gelatin capsules and pellets and delayed absorption was demonstrated. It was concluded that release of the drugs was due to bacterial degradation of the azo-polymer coatings in the colon.

However, these conclusions have subsequently been questioned (86). Capsules coated with azo-polymer and initially shown to disintegrate in the rat colon due to degradation of the polymer (87), were subsequently shown to disintegrate as a result of a time-dependent mechanism: the diffusion of water into the capsules resulting in mechanical failure (88). This led to the conclusion that the capsules used by Saffran may also have released insulin and vasopressin by the same mechanism and the suggestion that a far more rational approach to the synthesis of azo-polymers is required, taking into consideration the redox potential needed for reduction of the azo functions into amines and hydrophilicity of the polymer (86).

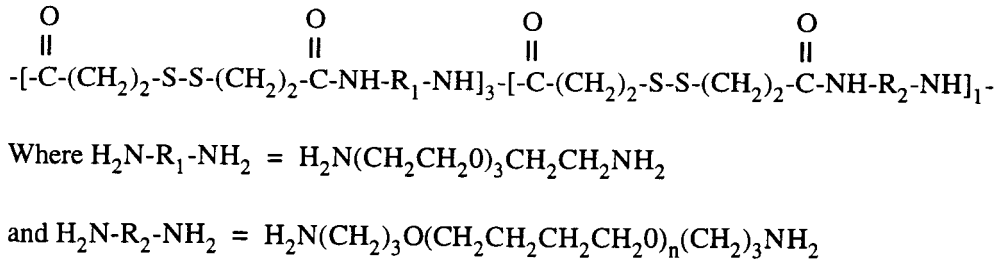
Indeed, Van den Mooter and colleagues have reported the synthesis of azo-polymers containing different ratios of methylmethacrylate and hydroxyethyl methacrylate (HEMA) (89,90). Hydrophilic polymers, those with a high HEMA content, showed greatest susceptibility to colonic degradation. It was concluded that a balance was needed to be achieved between hydrophilicity, to ensure effective reduction, and hydrophobicity, to provide adequate resistance to gastric and intestinal fluid.

Schacht et al. have reported similar results with azo-containing polyamides (83). Films cast from a hydrophilic azo-polyamide dissolved completely under reducing conditions. On the other hand, hydrophobic azo-polyamides changed from orange to pink when exposed to a reducing environment, but remained intact. The color change from orange to pink was attributed to conversion of the azo function to the hydrazine form. On exposure to air, the polymer changed back to orange. Although the film remained intact, it was suggested that physical changes resulting from conversion to the hydrazine form could provide the material with colon-targeting properties when coated onto dosage forms. Such a finding was also reported in azo-containing polyurethane films (91). It is possible that the physical changes in the polymer film resulting from hydrazine formation may have been responsible for the disintegration and release of drugs from the azo-coated dosage forms reported in the other studies.

Hydrogels have been produced based on acrylic acid, N,N-dimethylacrylamide and N-terbutyl-acrylamide cross-linked with azo aromatic compounds (92). The swelling of the polymer was pH dependent. At the low pH encountered in the stomach, the degree of swelling of the polymer was low. However, as it passed down the GI tract and the pH increased, the polymer began to swell. By the time it reached the colon, the hydrogel was sufficiently swollen to allow access to bacterial azoreductase enzymes. It was suggested that cleavage of the azo- bonds would allow release of active compound incorporated into the hydrogel matrix. However, the degradation of such hydrogels using in vitro and in vivo models was generally slow and measured in days rather than hours.

Disulphide Polymers

Synthetic polymers containing disulphide (-S-S-) groups, also reduced in the anaerobic environment of the colon, have been described (93). Figure 6 shows the



Where $H_2N\text{-}R_1\text{-}NH_2 = H_2N(CH_2CH_20)_3CH_2CH_2NH_2$

and $H_2N\text{-}R_2\text{-}NH_2 = H_2N(CH_2)_3O(CH_2CH_2CH_2CH_20)_n(CH_2)_3NH_2$

Figure 6. Structure of disulphide polymer developed as a colon-degradable coating.

structure of one of these polymers, prepared by copolymerization of 3,3′-dithiodisuccinimidyl propionate with α,ω-bisaminopropylpolytetramethylene oxide and tetraethyleneglycol diamine. DanBioSyst in conjunction with the University of Nottingham has been involved in formulation and clinical testing of this polymer (paper in preparation). The sub-acute toxicity of the polymer has been tested in rats in a 14-day oral dosing study. No significant toxicity was demonstrated allowing testing in man. In an in vitro fermenter system, polymer-coated tablets showed rapid (46 min) disintegration with complete dissolution of the coating. In a Phase I scintigraphic study in man, 5 out of 8 tablets coated with 13.5% w/w polymer disintegrated in the ascending or transverse colon. The remaining 3 tablets did not disintegrate during the study. Based on these encouraging results, further work to optimize the polymer is underway.

Glycosidic Prodrugs

Corticosteroid prodrugs have been developed by the attachment of the active agent to glycosidic carriers (94,95). The prodrugs should theoretically pass unabsorbed into the colon where the glycoside bonds are cleaved by the action of bacterial glycosidase enzymes making the corticosteroid available for therapeutic action. A comprehensive review of the in vivo performance of these agents ahs been published (96). A degree of selective delivery of the corticosteroid into the cecum was achieved in the rat and guinea pig. However, these animal models possess relatively high small intestinal glycosidase activity, and thus more selective delivery might be predicted in humans. Dexamethasone-β-D-glucoside was evaluated as a treatment for carrageenan-induced ulcerative colitis in guinea pigs. Compared to control conditions, the number of large intestinal ulcers was significantly fewer in animals receiving the prodrug or unconjugated dexamethasone. A 0.65-mmol/kg dose of prodrug was equieffective as 1.30-mmol/kg dexamethasone supporting the hypothesis that the prodrug achieved higher cecal and colonic levels of free drug.

Colon targeted corticosteroids termed as "pro-ante-drugs" have been reported. Corticosteroid derivatives which are readily metabolized into inactive metabolites following systemic absorption were synthesized ("ante-drugs"). To the ante-drugs were attached glycosidic functions to allow colon-targeting. Generation of free ante-drug in the large intestine of guinea pigs and rats was demonstrated (97).

Polysaccharides as Matrices/Coating Agents

A number of delivery systems based on polysaccharides which are selectively degraded in the colon have been reported. The major attraction of most of these materials is that they are already approved for use as pharmaceutical excipients. However, a property that most polysaccharides share is that they are hydrophilic and gel forming, and therefore methods have to be devised to ensure that drug does not prematurely diffuse from the dosage form before it reaches the colon.

A mixed coating comprising amylose and ethylcellulose has been reported to provide colon-specific delivery (98,99). The amylose was extracted from pea starch and was resistant to pancreatic enzymes but susceptible to degradation by colonic bacteria. To provide a film with sufficient water resistance, the amylose needed to be applied as a mixture with ethylcellulose. A coating comprising a 1:4 mixture of amylose:ethylcellulose was applied to pellets containing 5-ASA and there was prolonged resistance to release of drug under in vitro conditions simulating the stomach and small intestine (98). However, release of 5-ASA was rapid when the pellets were incubated in an in vitro colon fermenter model. This coating has also been tested in man. Pellets containing ^{13}C-glucose were coated with

amylose/ethylcellulose mixture and administered to human subjects together with a radiolabelled transit marker (99). The appearance of $^{13}CO_2$ in breath indicated release of ^{13}C-glucose from the pellets. In the majority of subjects, $^{13}CO_2$ did not appear until the pellets reached the cecum. However, the breath measurements indicated that the release of ^{13}C-glucose from the pellets in the colon was slow, indicating slow degradation of the coating.

Pectin has been evaluated as a colon-specific coating. Tablet cores containing a marker were compression coated with two thicknesses of pectin, equivalent to 700 mg or 1000 mg of pectin (100), hence producing a relatively large dosage form. The pectin coating provided a long delay in release of the marker. Release of the marker was accelerated by the addition of pectinolytic enzyme to the dissolution medium. Tablets coated with 700 mg of pectin and containing a radiolabelled core were administered to 6 volunteer subjects in a gamma scintigraphy study. All of the tablets disintegrated in the colon although it was unclear whether this was due to bacterial degradation of the pectin or time-dependent failure of the dosage form due to the diffusion of water into the tablet cores. Further studies indicated that the degree of methoxylation of the pectin and calcium content of the pectin layer could influence the solubility of the layer and its susceptibility to enzymatic degradation (101).

Pectin has also been mixed with ethylcellulose and used as a tablet coating. A solution of pectin was mixed with an aqueous ethylcellulose preparation (Surelease®) and spray-coated onto paracetamol tablets. Depending on the coat composition (the pectin content varied from 40% to 60%) and amount applied (20 mg–32 mg), between approximately 5% and 30% of the paracetamol was released after 6 h at pH 7.4. Addition of a pectinolytic enzyme to the dissolution medium accelerated drug release (102).

Tablets have been prepared from calcium pectate. The pectate salt was mixed with indomethacin and compressed into tablets and the release of drug evaluated in vitro. Under control conditions, release of indomethacin into pH 7 buffer was minimal (< 10% after 24 hr). Adding to the dissolution medium cecal contents from rats which had been induced to produce pectinolytic enzymes resulted in a significant increase in indomethacin release (approximately 60% after 24 hr). Similarly, a dissolution experiment in the presence of a bacterium able to hydrolyze pectin resulted in a significant increase in indomethacin release, although the total amount released after 6 hr was only about 20% (103).

Guar gum is another gelling polysaccharide which is selectively digested by colonic bacteria. Guar gum–based tablets containing the corticosteroid dexamethasone, have been radiolabelled and administered to healthy volunteers in a combined gamma scintigraphy and pharmacokinetic study (104). Although some of the tablets did not completely disintegrate until they were in the colon, in all cases drug was detected in the plasma when the tablets were still in the small intestine. This would suggest a hydrophilic matrix-type formulation which swells and slowly releases drug in the small intestine, but which may be susceptible to bacterial digestion in the colon.

Guar gum, locust bean gum, tragacanth, and xylan have been mixed with methacrylate copolymers (Eudragit®) and used to coat tablets. The in vitro release of drug from tablets coated with mixtures of Eudragit L and guar, or Eudragit RL and guar was enhanced in the presence of glycosidic enzymes (105).

Locust bean gum has been cross-linked and spray-coated onto tablets. Drug release was accelerated when galactomannan-degrading enzyme was added to the dissolution medium (106).

A delivery system based on the mucopolysaccharide, chondroitin, has also been reported. This polymer can be found in the human colon from sloughed epithelial cells and dietary meat. Chondroitin sulphate was chemically cross-linked, mixed with indomethacin and pressed into tablets. The release of indomethacin was accelerated in an anaerobic fermenter system which contained rat cecal content (approximately 50% release after 6 hr compared to 20% in control buffer), suggesting bacterial enzyme-induced degradation of the tablet matrix (107). However, the rats had been pre-fed with chondroitin in order to induce enzyme activity in the cecum and thus it is not clear how rapidly such a polymer would be degraded in the normal human colon.

It is evident from the polysaccharide systems described in this section, that the release of drug is generally slow in an environment which represents the small intestine. However, in a colonic environment, although drug release is significantly faster, it still remains at a relatively slow rate. For rapid degradation of materials in the colon, they need to be in a hydrated state, or ideally, in solution. Since there will often be the need to release drugs very rapidly into the colon, for example to ensure maximum absorption of a polypeptide drug, such bacterially-triggered delivery systems may not be the most appropriate ones to use.

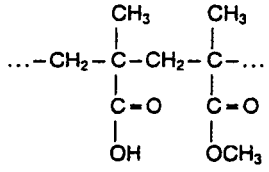
pH-Triggered Delivery Systems

Site-specific delivery into the small intestine has been achieved for many years by the use of entering coatings, and a wide range of suitable polymers are available (108).

As discussed earlier, the pH in the terminal ileum and colon is higher than in any other region of the gastrointestinal tract and thus dosage forms which disintegrate at suitably high pH levels have the potential for site-specific delivery into this region. However, because the pH is higher in the terminal ileum region than in the cecum, and dosage forms are often delayed at the ileocecal junction, careful selection of enteric coat composition and thickness is needed to ensure that disintegration does not occur until the dosage form moves through the ileocecal junction from the terminal ileum into the cecum.

The principal group of polymers utilized for the preparation of colon-targeted dosage forms has been the Eudragits (registered trademark of Röhm Pharma, Darmstadt, Germany), and more specifically Eudragits L and S (Fig. 7). These are anionic polymers which are water-impermeable at low pH, but become ionized and dissolve at intestinal pH. Eudragits L100 and S100 are copolymers of methacrylic acid and methyl methacrylate. The ratio of carboxyl to ester groups is approximately 1:1 in Eudragit L100 and 1:2 in Eudragit S100. The polymers form salts and dissolve above pH 6 and 7, respectively. Eudragit L100-55 is a copolymer of methacrylic acid and ethyl acrylate which dissolves above pH 5.5. This polymer disperses in water to form a latex and thus avoids the use of organic solvents in the coating process. (Eudragit L30D-55 is a ready-to-use aqueous dispersion of Eudragit L100-55). Eudragits L100, S100, and L100-55 are listed in the USP/NF 23 as Methacrylic acid copolymer A, B, and C, respectively.

i. **Eudragit L100 / S100**



ii. **Eudragit L100-55 / L30D-55**

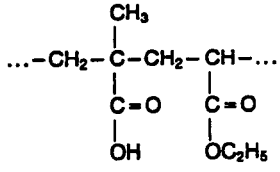


Figure 7. Chemical structure of Eudragit copolymers.

The use of Eudragit S as a colon-targetable coating was first reported in 1982 (109). Hard gelatin capsules containing barium sulphate as a radiopaque marker and sulphapyridine as a marker for drug release were coated with a 120 μm-thick coat of Eudragit S. Six subjects each swallowed 6 capsules. Twelve hours after administration, of the 36 capsules administered, 4 had broken in the distal ileum, 23 in the colon, and 9 remained intact. After 24 hr, 4 capsules remained intact.

This approach was extended to the evaluation of 5-ASA tablets, each containing barium sulphate and coated with an 80 μm–thick coat of Eudragit S. Eight patients received a total of 64 tablets. After 6 hr, 24 tablets were in the stomach, intact, while the remaining 40 tablets were in the terminal ileum and ascending colon, and only 2 of these were intact. At 12 hr 20 tablets were in the stomach, and 4 tablets remained intact in the terminal ileum/colon. At 24 hr, all tablets had reached the colon and had disintegrated (110). This work formed the basis for development of a commercial formulation of 5-ASA comprising a tablet coated with Eudragit S (marketed as Asacol® by various companies).

Since 5-ASA is well absorbed from the small intestine but poorly absorbed from the colon, urinary excretion of the drug is a good indicator of the quantity released at sites proximal to the colon. Urinary excretion of about 20% of the dose of 5-ASA has been reported following administration of Asacol tablets, a quantity comparable to sulphasalazine administration (77).

A problem that has been cited with Asacol is the occasional failure of the tablets to disintegrate with patients observing intact tablets in their stools (111). This is probably a result of the relatively high threshold pH above which the Eudragit S–based coating dissolves.

5-ASA tablets coated with Eudragit L are also available (Salofalk® and Claversal®). Because the coating on these tablets dissolves at a lower pH, these products are designed to deliver 5-ASA into the proximal small intestine and terminal ileum and as such, are suitable for the treatment of Crohn's disease affecting these parts of the gastrointestinal tract. A scintigraphic assessment indicated that in a group of 13 patients, more than 70% of administered Claversal tablets disintegrated in the

small intestine, on average 3.2 h after gastric emptying (112).

Ashford et al. (113,114) investigated the in vitro and in vivo performance of model tablets coated with Eudragit S. Tablets (10-mm diameter) with 20 mg of Eudragit S coating were administered to 7 volunteer subjects. In some of the subjects, the tablets resided at the ileocecal junction for a prolonged period, and in others there was surprisingly rapid transit through the ascending colon. It was concluded that this variability in transit meant that a pH-based coating was not the best means for achieving reliable delivery into the colon.

DanBioSyst has developed a simple-to-manufacture colon-targeting system (TARGIT®), that is based on injection-molded starch capsules coated with a mixture of Eudragits L and S (115). The mixture of Eudragits is chosen to provide a coating that begins to dissolve as the capsule enters the small intestine from the stomach. However, the thickness of coating is such that the capsule does not disintegrate until it reaches the colon. This formulation therefore has both a pH and time-dependent element to its disintegration performance and can be engineered to release drug at different regions within the colon. The TARGIT system has been tested with a range of drugs in a number of Phase I gamma scintigraphic and/or pharmacokinetic studies and has achieved colon-specific delivery in >90% of cases. Scintigraphic images of a TARGIT capsule moving through the gastrointestinal tract and disintegrating in the colon are shown in Fig. 8.

Time-Dependent Delivery Systems

The final approach to colon targeting uses time as the release trigger. From gamma scintigraphic studies, the time of passage of dosage forms from mouth to colon is now well understood. As discussed earlier, although gastric emptying tends to be highly variable, small intestinal transit times are less so. Small intestinal transit rates would dictate that for successful colon delivery, the device should not release drug until 3–4 hr after leaving the stomach.

A delivery device using this basic concept has been developed. The Pulsincap™ is similar in appearance to a hard gelatin capsule, but the main body is water-insoluble. The contents are contained within the body by a hydrogel plug which is covered by a water-soluble cap. If necessary, the whole unit can then be coated with an enteric polymer to avoid the problem of variable gastric emptying affecting dissolution performance. In vivo, once the cap has dissolved, the hydrogel begins to swell. When the swelling reaches a critical point, the plug pops out of the capsule body and the contents are released. Depending on the properties of the plug used, the time at which this occurs can be controlled (116,117). A Pulsincap has been used to assess the colonic absorption of captopril. A device with a 5-hr "pulse" was used, and in 10 subjects the actual point of drug release ranged from 246 to 389 min (118). The technology has reached an advanced stage of development, including testing the tolerance of the hydrogel in healthy volunteers (119).

A delivery system, called the Time Clock™, has been developed comprising a solid core coated with a mixture of hydrophobic material, surfactant, and water-soluble polymer. The coating is designed to slowly erode away and after a predetermined interval, drug is released. An in vitro and in vivo investigation has been described using tablets coated with a mixture of carnauba wax, beeswax, polyoxyethylene sorbitan monooleate, and HPMC (120). Placebo tablets disintegrated after 196 min of in vitro dissolution testing in water. In vivo, after a light breakfast, radiolabelled tablets disintegrated in the colon at a mean time of 333 min. Unlabelled tablets containing salbutamol began releasing drug after 125 min in vitro and 209 min in vivo.

Another dosage form utilizing a similar concept has also been described. Solid dosage forms are coated with an inner layer of HPMC and an outer layer of enteric polymer. When the outer layer has dissolved, the inner layer of HPMC gels and slowly erodes away. When erosion has reached a critical level, drug is released from the inner core of the dosage form. A system has been described comprising ketoprofen tablets spray-coated with high viscosity HPMC from a water/ethanol/PEG solution (121). The tablets provided delayed release of ketoprofen in vitro, with the delay being directly related to the coat thickness. Similar results were achieved using a water-based coating system. However, to produce a coating solution of suitable viscosity for spray-coating, it was necessary to use a low viscosity grade of HPMC. This in turn meant that a thicker layer of polymer was required to provide a satisfactory delay in drug release (122).

Osmotic pumps which provide colon-specific drug delivery have been described (123). The units are enteric-coated and are only activated in the small intestine. A drug-free layer is adjacent to the delivery orifice and this is released over the first 3–4 hr following activation. Therefore, after this period, when the units begin to release drug, they should be within the colon. There are no published reports on the in vivo performance of these units.

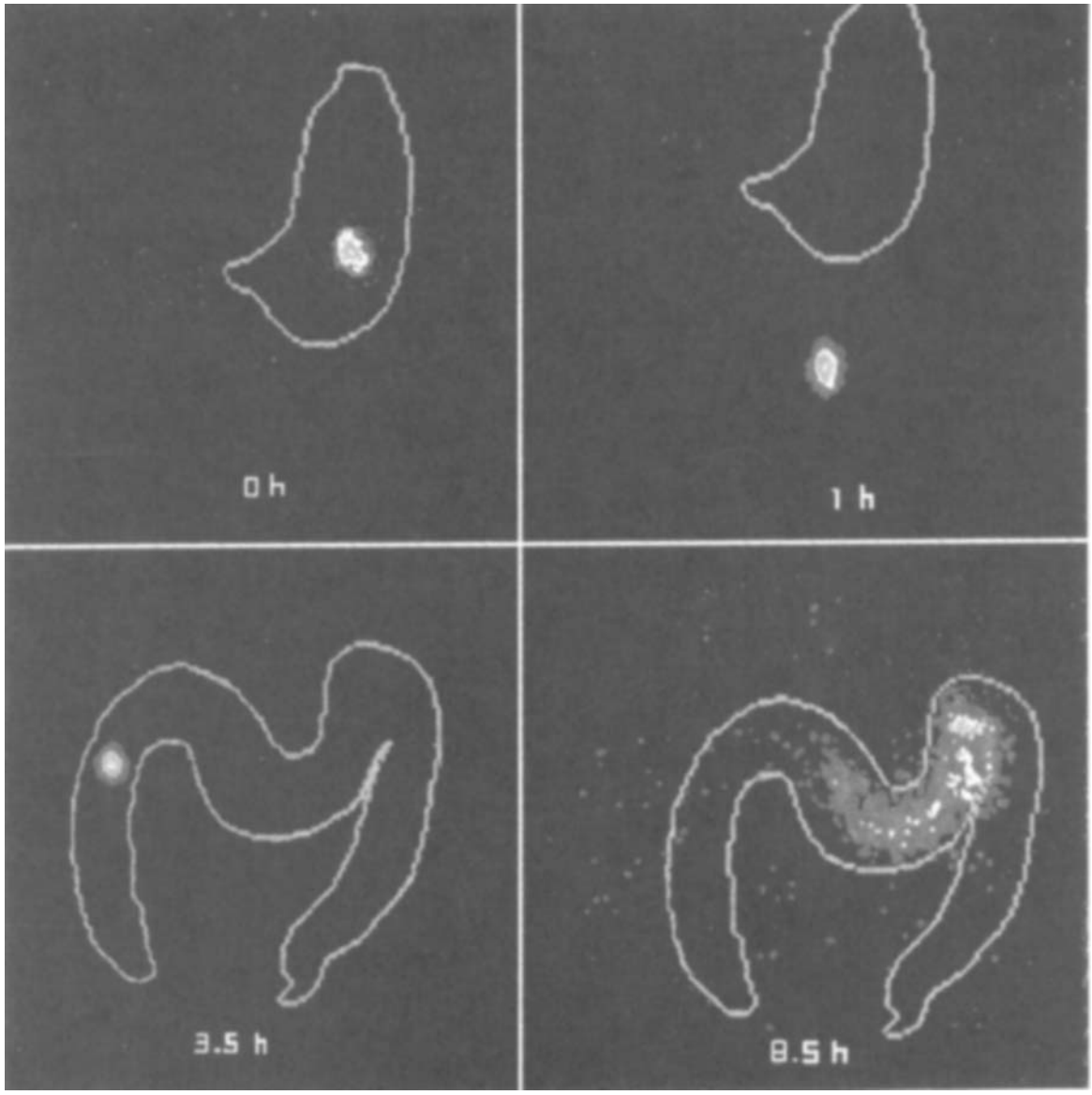


Figure 8. Scintigraphic images of a radiolabelled TARGIT® capsule in human following oral administration: 0 hr (capsule in stomach); 1 hr (small intestine); 3.5 hr (ascending colon); and 8.5 hr (dispersed in transverse and descending colon).

CONCLUSIONS

It is now appreciated that the colon can be an important site for the absorption and delivery of drugs. In the case of sustained-release dosage forms, they may spend a large proportion of their time in the gastrointestinal tract within the colon, and therefore an understanding of colonic drug absorption is important. Although the surface area in the colon is low compared to the small intestine, suggesting relatively poor drug absorption, this is compensated for by the markedly slower rate of transit. However, the colon is a more selective absorption site than the small intestine and tends to favor hydrophobic molecules, which are absorbed by the transcellular route.

The colon appears to be a viable site for the absorption of peptides and proteins. However, overcoming degradation by bacterial protease and peptidase enzymes

and the low permeability of the colonic epithelium remain major challenges. By the use of absorption-enhancing agents which increase the permeability of the colonic epithelium, therapeutically effective amounts of low molecular weight peptides can be absorbed, although the overall bioavailability is still relatively low. It is probable that such formulations will reach the market within the next few years.

The colon has a unique feature which allows site-specific drug delivery: the presence of a large bacterial population. This allows the design of enzyme- and/or redox-triggered delivery systems. The exploitation of the properties of the colonic bacteria has been extremely successful in the development of prodrugs of 5-ASA. However, it has been less successful in the development of polysaccharide-based dosage forms or synthetic polymer coatings. Polysaccharides are invariably too hydrophilic by themselves to provide adequate water resistance and allow a coated tablet or capsule to pass intact into the colon. Even if the coating does provide resistance, the susceptibility to bacterial degradation may be surprisingly low; while aqueous solutions of polysaccharides may be readily digested by colonic bacteria, when these materials are formed into a dense, slowly hydrating layer (such as found on a coated tablet or capsule), the rate of microbial degradation becomes very slow. Water permeability is also an issue with synthetic polymers. It has been demonstrated that azo-polymers will only degrade if they are sufficiently hydrophilic. If not, the azo function in the hydrophobic polymers will undergo a reversible chemical change to form a hydrazine. From a toxicological viewpoint, this could be seen as an advantage, since the formation of low molecular weight degradation products would be avoided. However, it is unclear to what extent the change in physical properties from hydrazine formation can affect drug release from a dosage form coated with such a polymer. Apart from technological issues, the most significant factor that may hinder the development of a novel synthetic polymer that degrades specifically in the colon is an economic one; a significant benefit over existing delivery technologies will need to be demonstrated to justify the considerable cost of taking such a polymer from the laboratory, through toxicological evaluation, scale-up, and the regulatory process, and onto the market.

As has been illustrated, delivery systems that rely on pH and/or time dependent mechanisms for drug release will also provide colonic delivery, although these systems are clearly inherently less reliable in achieving consistent site-specific delivery in the colon. However, they have been shown to be sufficiently reliable for most applications and, in the case of delivery systems using enteric coatings, are relatively inexpensive and easy to manufacture. However, an area which needs more investigation is the performance of colonic delivery systems in patients with colonic diseases, especially those diseases which may have an impact on their dissolution and disintegration characteristics via changes in colonic pH or transit.

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