Chapter Seven

Drug Delivery to the Large Intestine and Rectum

INTRODUCTION

The large intestine is responsible for the conservation of water and electrolytes, formation of a solid stool, and storage of faeces until a convenient time for defaecation. Its function is quite distinct from that of the small intestine whose primary role is the digestion of food and absorption of simple nutrients.

Administration by the rectal route is preferable for drugs which produce emesis or are irritant when given orally. For the purposes of drug delivery, the colon has to be considered as two regions; the distal colon, which can be reached from the anus, and the proximal colon, which is only accessible via the oral route. The splenic flexure limits the area of exposure of drugs administered by the anal route to the descending and sigmoid colon, rectum and anus. Instillation of large volumes to overcome this restriction triggers the defaecation reflex. Nevertheless the rectal route is popular in Europe, though not in the U.S.A! Formulations targeted to the proximal colon have to be delivered via the oral route and must be protected against the hostile environment of the stomach and small intestine. Transit through the colon is slower than other areas of the gastrointestinal tract and so there is an opportunity for sustained drug delivery from the ascending and first part of the transverse colon.

ANATOMY AND PHYSIOLOGY OF THE COLON

The colon extends from the ileo-caecal junction to the anus and is approximately 125 cm long *in vivo*. The large intestine is wider and shorter than the small intestine. The lumen progressively diminishes from a maximum diameter at the caecum (about 8.5cm) to the sigmoid segment (about 2.5 cm). It can be divided into the caecum, ascending, transverse, descending, and sigmoid colon, rectum and anus (Figure 7.1).

The caecum is the widest part of the colon and is a downward pointing blind pouch approximately 8.5 cm long with the appendix attached to its apex, and its base at the ileocaecal junction. It is attached to the floor of the right iliac fossa by the peritoneum, within the folds of which lies the appendix. It receives undigested food material from the small intestine and is considered the first region of the large intestine. It is separated from the ileum (the final portion of the small intestine) by the ileocecal valve (also called Bauhin's valve). The ileocaecal valve limits the rate of food passage into the caecum and may help prevent material from returning to the small intestine. In humans, the caecum's main functions are to absorb fluids and salts that remain after the completion of intestinal digestion and absorption, and to mix its contents with mucus for lubrication. The internal wall is composed of a thick mucous membrane beneath which is a deep layer of muscle tissue that produces churning and kneading motions.

The ascending colon is approximately 20 cm long and extends from the caecum to the hepatic flexure, which lies lateral to the right kidney and in contact with the inferior surface of the liver. The transverse colon is normally over 45 cm in length and hangs loosely between the hepatic and the splenic flexures, often following the greater curvature of the stomach. The splenic flexure is usually located higher than the hepatic flexure. The descending colon

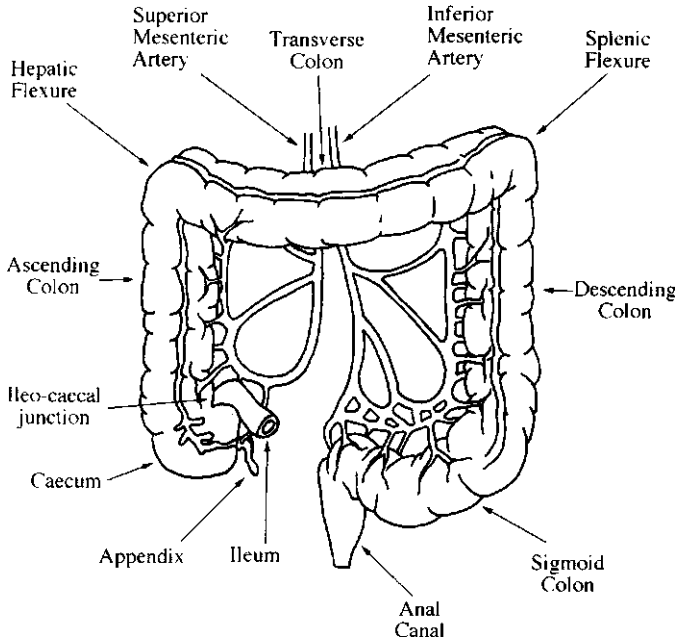

Figure 7.1 Anatomy and perfusion of the colon

extends downwards from the splenic flexure to the pelvic brim and is approximately 30 cm long. The colon then turns towards the midline to form the coiled sigmoid colon, which is about 40 cm in length. This in turn joins the rectum in front of the third part of the sacrum and travels for approximately 12 cm before joining the anal canal. This is 3 cm long and its diameter is narrower than that of the rectum to which it connects. It is identified by the presence of the anal sphincters which replace the muscular coats of the rectum. The sling of the puborectales muscle supports the ano-rectal junction.

In humans the rectum is formed by the last 15 to 20 cm of the large intestine. The internal cavity of the rectum is divided into three or four chambers; each chamber is partly segmented from the others by permanent transverse folds (valves of Houston) that apparently help to support the rectal contents. A sheath of longitudinal muscle surrounds the outside wall of the rectum, making it possible for it to shorten in length.

Interspecies differences in structure

The variation in relative dimension of the large intestine is largely correlated with diet. In herbivores, such as horses and rabbits, which depend largely on microbial fermentation for nutrition, the large intestine is very large and complex. Omnivores like pigs and humans have a substantial but smaller large intestine. Carnivores such as dogs and cats have a small and simple large intestine. The structure and function of the caecum varies in many animals. Vertebrates such as rabbits and horses, which live on a diet composed only of plant life, have a larger caecum that is an important organ of absorption, since it contains bacteria that help digest cellulose. Animals that eat only meat have a reduced or absent caecum. In cats and dogs, muscle contractions of the caecum are much more vigorous and are reversible. Materials already passed to the next region of the large intestine can be brought back to the caecum for mixing with new food substances.

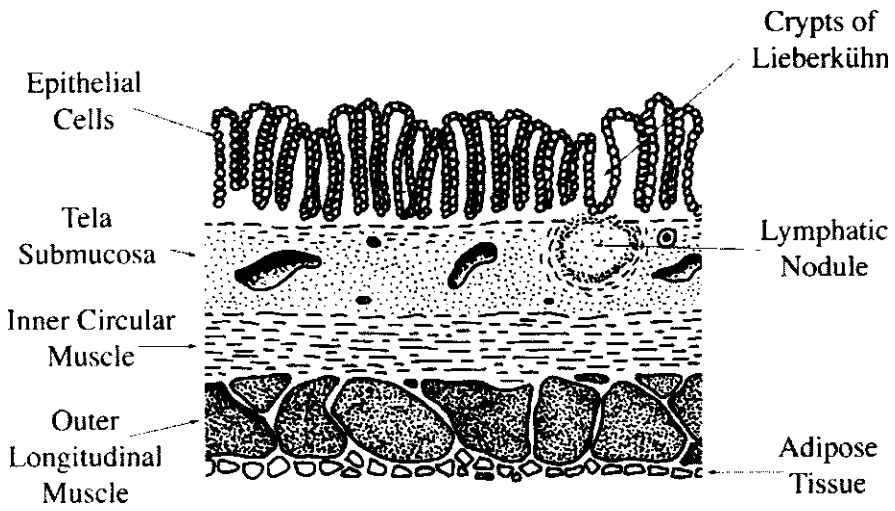

Figure 7.2 Structure of the colon wall

Colonic structure

The wall of the colon is divided into four layers: the serosa, external muscular region (muscularis externa), submucosa and mucosa (Figure 7.2). The squamous epithelium of the serosa is covered with adipose tissue which forms distended fat pouches of peritoneum, known as appendices epiploicae. These are larger and more numerous in the distal half of the colon and are one of its distinguishing features. The serosa is absent from the rectum and anal canal.

The muscularis externa consists of an inner circular muscle layer and an incomplete outer longitudinal layer composed of three separate 0.8 cm wide, longitudinal strips known as teniae coli. These bands converge in the caecum at the root of the appendix. They travel the length of the colon and eventually widen and join to form a continuous outer longitudinal muscle layer which covers the rectum. Between the teniae coli is a thin layer of longitudinal muscle which allows the inner circular muscle layer to bulge outwards. This outward bulge is interrupted at intervals by contractions of the circular muscle, giving the colon its characteristic sacculated appearance. These sacculae are also known as haustra and are more pronounced in the proximal half of the colon. Their size and shape varies with the contractile activity of the circular muscle.

Colonic mucosa

The colonic mucosa is divided into three layers: the muscularis mucosae, the lamina propria and the epithelium. The muscularis mucosae is a layer of smooth muscle approximately 10 cells thick which separates the submucosa from the lamina propria. The lamina propria supplies structural support for the epithelium and is well supplied with blood vessels and lymphatics. It also contains numerous T lymphocytes, macrophages, plasma cells and some lymph nodules. These cells play an important role in the immune function of the colon, and help to protect it from bacterial invasion and attack.

There are many histological similarities in the structure of the mucosa in the large and small intestine. The most obvious difference is that the mucosa of the large intestine is devoid of villi. The colonic epithelium consists of a single layer of columnar cells lining the lumen, and is punctuated by numerous crypts, termed crypts of Lieberkühn. These are

responsible for the production and differentiation of the absorptive, goblet and endocrine cells that make up the colonic epithelial layer. The goblet cells are responsible for the production of mucus which is important in minimising friction between the mucosal surface and the semi-solid luminal contents.

The mucosa is thrown into irregular folds known as plicae semilunares which, along with the microvilli of the absorptive epithelial cells, serve to increase the surface area of the colon by 10 to 15 times that of a simple cylinder of similar dimensions. The terminal portion of the digestive tract in most animals is distinguished from the rectum because of the transition of its internal surface from a mucous membrane layer (endodermal) to one of skin-like tissue (ectodermal). The anal opening is keratinized skin that has several folds while contracted. When open, the folds allow the skin to stretch without tearing. In the skin around the anal opening but not immediately adjacent to it are glands that give off perspiration. Both the upper and lower portions of the anal canal have circular and longitudinal muscle layers that allow expansion and contraction of the canal. The luminal surface of the rectum is covered by a membrane formed from columnar epithelial, endocrine and goblet cells.

Very few Paneth cells are found in the colon, although some exist in the caecum and ascending colon. It is believed that Paneth cells are involved in a variety of functions including secretion of digestive enzymes, production of trophic factors and elimination of heavy metals. They have abundant zinc-rich secretory granules which contain lysozyme, glycoprotein and other proteins.

The gut associated lymphoid tissue (GALT) is unevenly distributed throughout the GI tract. The lymphoepithelial regions of the colon are known as lymphoglandular complexes (LGC). They resemble sites in the small intestine which are associated with antigen sampling, but very little is known about this tissue.

Mucus

Mucus is produced by goblet cells and acts as a lubricant protecting the colon from abrasion from solid matter, particularly in the distal colon. Mucins are degraded by colonic bacterial flora. Much of the colonic mucin is sulphated, the degree of sulphation being greater in the distal colon and decreasing proximally towards the terminal ileum[1]. Histochemical studies have shown a relative depletion of colonic sulphomucins in both ulcerative colitics and patients with Crohn's disease[2]. Desulphation of the mucus will alter the net charge on the mucin and therefore change its physical properties, rendering it more susceptible to bacterial sialase attack[3].

Gut wall metabolism

The colon and small intestine resemble each other in the spectrum of metabolizing enzymes, but since the mucosal surface area is much higher in the upper gut, the total metabolic activity of the colonic wall is much lower. Thus enzyme systems should be easier to saturate than in the jejunum and ileum, and the problem of enzymatic degradation of drugs should be reduced.

Blood supply

The blood supply to the colon and upper rectum derives from the superior and inferior mesenteric arteries, and venous return is via the superior and inferior mesenteric veins (Figure 7.1). These join the splenic vein as part of the portal venous system to the liver. Thus any drugs absorbed from the colon and upper rectum are subjected to first pass elimination by the liver. Measurement of blood flow through the colon is difficult and reported values range from 8 to 75 ml. min^{-1} [4]. Blood flow through the colon is considerably less than that

to the small intestine, and the proximal colon receives a greater share of the blood flow than the more distal part[5].

The anal canal connects with the rectum at the point where it passes through a muscular pelvic diaphragm. The upper region of the anal canal has 5 to 10 vertical folds in the mucous membrane lining, called the anal, or rectal, columns; each column contains a small artery and vein. These are the terminal portions of the blood vessels that furnish the rectal and anal areas; they are susceptible to enlargement, commonly known as haemorrhoids. The mucous membrane of the upper portion of the rectum is similar to that in the rest of the large intestine; it contains mucus-producing and absorptive cells. Drugs absorbed from the lower rectum and anal canal are transported via these haemorrhoidal plexuses and internal iliac veins to the vena cava, and thus have the advantage of avoiding first pass elimination. However, not all rectally absorbed drug passes through this route, as the veins in this region are heavily anastomosed, causing a fraction of the blood flow to return via the hepatic portal vein to the liver. In cases of portal hypertension, this effect is reduced and a larger proportion of a rectally administered drug can avoid first pass metabolism.

Nervous and humoral control

Parasympathetic supply to the colon is provided by the vagi to the proximal colon and pelvic nerves to the distal colon, whereas sympathetic supply is via the splanchnic and lumbar colonic nerves which supply the proximal and distal colon respectively. Axons from both branches of the autonomic nervous system impinge on the neurons of the myenteric plexus. Vagal stimulation initiates segmental contractions in the proximal colon, whereas pelvic nerve stimulation causes tonic propulsive contractions in the distal colon. Stimulation of either the splanchnic or lumbar sympathetic nerves causes the colonic muscles to relax.

Plexuses of Auerbach, involved with colonic motility, and Meissner, associated with mucus secretion, have an integrated system enabling stimuli to be detected and the appropriate response produced. The muscle of the large intestine can be stimulated by stretching, and a number of chemical substances such as acetylcholine and histamine can cause contraction or enhance motility. Adrenaline and noradrenaline can depress smooth muscle activity.

The central nervous system (CNS) modifies many functions of the gastrointestinal tract. In cats, stimulation of the cerebrum, midbrain and hypothalamus increases colonic motility. The colon appears to receive impulses from the CNS and upper gastrointestinal tract via the spinal cord. This is supported by the association of thoracic spinal cord injury with intractable constipation[6]. If the proximal region of the colon is distended, contraction distally is inhibited by impulses passing along intermesenteric neurons between pre- and para- vertebral ganglia and then via splanchnic or lumbar colonic nerves. With extrinsic regulation the parasympathetic neurons appear to be excitatory and the sympathetics inhibitory in the musculature of the colon.

A number of hormones influence colonic motility. Gastrin can intensify contractions and may decrease the evacuation time of the colon. Cholecystokinin has been proposed as a mediator of the lipid generated increase in rectosigmoid motor activity. However infusion of cholecystokinin at physiological concentrations does not reproduce the complex milieu of events that occur postprandially. Neurotensin is present in the myenteric plexus and mucosa of the colon and may also play a part in the increase in colonic motility seen on ingestion of fat as the serum levels rise. Substance P appears to stimulate the circular smooth muscle, unlike progesterone, which acts an inhibitor of muscle contraction, thus perhaps accounting for some of the changes seen in colonic motility during the menstrual cycle and pregnancy. Secretin and glucagon also inhibit colonic motility. Despite the influence of

Table 7.1 Comparison of the environment in different parts of the gastrointestinal tract

Region	Length (m)	Surface Area (m^2)	pH	Residence Time	Micro-organisms
Oesophagus	0.3	0.02	6.8	>30 seconds	unknown
Stomach	0.2	0.2	1.8-2.5	1-5 hours	$\leq 10^2$
Duodenum	0.3	0.02	5-6.5	>5 minutes	$\leq 10^2$
Jejunum	3	100	6.9	1-2 hours	$\leq 10^2$
Ileum	4	100	7.6	2-3 hours	$\leq 10^7$
Colon	1.5	3	5.5-7.8	15-48 hours	$\leq 10^{11}$

hormonal and neural mechanisms on colonic motility, the major control for the transit of luminal contents is exerted by the smooth muscle itself.

Colonic environment

The colonic environment markedly differs from other parts of the gastrointestinal tract as illustrated in Table 7.1. The absorptive capacity of the colon is much less than that of the small intestine, due mainly to the reduced surface area. The mucosal surface of the colon is similar to that of the small intestine at birth, but rapidly changes by losing villi leaving a flat mucosa with deep crypts. As the gut ages there is a decrease in the number of non-goblet crypt cells and this is related to an increase in faecal water[7].

Water and electrolytes

The colon has a very high absorptive capacity; for every 2 litres of water entering the colon, the residual water in the stools will be less than 200 ml. The flow of chyme from the ileum to the colon in healthy human beings is 1–2 litres.h^{-1}. The colon is capable of absorbing up to 4 L of water per day and can withstand an infusion rate of 6 ml.min^{-1} before there is any increase in faecal water[8 9]. The large capacity of the colon to absorb fluid may, however, be overwhelmed by a large fluid input and unabsorbed solutes, such as bile acids, fatty acids, or carbohydrates can also impair this adaptive capacity, possibly resulting in diarrhoea. Absorption of water and sodium is negligible from the rectum. Solids are consolidated to 200–300g of wet material which is equivalent to 30–40 g of dry matter, which is mainly bacterial in origin but contains undigested organic matter and fibre.

The colon is responsible for the absorption of sodium ions, chloride ions and water from the lumen in exchange for bicarbonate and potassium ions. The absorption of sodium is an active process and involves its diffusion across the apical membrane of epithelial cells via water filled channels. Sodium absorption in the colon is enhanced by the hormone aldosterone. A sodium-potassium exchange pump system in the baso-lateral membrane then moves sodium against steep concentration (14 mM to 140 mM) and electrical (-30 mV to +20 mV) gradients into the intercellular space. This movement of sodium creates an osmotic gradient which causes a net movement of water from the colonic lumen via the epithelial cells, through the tight junctions between epithelial cells into the intercellular spaces.

In healthy individuals, approximately 10 mEq of potassium enters the colon each day whilst 5 to 15 mEq are lost in the faeces during the same time period. Potassium secretion is determined by the luminal concentration of potassium, with concentrations of below 15 mEq leading to net secretion. This is accomplished by passive movement of potassium ions along an electrochemical gradient from plasma to lumen, and is facilitated by the tight junctions between epithelial cells which are highly permeable to potassium ions. The

sodium-potassium pump in the basolateral membrane of epithelial cells creates a high intracellular potassium concentration (80 mM), of which only a small proportion is lost to the colonic lumen, since the apical epithelial membrane is essentially impermeable to potassium.

pH

Studies using a pH sensitive radiotelemetry capsule in normal, ambulatory volunteers have shown that the mean pH in the colonic lumen is 6.4 ± 0.6 in the ascending colon, 6.6±0.8 in the transverse colon and 7.0±0.7 in the descending colon[10].

Many factors such as disease, diet, pharmaceutical formulations or therapeutic agents may alter the pH or the difference in pH between the ascending and descending colon. For example, administration of the laxative disaccharide lactulose causes the production of large amounts of lactic acid by the caecal bacteria, acidifying the proximal colon to 5.5–5.0. Less pronounced decreases are produced by guar gum and isphagula. Evidence exists suggesting that there are substantial changes in gastrointestinal pH in patients with malabsorption due to cystic fibrosis and in ulcerative colitis the pH may drop below 5[11]. Current dosage forms designed for release in the proximal bowel employ enteric coatings, and are therefore dependent on luminal pH. Alteration of the pH profile of the gastrointestinal tract in various disease states may be an important factor influencing the bioavailability of drugs delivered in this form.

Bacteria

The gastrointestinal tract is sterile at birth, but colonization typically begins within a few hours of birth, starting in the small intestine and progressing caudally over a period of several days. In most circumstances, a "mature" microbial flora is established by 3 to 4 weeks of age. The colonic microflora contain up to 400 different species of both aerobic and anaerobic bacteria and make up approximately 30% of faecal dry weight. The most prevalent anaerobes are *Bacteroides* sp. and *Bifidobacterium* whilst the most numerous aerobes are *Escherichia coli,* enterococci and *Lactobacillus*. The major site of bacterial activity is the caecum where the anaerobic bacteria ferment substrates in a liquid mixture. The principal sources of nutrition for the bacteria are complex carbohydrates including starches, non-starch polysaccharides including dietary fibre (celluloses, gums and pectins) and smaller saccharides such as lactose, sorbitol and xylitol. It is thought that 2–20% of dietary starch escapes absorption in the small bowel. Synthesis of vitamin K by colonic bacteria provides a valuable supplement to dietary sources and makes clinical vitamin K deficiency rare.

Cellulose is a common constituent in the diet of many animals, including man, but no mammalian cell is known to produce a cellulase. Several species of bacteria in the large bowel synthesize cellulases and digest cellulose, and the major end products of digestion of this and other carbohydrates are volatile fatty acids, lactic acid, methane, hydrogen and carbon dioxide. Fermentation is thus the major source of intestinal gas. Volatile fatty acids (acetic, proprionic and butyric acids) generated from fermentation can be absorbed by passive diffusion in the colon and metabolised in the epithelial cells and liver. Short chain fatty acids remaining in the colon are neutralised by bicarbonate ions which are secreted into the lumen.

In man, the metabolic activity of the caecal bacteria can be demonstrated by ingestion of lactulose or baked beans which are fermented by the caecal bacteria, causing a rise in breath hydrogen. This is used as a method of estimating the time of mouth to caecal transit.

Colonic bacteria possess exocellular lipases which are able to hydrolyse fatty acid esters at the 1 and 3 positions of the triglyceride molecule. They also produce enzymes capable of metabolising long chain fatty acids. Approximately 25% of faecal fatty acids are hydroxylated by colonic bacteria, for example oleic acid is hydroxylated to form hydroxystearic acid. The presence of hydroxylated fatty acids in the colon has an inhibitory effect on colonic electrolyte and water transport, and at high concentrations they cause net secretion of water and electrolytes, which results in diarrhoea and therefore a significantly increased colonic transit rate. Infusion of oleic acid (4.3 g per 100 ml) into the mid-ascending colon accelerated colonic transit rate and defaecation when compared to a control infusion[12].

The microbial population exerts a profound effect on the structure and function of the digestive tract, as the morphology of the intestine of germ-free animals differs considerably from normal animals. Villi of the small intestine are remarkably regular, the rate of epithelial cell renewal is reduced and, as one would expect, the number and size of Peyer's patches is reduced. The caecum of germ-free rats is roughly 10 times the size of that in a conventional rat.

Colonic motility

Patterns of motility

The colon is an intermittently active organ and three patterns of motility are observed:

(i) segmental contractions which chop and mix the contents, increasing contact with the mucosa where absorption can occur.

(ii) antiperistaltic contractions which propagate toward the ileum. These serve to retard the movement of contents through the colon, allowing additional opportunity for absorption of water and electrolytes to occur. Peristaltic contractions, in addition to influx from the small intestine, facilitate movement of contents through the colon.

(iii) mass movements constitute a type of motility not seen elsewhere in the digestive tube. They are also known also as giant migrating contractions; this pattern of motility resembles a very intense and prolonged peristaltic contraction which strips an area of large intestine clear of contents.

Segmental activity consists of local contractions which are usually effected by circular muscle and lead to the mixing of luminal contents, whereas propulsive activity is largely due to contraction of longitudinal muscle. In the colon, the predominant activity is segmental, with the propulsive type of movement occurring infrequently (3–4 times daily in normals) (Table 7.2).

Table 7.2 Patterns of colonic motility[13]

Type of movement	Frequency of occurrence		Distance Travelled	Rate (cm. min)
	At rest %	Postprandial %		
Haustral shuttling	38	13	0	0
Haustral propulsion	36	57	5 - 10 cm	2.5
Haustral retropulsion	30	52	5 - 20 cm	2.5
Multihaustral propulsion	9	17	Variable	2.5 - 5
Peristalsis	6	8	18 - 20 cm	1 - 2
Mass	Rare	12	> 30 cm	5 – 35

Once food waste reaches the sigmoid colon, it remains there until it is ready to be excreted from the body. As the faecal material enters the rectum, the walls distend to accommodate it. When sufficient pressure occurs within the distended rectal cavity, the urge to eliminate wastes begins. When receptors of the nervous system within the rectal wall are stimulated by its stretching, they send impulses to the anal canal, chest and abdominal-wall muscles, and the medulla of the brain, which makes the individual conscious of the need to defaecate.

Electrical activity

Changes in the electrical potential of the smooth muscle coat are often used to assess gastrointestinal motility. Two types of electrical activity have been recorded in the colon i) slow wave activity and ii) spike potentials. The former consist of regular phasic depolarisations of the cell membrane which originate in the circular muscle layer of the transverse colon[14]. When compared with that of the stomach and small intestine, colonic slow wave activity is of low frequency and irregular. The slow wave pacemaker in the proximal or transverse colon maintains co-ordinated regular activity throughout the colon, and appears, at least in the cat, to migrate towards the caecum[15 16]. The retrograde propagation of slow waves in the proximal segment allows longer mucosal exposure for the intraluminal contents resulting in more complete absorption[17]. In man, the dominant slow wave frequency is 11 cycles per minute in the transverse and descending colon, slightly less in the caecum, ascending and sigmoid colon, whilst that in the rectum is the highest observed in the gastrointestinal tract at 17 cycles per min.

Spike potentials may be superimposed on the slow waves or may exist as bursts unrelated to slow wave activity, and are thought to initiate functional colonic contractions. Spike bursts of long duration (>10s) increase after eating and may increase luminal transit. Short duration spike bursts (<3.5s) are seen in patients with constipation and are not associated with movement of the intestinal contents. Such contractions only occur when the membrane potential rises above a prevailing threshold level which is set by both neural and humoral mechanisms.

Gastrocolic reflex

After eating, there is a rapid increase in spike and contractile activity in the colon[18–20]. The calorific content appears to have a more important effect on the degree of motility than the size or pH of the meal. Fat is a more important stimulant of motility than either carbohydrate or protein. Ingestion of fat alone produces both an early (10 to 40 min) and late (70 to 90 min) increase in colonic motility[19]. The late response can be abolished by the simultaneous ingestion of protein, and both responses are inhibited by the ingestion of amino acids. This colonic response to feeding is known as the gastrocolic reflex, and must be an integrated response to both fat and protein induced mediators. The gastrocolic response is initiated by a sensory receptor in the gastroduodenal mucosa[20].

Three components have been identified in the response of the colon to the ingestion of a meal: an initial cholinergic propulsive reflex, followed by a cholinergic segmenting reflex and finally a noradrenergic segmenting reflex[21]. Intravenous infusion of anticholinergic drugs prior to a meal abolishes the early colonic effects, thus supporting a cholinergic neural mechanism for mediation of the early response to eating. It is possible that there may also be a humoral component to this early response, in that the release of gastrointestinal hormones may be responsible for stimulating the cholinergic neural pathways. The late response, however, is unaffected by pre-treatment with anticholinergic drugs, thus implicating an essentially humoral pathway which may involve release of gastrin, cholecystokinin (CCK) or another gastrointestinal hormone. A postprandial

increase in gastrin levels has been observed and CCK is released from the duodenum in the presence of fat. CCK stimulates gall bladder contraction and increases motility in both the small intestine and colon. Gastrin, in the G17 short chain form, and CCK stimulate colonic motility at serum concentrations within the physiological range[22]. Intravenous and intraduodenal amino acids stimulate the release of pancreatic glucagon, which has been shown to be a potent inhibitor of colonic myoelectric and motor activity. Enkephalins, endogenous pentapeptides, have been implicated since the response to a meal can be blocked by naloxone, an opiate antagonist[20]. Met-enkephalin analogues inhibit colonic motility through a peripheral mechanism thought to involve the myenteric cholinergic plexus whereas leu-enkephalins stimulate motility through a centrally-acting mechanism[20 23].

Despite this almost immediate colonic motor response to eating in normal subjects, the right colon does not empty soon after a meal, although this phenomenon can be seen in patients with the irritable bowel syndrome[24]. Studies to elucidate this apparent anomaly have shown that non-propagating motor activity increases in all colonic segments immediately after eating a 1000 kcal meal. When propagating contractions do occur postprandially these are associated with a rapid movement of intraluminal contents[25]. The greatest increase in motor activity is seen in the descending colon[26] and this is often associated with retrograde movement of colonic contents from the descending to the transverse colon[25].

Defaecation

The characteristic brown colour of faeces is due to stercobilin and urobinin, both of which are produced by bacterial degradation of bilirubin. Faecal odour results from gases produced by bacterial metabolism, including skatole (3-methylindole), mercaptans, and hydrogen sulphide. In most individuals, dietary and social habits condition the time of defaecation. The majority of adults defaecate once a day, although frequencies from 2 per day to once every 2 days are considered normal.

Several times each day, mass movements push faeces into the rectum, which is usually empty. Distension of the rectum stimulates the defecation reflex. This is largely a spinal reflex mediated via the pelvic nerves, and results in reflex relaxation of the internal anal sphincter followed by voluntary relaxation of the external anal sphincter and defaecation. Colonic emptying occurs during defaecation, which is not only a process of rectal evacuation[27]. In humans and house-trained animals, defaecation can be prevented by voluntary constriction of the external sphincter. When this happens, the rectum soon relaxes and the internal sphincter again contracts, a state which persists until another bolus of faeces is forced into the rectum.

Physiological factors affecting colonic motility

Eating and morning awakening appear to be the major stimuli in eliciting colonic motility. There is also evidence that the menstrual cycle and pregnancy cause disturbances in gastrointestinal function. Transit is delayed in the luteal phase of the cycle, i.e. when serum progesterone levels are highest, and thus progesterone may depress colonic motility[28].

There are studies showing that no difference exists in colonic transit rates between men and women[29 30], whilst other studies have reported a prolonged colon transit in women[28 31 32]. A study aimed specifically to resolve this dispute has failed to find any difference in colonic transit of radiopaque markers in 10 women in the follicular phase, in 10 women in the luteal phase of the menstrual cycle, in 5 women on oral contraceptives and in 11 males[33]. A wide variation in stool weight exists between subjects on a standard diet and response to wheat fibre[34]. This variation is significantly related to sex but not to age, height or weight. Stool weight in men (162±11 g. day^{-1} mean±se) was approximately double

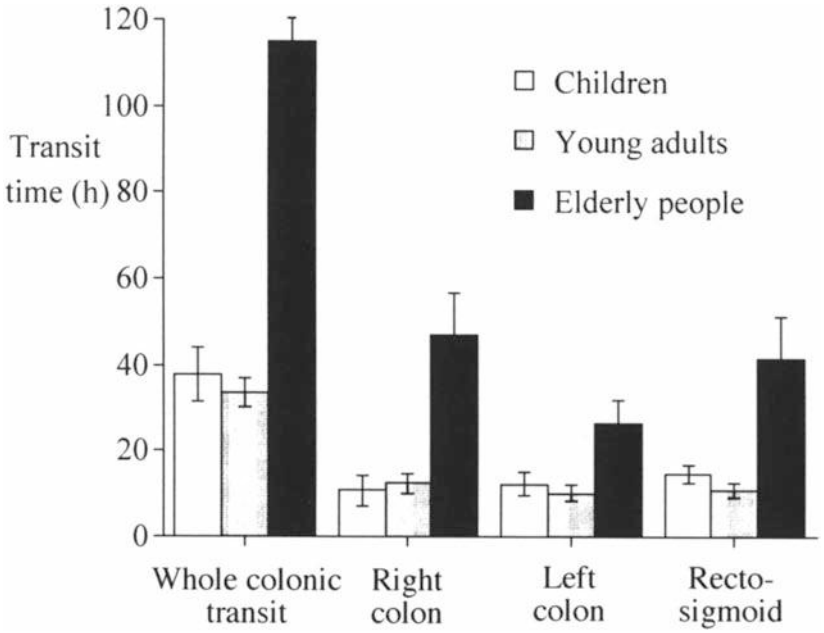

Figure 7.3 The effect of age on transit thriugh the colon

that in women (83±11 g. day^{-1} mean±se) and could be explained entirely by differences in transit. The increase in stool weight with fibre was significantly related to dose with approximately 1 g of non-starch polysaccharides (the main component of dietary fibre) increasing stool weight by 5 g per day. Smaller increases in stool weight were seen in females, persons with initially low stool weights and small people. Faecal pH was lower in men than in women and was related to methane production. Methane producers had higher faecal pH than non-producers (7.06 compared to 6.65), lower stool weight (93±12 g. day^{-1} compared to 156 ±13 g. day^{-1}) and slower transit times (84.6±11.7 h compared to 48.6±6.6 h). These studies show that, when on similar diets, women have much lower stool weights and slower transit times than men. Children appear to have similar colonic transit times to adults, although colonic transit is significantly delayed in the elderly (Figure 7.3).

The effect of stress on gastrointestinal transit remains controversial. Colonic motility can be increased by emotional stress[35]. It is generally recognized that abdominal pain increases and bowel function becomes irregular in patients with the irritable bowel syndrome in periods of emotional stress, and that the symptoms often improve as the anxiety diminishes.

Although exercise is often recommended as therapy for constipation, the relationship between gastrointestinal transit and exercise is unclear[36]. Certainly immobility leads to constipation, but increased exercise above the norm appears to have no effect. However, one study reported that moderate exercise decreases whole gut transit time from a mean of 51 hours to 37 hours when riding and 34 hours when jogging[37].

The effect of diet

Whole bowel transit time is generally between 24 and 36 hours in healthy individuals, but values ranging from 0.4 to 5 days have been reported in the literature[38 39]. Transit through

the large bowel is highly influenced by the pattern of daily activity. The highest calorie intake in the western world occurs in the evening and colonic motility decreases at night.

Dietary fibre in the form of bran and wholemeal bread, fruit and vegetables, increases faecal weight by acting as a substrate for colonic bacterial metabolism. This increased faecal bulk is associated with a reduced colonic transit time, although the mechanism is uncertain. In the healthy colon, an additional 20 g per day of bran increases faecal weight by 127% and decreases the mean transit time from 73±24 h to 43±7 h[40]. Not all fibres produce an equal effect on the colon, since the same quantity of fibre as cabbage, carrot or apple produced a smaller effect. The disparate effect of fibre provided as either rice bran or wheat bran was also demonstrated by a two-fold increase in faecal mass and stool frequency with rice bran over wheat bran, despite a similar accelerating effect on transit time with both types of fibre[41]. These differences almost certainly depend upon differing metabolism of the fibre by colonic bacteria.

Dietary fibre is either soluble and viscous, i.e. resistant starch, gums, mucilages and pectins, which amounts to approximately 30% of ingested fibre, or insoluble fibre such as cellulose. The relationship between bacterial degradation of fibre and the effect on faecal mass and whole gut transit time is complex. Three viscous polysaccharides, guar gum, ispaghula and xanthan gum varied in their responses to bacterial degradation *in vitro*[42]. Guar gum was rapidly fermented *in vitro* by faecal bacteria with concomitant loss of viscosity and reduction in pH; ispaghula maintained its viscosity during incubation, but the pH fell significantly, and xanthan gum incubations showed considerable individual variation. Faecal mass was increased only by ispaghula. Whole-gut transit time was reduced by gum feeding to a significantly greater extent in those subjects whose faecal bacteria reduced the viscosity of that gum, than in those subjects where the viscosity was maintained. The rate of proximal colonic transit is directly influenced by the presence and the metabolism of polysaccharides[43]. Using a lactulose-induced catharsis model of accelerated proximal colonic transit in healthy volunteers, ispaghula husk was found to significantly delay proximal colonic transit, whilst guar gum, being more rapidly degraded by bacterial metabolism, caused an accelerated proximal colonic transit (Figure 7.4).

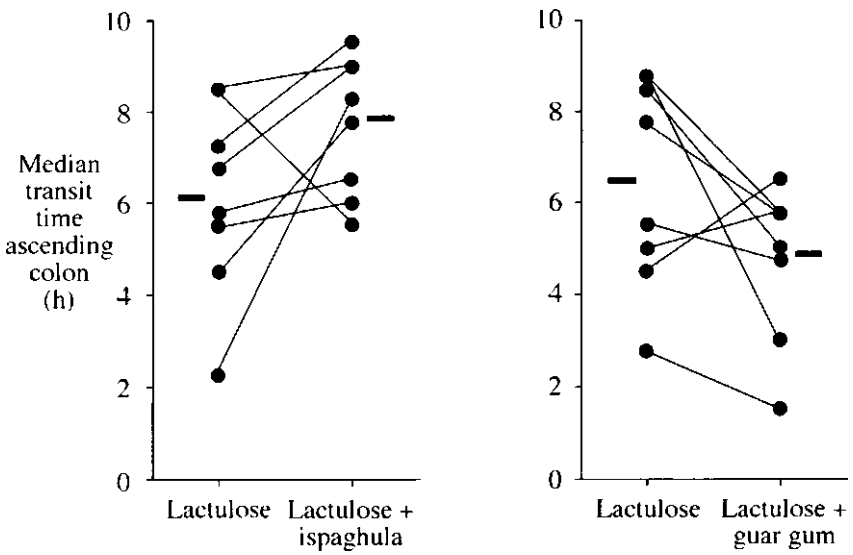

Figure 7.4 The effect of fibre on lactulose-induced catharsis

The diet of an individual is closely linked with the proliferation of the colonic mucosa. Food deprivation and "elemental diets' can result in intestinal atrophy and decreased cell production[44 45]. Refeeding of starved rats with a fibre-free elemental diet supplemented with fermentable fibre stimulates colonic and small intestinal epithelial cell proliferation, whilst the addition of inert bulk to the elemental diet has no such effect[46]. This proliferative effect of fermentable fibre on the gut epithelium was not observed in germ free rats, suggesting that epithelial proliferation is effected by the products of bacterial fermentation rather than the presence of fermentable fibre.

Colonic intraluminal pressure decreases after eating either wheatbran or cellulose[47], however, the physical characteristics of the dietary fibre may be important since coarse bran ingestion decreases colonic motility whereas ingestion of fine bran increases intracolonic pressure[48].

Normal constituents of the colonic lumen include some unmetabolised carbohydrate, protein and bile salts, but very little fat. A considerable amount of starch enters the colon to contribute further substrate for bacterial fermentation. Fermentation produces short-chain fatty acids (SCFA's), notably acetate, propionate and butyrate. SCFA's, whilst being normal constituents of the colon, are not found in the terminal ileum except under conditions of colo-ileal reflux. The effect of SCFA's on the ileum is to stimulate propulsive motility, causing the ileum to be emptied[49] and subsequent return of the SCFA's to the right colon where they aid water absorption. This reflux may be important in preventing bacterial overgrowth in the terminal ileum. Accumulation of SCFAs causes the pH to fall[50].

Long-chain fatty acids (LCFA's) should not normally reach of the colonic lumen and generally are only found in patients with fat malabsorption. LCFA's are cathartic, a fact which may further contribute to the lack of fat metabolism, and have been shown to stimulate unusual motor patterns; an emulsion of oleic acid infused into the ascending colon accelerated colonic transit by induction of high amplitude, prolonged, propagating pressure waves originating near the ileocaecal junction[12]. This was associated with a narrowing of the ascending colon with a reduced reservoir function and may be the mechanism by which diarrhoea is produced in patients with fat malabsorption.

Coffee produced an increase in the motility of distal colon within four minutes of ingestion of both regular and decaffeinated coffee in 8 responders, but not in 6 non-responders[51]. The increase in rectosigmoid motility lasted at least 30 minutes.

Influence of drugs

Although constipation is associated with a slow transit through the left colon in most patients, right colon transit is essentially normal. By contrast, accelerated proximal colonic transit is a common feature of many diseases and treatment is often designed to reduce the transit rate to allow sufficient absorption of nutrients and electrolytes. An increased intestinal transit time is associated with a decreased stool weight and bacterial mass[52].

Codeine phosphate or loperamide are commonly employed to produce a reduction in stool volume and correction of accelerated colonic transit in patients with diarrhoea[53]. These drugs exert their antidiarrhoeal effect through a change in the gastrointestinal motor function, leading to an increased capacitance of the proximal gut, and a delay in the passage of fluid through the gastrointestinal tract[54 55].

Morphine delays transit in the caecum and ascending colon, increases colonic capacitance and reduces bowel movements in man[56 57]. The potency of opiates may be due to their action to modulate the normal neural controls via the enkephalinergic neurones in the colon. The possible role of endogenous opioids has been explored using naloxone, an opiate receptor antagonist. This has been shown to cause an accelerated transit through the colon in cats and in man, but without increasing the number of bowel movements[56 58].

Loxiglumide is a specific and highly potent CCK-receptor antagonist which inhibits postprandial gall bladder contraction and causes an accelerated gastric emptying[59–61]. The effect of CCK-receptor antagonists on the colon is uncertain since loxiglumide shortens colonic transit time in healthy controls[61], but prolongs colonic transit time in patients with accelerated colonic transit.

Drug absorption from the colon

The transport pathways of the colon allow rapid and specific active bi-directional transport of ions across the epithelial layer. Unlike the small intestine, there are no documented active transporters for organic nutrients in the mature organ and, therefore, no chances for drug molecules to be absorbed in a piggy-back fashion[62]. The apparent lack of organic nutrient transporters may limit the potential for drug design with respect to carrier mediated transport across the colon, hence drug absorption is a consequence of the general properties and features of the colon. These include transmucosal and membrane potential differences and the bulk water absorption which may allow drug absorption via osmotic solvent drag.

Animal models suggest that sugars such as sucrose and glucose, and amino acids, are poorly absorbed from the adult colon[63 64], but the relevance to humans has to be demonstrated, since diet has a major effect on colonic physiology and these studies were carried out in the rat and horse. An *in vitro* study of the permeability of the rat colonic mucosa suggests that the colon excludes molecules on the basis of size and charge[65]. It has been calculated that the pore size is 2.3Å in the human colon compared to 8Å in the jejunum and 4Å in the ileum[66].

The dissociation of a drug at the absorption site will depend on the pH of the microclimate at the mucosal wall and not the pH of the bulk phase. It is estimated that the unstirred microclimate near the mucosal wall has a thickness or extent of about 840 μm[67]. The concentration of K^+ is lower in the microclimate than the luminal contents, and it is independent of bulk K^+ concentration.

The fluidity of the caecal and ascending colon is gradually reduced as the water is reabsorbed. The reduction in the water content means that there is less mixing in the bulk phase and therefore less access to the mucosal surface, along with less water available for drug dissolution. Gas bubbles present in the colon also will reduce contact of drug with the mucosa.

Some viscous soluble dietary fibres may increase the thickness of the unstirred water layer by reducing intraluminal mixing[68]. Dietary fibres such as pectin and chitosan have cation-exchange properties which may bind drug molecules. These physical factors will all act to slow drug absorption in the colon, with increasing effect as water is removed and the transport properties of the faecal mass are reduced.

DRUG DELIVERY

A wide range of colonic transit times must be taken into consideration during the design of drug delivery systems. Rapid transit will allow little time for the drug to be released before the dosage form is excreted, whilst prolonged colonic residence may result in the accumulation of drug from multiple doses.

After the hepatic flexure, the consolidation of faecal matter gradually increases the viscosity of the luminal contents. This results in increasing difficulty of drug diffusion to the absorbing membrane. Only the ascending colon is sufficiently fluid to present a favourable environment for drug absorption. Absorption of even the most water-soluble drugs is reduced after the mid-transverse colon, due to the lack of water. For example, ciprofloxacin demonstrates a clear reduction in drug uptake with a more distal delivery[69]. On rare

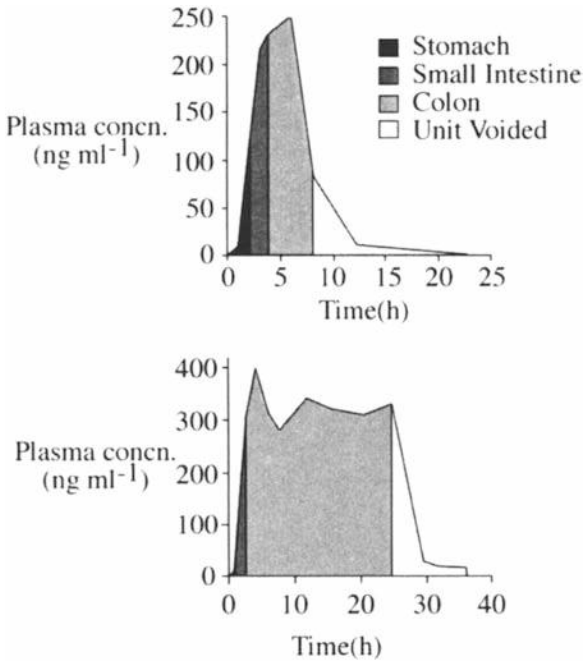

Figure 7.5 Plasma concentration-time profiles for oxprenolol delivered from an Oros® device in an individual with a short (top diagram) and long (bottom diagram) colon transit time

occasions, drug absorption can be seen from the distal regions due to the drug affecting the fluidity of the contents of the transverse and descending colon.

Current knowledge suggests that it is possible to optimise delivery systems for topical release of drugs to the colon, since transit through the small intestine is relatively predictable and independent of diet. The major problems for colonic absorption are reduced surface area, wider lumen, sluggish movement, low volume of available dissolution fluid and the reduced permeability of the colonic epithelium to polar compounds. Thus it would be expected that the absorption of most drugs from the colon would be slower than from the small intestine. This is balanced by the slower transit through the colon. The potential of the colon as an area for drug absorption is illustrated in Figure 7.5, which shows the plasma concentration-time profiles of oxprenolol delivered in an Oros® device for two individuals with differing colonic transit times. The effect of the extended colon residence on the plasma drug concentration is clearly illustrated. An additional advantage for colonic delivery may lie in the much lower activity of proteinases in the colon, which is 20–60 fold less than in the small intestine, suggesting that absorption of labile peptides might be possible. Achieving therapeutically relevant doses of proteins and peptides when administered via the colon still remains a major challenge.

Transit

The data available concerning movement of material through the colon was previously confined to measurements of whole gut transit time, However, gamma scintigraphy now enables transit to be followed in each section of the colon (Table 7.3).

Table 7.3 Colonic transit of single unit dose forms

Time of dosing	Morning	Morning	Morning	Evening
	Fasted	Light Breakfast	Heavy Breakfast	
Ascending colon	3.6 ± 1.2	2.48 ± 1.45	4.8 ± 3.9	8.9 ± 4.34
Transverse colon	5.8 ± 2.9	-	-	11.25 ± 3.24

There is a large variability in the data, but in general, units administered prior to retiring for the night have a slower colonic transit than those dosed in the morning, which is in keeping with the suppressed electrical and contractile activity[70–73], and decreased tone in the colon overnight[74]. There are conflicting values in the literature for the average transit time from caecum to splenic flexure; in one study it was reported to be 14 hours[31]; however another study reported that 50% of large units reach the splenic flexure within 7 hours of entering the colon, and the size and density of such units had little effect on the transit times[75]. Steady state experiments, conducted by repeated daily administrations of technetium-99m labelled resin, demonstrate that the transverse colon remains relatively empty during the day.

Studies examining the transit of different sized particles through the colon have suggested that large objects move more rapidly than smaller ones. In a study on a limited number of healthy volunteers (n=6), a pressure sensitive radiotelemetry device (25×9 mm) was seen to move ahead of dispersed pellets (0.5–1.8 mm) in the ascending and transverse colon (Figure 7.6)[76]. Similarly a tendency for transit rates to increase with increasing unit volume (0.3 to 0.8 to 1.8 $cm^{3)}$ has also been demonstrated[75]. Differential transit rates have also been noted between 0.5–1.8 mm pellets and 6 mm plastic markers[77]. In contrast, others have found no difference in the passage of 0.2mm and 5mm particles[78] or between 0.2mm, 5mm, and 8.4mm particles[79] through the ascending colon. Interestingly, in this latter study, there was a trend towards a shorter residence time within the ascending colon for 0.2mm

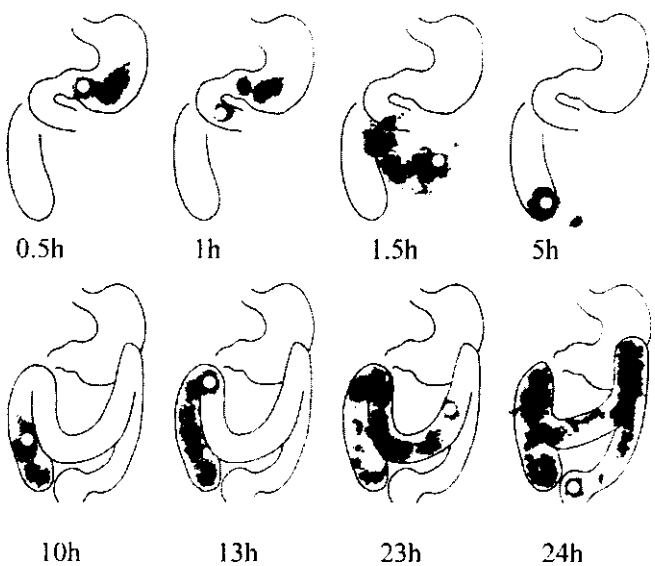

Figure 7.6 Transit of a large non-disintegrating unit and pellets through the gastrointestinal tract—a scintigraphic study

compared to 5mm particles, which became significant following laxative administration. Selective retention of small particles is known as colonic sieving and may be important in drug delivery, although the upper cut-off size limit for retention of particles has yet to be established. The sieving behaviour in disorders such as ulcerative colitis, where the degree of haustration is reduced, may influence the upper size limit for retention.

If units become too large, they can have prolonged transit due to periods of stasis at the ileo-caecal junction, hepatic and splenic flexures. Care should be taken when using large rigid units to study drug absorption from the colon, since an unphysiologically long colonic transit time would suggest an erroneously long time for drug absorption. The absorption times would then be significantly reduced when the drug was administered in a more normally sized dosage form.

The sieving effect causes dispersible dosage forms such as pellets to become widely distributed in the colon, whilst large single units or fragments of tablets travel rapidly through the colon ahead of the smaller pellets (Figure 7.7). This phenomenon is related to the observation that batches of markers of increasing sizes given with successive meals become interdispersed within the large intestine[80] which could be explained by the larger particles moving fastest. In the descending colon, the particles come together before defaecation. This data suggests that optimisation of drug delivery to the proximal colon may be achieved with a multiparticulate preparation which remains intact for approximately the first 5 hours after administration to the fasted patient. This would allow time for gastric emptying and transit through the small intestine. The drug preparation should then disperse allowing release of the material over the following 10 to 12 hours in the ascending and transverse colon. Extending the release profile over a longer period would not be an added advantage due to the variability of excretion patterns and the slower diffusion through consolidating faecal material.

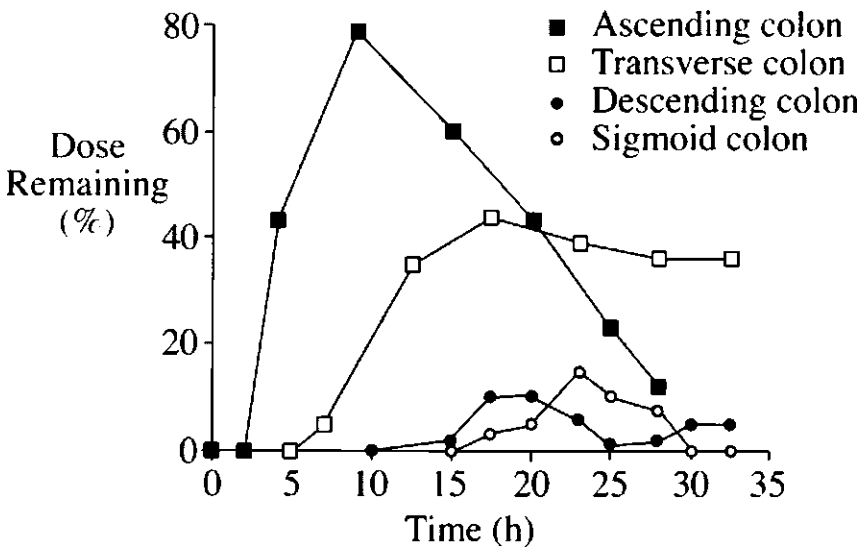

Figure 7.7 Distribution of pellets within the colon following pulse release at the ileocaecal junction

Dietary factors

Diet, in particular dietary fibre, could play a significant role in the absorption of drugs from the colon. Individuals ingesting a vegetarian diet or taking stool bulking agents may possibly show a difference in colonic drug absorption when compared with individuals ingesting a relatively low fibre diet. However, increased dietary fibre leads to decreased gastrointestinal transit times, which may offset any absorptive benefit gained by increasing the mucosal surface area in the colon[81]. Since fibre alters the transit through the colon it would be expected to have the greatest influence on the absorption of drugs from sustained release preparations. In young vegetarians the mouth to anus transit of a single unit can be less than 6 hours, indeed, for one "normal" subject, the total transit time was 2 hours (Washington et al, unpublished observation).

Temporal factors

Once-a-day dosing for a sustained release medication is usually taken to mean administration in the morning, and for a typical individual, housekeeper sequences clear the stomach of material by 1100 hours. The formulation would then arrive in the ascending colon by 1300–1400 hours. Intake of a light lunch will increase colonic motility via activation of the gastrocolic reflex. This has the effect of shortening the time of contact with the ascending colon. If the same once-a-day medication is administered between 1600 and 1700 hours, the unit will leave the stomach before the main meal at night and will be in the ascending colon by the time the patient has retired to bed. At night, the motility of the ascending colon will become quiescent. Motility increases in the first 30 minutes after waking, with the initiation of high amplitude contractions. In the majority of the population, this is causes an urge to void, and the colonic activity moves the contents of the proximal region to the distal colon. Consequently, afternoon dosing results in prolonged contact with the proximal colon compared to morning dosing.

Targeting the proximal colon

The proximal colon is relatively inaccessible. Even large volume enemas will only just reach the transverse colon[82]. Any substance administered orally has to pass through the hostile environment of the stomach and through the small intestine where it is likely to be digested and absorbed. Protecting the drug from these factors and releasing it at the base of the ascending colon to optimise colonic exposure has been the subject of much research.

Several approaches have been expored to achieve site specific delivery to the colon. These most commonly include:

i) utilizing the pH change which occurs on transit from the small to the large intestine[83]
ii) providing release of a drug after a pre-determined time[84–86]
iii) colon-targeting lectins[87]
iv) utilizing degradation mechanisms of bacteria specific to the colon[88 89]

pH

Eudragit and other enteric coatings are widely used to produce acid resistant formulations, and with appropriate control of dissolution time may be reasonably effective in achieving release of drug in the ascending colon. For colonic delivery, Eudragits L and S, which are anionic copolymers of methacrylic acid and methyl methacrylate, have been widely used. These polymers are insoluble at low pH but form salts and dissolve above pH 6 and 7, respectively. Eudragit L100–55, a copolymer of methacrylic acid and ethyl acrylate, is water soluble which avoids the need for organic solvents in the coating process[90].

The first study which employed Eudragit S for colon-targeting used sulphapyridine as a marker for drug release[84]. Hard gelatin capsules containing the drug, and barium sulphate to aid radiological visualisation, were coated with the polymer and administered to 6 subjects who each swallowed 6 capsules. Twelve hours after administration, 4 capsules had broken in the distal ileum, 23 in the colon and 9 remained intact. The same approach was used with 5-aminosalicylic acid (5-ASA) but the thickness of the polymer coating was reduced from 120 to 80 μm[91]. This formed the basis of the commercial formulation of 5-ASA tablet. There has been at least one report of patients taking 5-ASA and reporting the transit of intact tablets in their stools. This is probably a result of the high pH at which the Eudragit S-based coatings dissolve.

The study of Eudragit S coated tablets (10 mm diameter) in 7 volunteer subjects using gamma scintigraphy yielded some interesting results[92]. In some subjects, stasis at the ileocaecal junction was noted. Other subjects had rapid transit through the colon, leading the authors to speculate whether the variability in transit meant that a pH-based coating was an unreliable means of delivery to the colon.

Recently the potential for pH-sensitive dextran hydrogels to be used as colon-specific delivery systems has been investigated *in vitro*[93 94].

Time

The constancy of transit of dosage forms through the small intestine has been well established. It has been speculated that if a unit could be timed to release drug around four hours after leaving the stomach, the unit should be at the base of the ascending colon at the time of drug release. Approaches to achieve targeted colonic delivery based on hydrogel technology, exemplified by the Pulsincap™ delivery system (Figure 7.8), appear to largely succeed. The Pulsincap comprises an impermeable capsule body containing the drug formulation, sealed at the neck edge with a hydrogel polymer plug[95]. On ingestion, the capsule becomes exposed to gastric fluids and the water soluble gelatin cap dissolves, allowing the hydrogel plug to hydrate. At a pre-determined and controlled time point after ingestion, the swollen plug is ejected from the capsule body thereby enabling the drug formulation to be released. The time of plug ejection is controlled by the length of the hydrogel plug and its position relative to the neck of the capsule body.

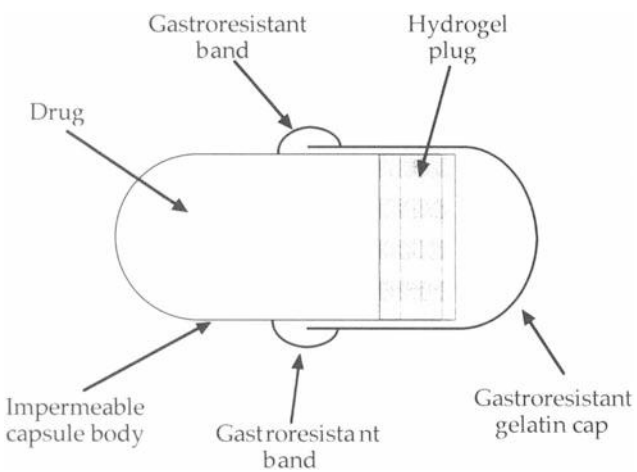

Figure 7.8 Enteric-coated Pulsincap™ dosage form

Other devices employing time-dependent erosion have been utilized; for example a system termed the 'Time Clock' is composed of a solid core coated with a mixture of hydrophobic material (waxes), surfactant, and water-soluble polymer (HPMC). The coating is designed to slowly erode away and after a predetermined interval the drug is released. Another approach is to use a dosage form coated with an outer enteric polymer and an inner layer of HPMC. The outer layer dissolves exposing the inner layer of HPMC, which gels and slowly erodes away. When erosion has reached a critical level, the drug is released from the inner core of the dosage form.

Finally, a variant of the osmotic pump has been patented which provides colon-specific drug delivery. The enteric-coated pump is activated on leaving the stomach. A drug-free layer adjacent to the delivery port exhausts over the first 3–4 hr following activation. The units then begin to release drug within the colon.

Bioadhesives

Lectins from fruits and vegetables have emerged as possible candidates for site-specific bioadhesion. They are readily available and, with the exception of kidney bean lectin, are considered non-toxic. The majority of studies have been conducted with lectins from *Lycopersicon esculentum,* the tomato, since these are resistant to intraluminal digestion and do not change the integrity of the cell upon binding[96]. Lectins show potential for uptake by endocytosis; however the amount that reaches the blood stream is minimal as they may accumulate in the interior of the cell. The specificity of lectin-based systems to target the colon has yet to be demonstrated.

Bacterially triggered systems

Sulphasalazine (salicylazosulphapyridine) was one of the earliest prodrugs used in the treatment of inflammatory bowel disease. It contains 5-aminosalicyclic acid (mesalazine) linked covalently to sulphapyridine. 5-aminosalicyclic acid (5-ASA) is not effective orally because it is poorly absorbed, and is inactivated before reaching the lower intestine; therefore prior to its administration as a prodrug, its was only effective when given as a suppository or a rectal suspension enema. The prodrug sulphasalazine is similarly poorly absorbed after oral administration, but it is reduced to its active components by bacterial azoreductase in the colon. Additional prodrugs which rely on bacterial activation have also been introduced, including olsalazine (sodium azodisalicylate, a dimer of 5-aminosalicylate linked by an azo bond), ipsalazine (5-ASA:p-aminohippurate) and balsalazine (5-ASA:4-amino benzoylglycine) (Figure 7.9).

Bacterial metabolism includes enzymatic systems unique to a small region of the bowel, the most widely investigated being the bacterial azoreductase system, and several polymers have been devised which should be degraded by these enzymes. Hydrogels based on acrylic acid, N, N-dimethylacrylamide and N-terbutyl-acrylamide cross-linked with azoaromatic groups show pH-dependent swelling. At low pH the polymer does not swell. As it passes out of the stomach into the higher pH of the small intestine swelling occurs and, on reaching the colon, the hydrogel becomes sufficiently swollen to allow access to bacterial azoreductase. However, *in vitro* studies suggest that the polymer swelling is too slow to be successful *in vivo*. Alternative approaches have been described using azo-polymers containing different ratios of methylmethacrylate and hydroxyethyl methacrylate (HEMA)[97,98]. Hydrophilic polymers, those with a high HEMA content, showed the greatest susceptibility to colonic degradation. It was concluded that a balance needed to be achieved between hydrophilicity, to ensure effective reduction, and hydrophobicity, to provide adequate resistance to gastric and intestinal fluid. Early data suggested that oral delivery of

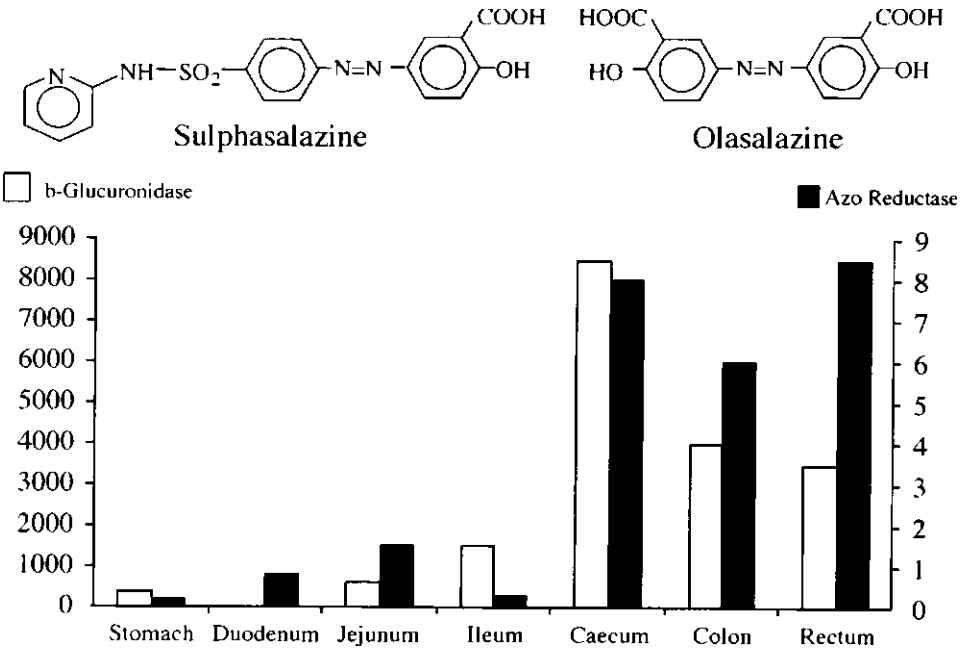

Figure 7.9 Azo prodrugs and enzyme activity in the gastrointestinal tract

peptides such as vasopressin and even insulin was possible using these polymers to protect the peptide[99] although later investigations with these materials were less successful.

Concentrated senna extract contains anthracene derivatives in the form of glycosides which can be hydrolysed to anthraquinones, anthranols and oxanthrones. When sennosides are delivered directly to the colon no laxative activity occurs, but incubation of the compound with faeces or *E. coli* liberates free anthraquinones which promote peristalsis. More recently, drug glycosides have been synthesized and tested for their ability to deliver drugs, such as glucocorticosteroids and spasmolytic agents, to the large intestine. Glucuronide prodrugs of the budesonide and menthol have been tested in animal models with promising results[100].

Complex carbohydrates are metabolized by caecal bacteria, hence matrices and coatings based on pectin, guar gum and starch have received extensive study for colon specific delivery systems[101 102]. Guar gum, locust bean gum, tragacanth, and xylan have been mixed with methacrylate copolymers (Eudragit O) and used to coat tablets. The beta-1,4- or alpha-1, 6-glycosidic links in locust bean galactomannan and dextran are biodegraded quickly in the human colon, but these carbohydrates are quite water-soluble and they must be transformed into insoluble derivatives[103]. Cyclodextrins are fermented to small saccharides by colonic microflora, whereas they are only slightly hydrolyzable and thus are not easily absorbed in the stomach and small intestine[104].

Pectin and calcium pectate have been evaluated by several groups as colon-specific coatings and matrices[105–107]. Tablets prepared from calcium pectate mixed with indomethacin were compressed into tablets and the release of drug was evaluated *in vitro*[108]. Under controlled conditions, release of indomethacin into pH 7 buffer was minimal (<10% after 24 h). Adding caecal contents from rats that had been induced to produce pectinolytic enzymes to the dissolution medium resulted in a significant increase in indomethacin release (approximately 60% after 24 h). Similarly, a dissolution experiment in the presence of a

Table 7.4 Bacterial metabolism of some drugs

Enzyme	Micro-organism	Example of metabolic reaction
Nitroreductase	*Bacteriodes sp.*	Reduction of aromatic and heterocyclic nitrocompounds
Azoreductase	*Clostridia, lactobaccilli*	Reductive scission of azo-bonds
Sulphoxide reductase	*E. coli*	Removal of oxygen from sulphoxides
Glucosidase	*Strep. Faecalis, eubacteria*	Hydrolysis of β-glycosides
Glucuronidase	*E. coli A. aerogenes*	Hydrolysis of β-gluronides of phenols and alcohols
Sulphatase	*Streptococci, cloistridia*	Cleavage of O-sulphates
Amdases & Esterases	*Enerobacter sp.*	Hydrolysis of amides or esters of carboxylic acids

bacterium able to hydrolyze pectin resulted in a significant increase in indomethacin release, although the total amount released after 6 h was only about 20%.

Bacterial degradation of drug

Once a drug has been released into the colonic lumen it is possible for it to be metabolised by colonic bacteria, which may result in the release of toxic products or the metabolism of the active drug to an inactive metabolite. For example, the bioavailability of digoxin from a delayed release formulation is reduced when compared with its bioavailability from conventional formulations, due to its degradation by colonic bacteria to the inactive dihydro-digoxin[109].

Drugs such as stilboestrol, morphine and indomethacin are excreted in the bile as inactive sulphate or glucuronic acid conjugates. These conjugates are metabolized by bacterial enzymes (Table 7.4) to release the active form of the drug, which can then be reabsorbed and prolong pharmacological action.

Effect of disease and co-medication on colonic drug absorption

Gastrointestinal diseases are known to have a significant effect on the absorption of some orally administered drugs. Enteric coated formulations designed for release in the colon have been shown to release their contents in the stomach of achlorhydric patients. Such patients may have bacterial overgrowth in the small intestine which could lead to the premature release of drugs such as sulphasalazine or sennosides, thus rendering the therapy ineffective, as the drug would be absorbed before reaching the colon.

Increased permeability of the mucosal lining, allowing entry of microbial or dietary antigens, has been proposed as a possible cause in the pathophysiology of chronic inflammatory bowel disease. Interestingly, in Crohn's disease of the colon, there is abnormal permeability in apparently uninvolved proximal small intestine as well as in the colon[110]. Patients with Crohn's disease are subject to gastrointestinal strictures where a controlled release matrix may lodge and cause epithelial damage due to the release of concentrated drug at one site over a prolonged period of time[111].

Normal subjects have rapid diffuse spread of water soluble radioisotopes through the colon, with the majority of activity being lost to faeces after 24 h[112]. In patients with intractable constipation, some will show normal transit, but in those with colonic inertia the major site of isotope hold-up is the transverse colon and splenic flexure. Other constipated patients show delay of label at a later stage and accumulation of activity in the descending and rectosigmoid colon. Diarrhoea causes changes in the electrolyte and water content of

the colonic lumen which therefore alters luminal pH, resulting in changes in the rate of absorption of drugs from the lumen. As a result the effectiveness of colonic delivery may be unpredictable in patients with constipation or diarrhoea. The increased rate of transit would also be responsible for the premature voiding of sustained release formulations, and would also be expected to alter the sieving function of the colon. Diarrhoeal diseases are known to cause decreased gut transit time, and hence incomplete metabolism, of pro-drugs such as sulphasalazine. To date, however, little detailed information exists in the literature concerning the effect of motility disorders on colonic delivery.

RECTAL ADMINISTRATION OF DRUGS

The rectal route of drug administration offers several advantages, including

a) a relatively large dosage form can be accommodated in the rectum
b) the rectal route is safe and convenient for elderly and young patients
c) drug dilution is minimized as the residual fluid volume is low
d) the rectum is generally empty
e) absorption adjuvants have a more pronounced effect than in the upper gastrointestinal tract
f) degradative enzymes in the rectal lumen are at relatively low concentrations
g) therapy can easily be discontinued
h) first-pass elimination of drug by the liver is partly avoided

The rectal route is often used when administration of dosage forms by mouth is inappropriate, for example, in the presence of nausea and vomiting, in unconscious patients, if upper gastrointestinal disease is present which could affect the absorption of the drug, or if the drug is unpleasant tasting or acid-labile.

Drug absorption and avoidance of first-pass metabolism

Several factors have to be overcome for a drug to be absorbed after rectal administration. If the drug is administered as a suppository, melting or liquefaction of the base has to occur and the degree of this will partly determine the spreading of the dose through the rectum. The drug must then dissolve in the limited rectal fluid available, which has been estimated to be between 1 and 3 ml. The amount of drug available for absorption can be further reduced by degradation by luminal contents, adsorption to luminal contents and defaecation. The drug must then diffuse across the unstirred water and mucous layers adjacent to the epithelium.

Drugs may be absorbed across the epithelial cell or via tight junctions, and it is believed that only passive transport occurs. Venous return from the colon and upper rectum is via the portal vein to the liver. If a drug is delivered to the upper part of the rectum, it is transported into the portal system (Figure 7.10), and is therefore subject to first pass metabolism in the liver. The only way of avoiding first-pass metabolism is to deliver the drug to the lower part of the rectum. This simple principle is complicated by the presence of anastomoses which do not allow a precise definition of the areas which drain to the portal and systemic circulation. A 100% increase in the availability of lignocaine was demonstrated when administered rectally rather than orally, and it was calculated that the mean fraction of the rectally administered dose escaping first-pass metabolism was 57%[113]. Other drugs with high first pass metabolism, such as salicylamide and propranolol, did not demonstrate as large an increase in bioavailability when administered rectally. However, this may be due to incomplete absorption since these drugs exhibited a much larger bioavailability when administered rectally rather than orally to rats[114].

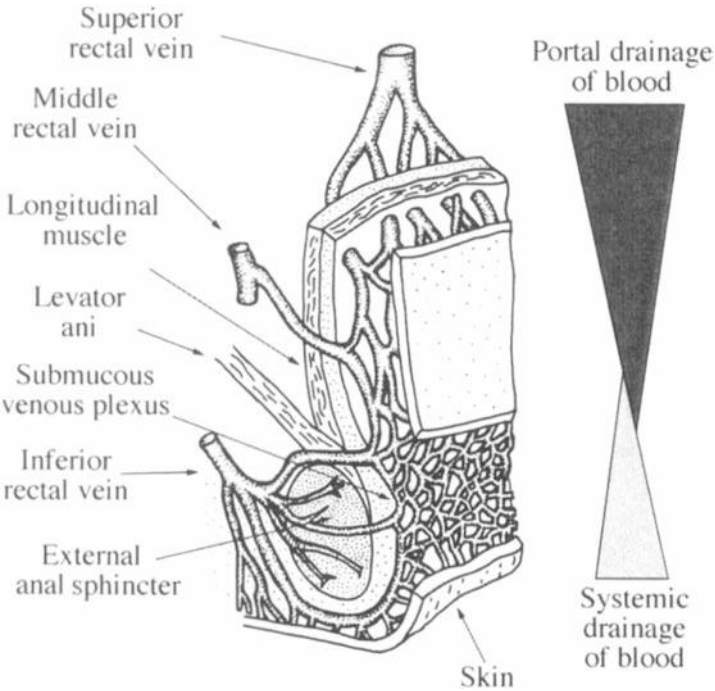

Figure 7.10 Structure and perfusion of the rectum

Dosage forms for rectal delivery

Drugs can be administered in several formulations via the rectal route. Suppositories are normally either solid suspensions or solid emulsions, whereas rectally administered gelatin capsules can contain liquid formulations. Micro-enemas have a volume of between 1 and 20 ml, and macro enemas 50 ml or more, both of which may be administered as either solutions or suspensions. The suspension suppository is the most widely used formulation, and it has been demonstrated that the release characteristics are dependent upon physiological factors, physicochemical properties of the drug, the suppository base and local environment within the rectum. In general, aqueous solutions of drugs are absorbed more quickly from the rectal route than the oral route, but absorption is usually slower with non-aqueous formulations, due to the limited amount of water available for drug dissolution.

There has been some work exploring the use of controlled release to the rectum, to achieve prolonged and sustained drug delivery. The studies were performed using an osmotically driven device with zero-order release characteristics. It appears to be a promising delivery system for drugs such as nifedipine which effectively reduced blood pressure without the unwanted side effect of increased heart rate[115]. Hydrogel systems with near zero-order delivery have also been used to deliver morphine intrarectally[116].

Adjuvants and enhancers

Transport from the rectal epithelium primarily involves two transport processes: paracellular and transcellular routes. As in other parts of the gut, the opening of tight junctions by absorption enhancers has been extensively investigated. Putative enhancers include enamine derivatives, salicylates, calmodulin inhibitors, surfactants, chelating agents, fatty acids and lectins. It is generally agreed that the rectum is potentially an important route

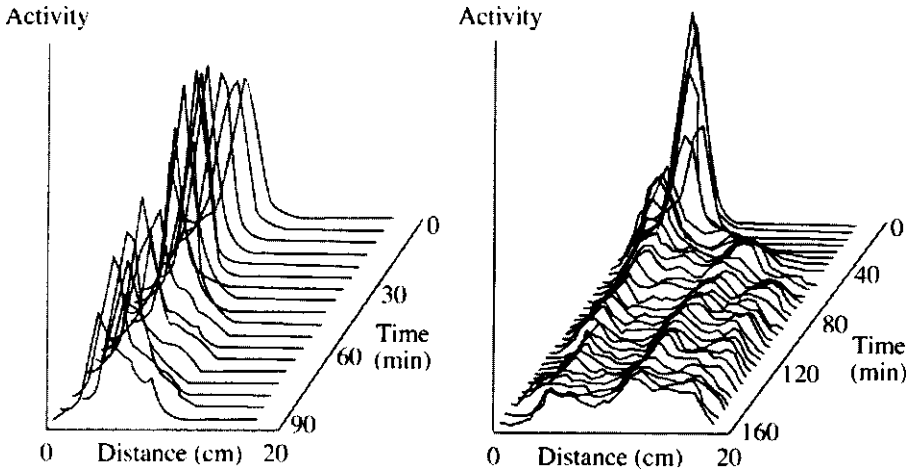

Figure 7.11 Spreading of a Witepsol suppository expressed as activity-distance plots as a function of time without (left) and with neostigmine (right)

for peptide absorption, although enhancers would be required to increase flux through this region. For example, bioavailability of a small peptide such as vasopressin is increased to nearly 30% in the presence of sodium taurodihydrofusidate. It should always be borne in mind that the enhancement via the paracellular route is non-selective, with the risk of absorption of bacterial endotoxins caused by lysis of bacterial cell walls.

Spreading of rectal dosage forms

In order to treat the colon via the rectal route, rather than simply aiming for rectal absorption, the preparation must spread efficiently. This limits topical treatment of the colon to areas distal to the splenic flexure. A number of attempts have been made to increase penetration through the use of novel formulations, using scintigraphy to evaluate the distribution of the formulation.

Tukker et al studied the spreading of suppositories and the effect of added surfactant (Witepsol H-15) in recumbent dogs[117]. The addition of surfactants markedly increased the penetration into the colon. Similarly pre-administration of neostigmine, which increases colonic motility, markedly increased the spreading of the suppository (Figure 7.11).

The spreading behaviour of suppository bases and incorporated suspensions has also been studied in humans[118]. The bases, Witepsol H15 and Labrafil WL2514 were labelled by the incorporation of small amounts of iodine-123 labelled oily markers (arachis oil and Labrafil WL2700 respectively). The suspension consisted of micronized cationic exchange resin incorporated throughout the base at a disperse phase loading of 10% w/v. Most of the spreading of both base and suspension occurred in the first hour after administration, and the area of spreading was small, with a maximum of 8 to 10 cm. The time from defaecation to administration of the suppository appeared to affect the degree of spreading, with the greatest spreading occurring when defaecation occurred immediately prior to dosing[119].

Disease activity in ulcerative colitis had no effect on the spreading behaviour of different volumes of mesalazine enemas, but the adminstered volume had a significant effect[120]. A 30 ml enema remained mainly in the sigmoid colon (99%), a 60 ml enema was distributed through the rectum (9%), the sigmoid (61%) and the descending colon (15%) and a 100 ml enema was distributed between the sigmoid (66%) and descending colon

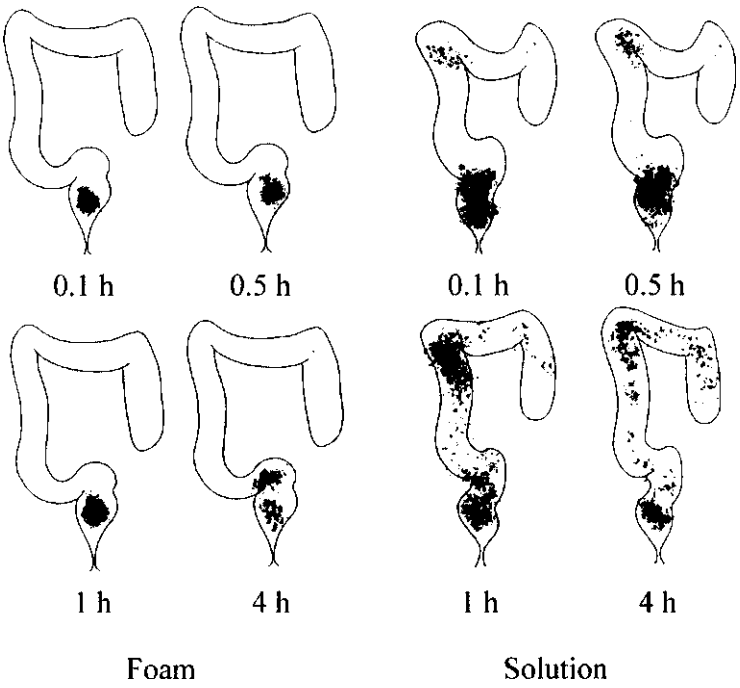

Figure 7.12 Spreading of liquid and foam enema after rectal administration

(25%). Consequently it appears that increasing the administered volume causes the dose to spread more effectively into the colon.

In an attempt to increase the penetration of small volumes of liquid, foam enemas have been studied[121]. However retrograde spreading of foams was lower than solution enemas, being limited to the sigmoid colon (Figure 7.12).

Therapeutic agents administered rectally

Anticonvulsants

Traditionally the need for rapid attainment of a therapeutic blood concentration of a drug has meant that intravenous drug delivery has been the only method available for the treatment of status epilepticus or serial seizures. However, the technical problems associated with intravenous administration have prompted the evaluation of rectal dosage forms as a practical alternative.

Diazepam is rapidly absorbed from rectally delivered solution in propylene glycolwater-ethanol in healthy volunteers[122]. Suppository formulations of diazepam appear to be effective and safe in the prevention of recurrent febrile convulsions in children, suggesting that formulations with non-instantaneous release may be adequate for prophylactic therapy[123]. In adult epileptic patients, 10mg of diazepam in 2ml of an intravenous solution was administered rectally, and this resulted in serum concentrations comparable with those obtained after oral administration of a 10mg tablet; absolute rectal bioavailability amounted to 81%[124]. 'Valium' suppositories however have a bioavailability of just less than 70%, but have a very slow rate of absorption, with a T_{max} ranging from 90 to 480 mins[125].

Clonazepam, rectally administered as a suspension in 2.2 to 3.8ml of a propylene glycol-water mixture, also containing acetic acid, ethanol and benzylalcohol (Rivotril)

demonstrated rapid absorption. However, the intersubject variability was substantial. Sodium valproate is completely, although not rapidly, absorbed from an aqueous microenema (T_{max}=2.2h) in healthy volunteers, whereas the absorption from a Witepsol H15 suppository was lower (T_{max}=3.3h, bioavailability 89%). The rectal bioavailabilitv of sodium valproate appears to be better than that of enteric coated tablets which are erratically absorbed.

Rectal absorption of phenobarbital and its sodium salt from aqueous microenemas and suppositories is relatively slow[126]. The sodium salt, dissolved in a vehicle containing 10% alcohol and 75% propylene glycol, resulted in a rectal bioavailability of 90% relative to intramuscular administration. However, rectal absorption was delayed compared to intramuscular delivery (T_{max}=4.4 h compared to 2.1 h). Consequently, this formulation could be considered as an alternative to intramuscular injection, but is not appropriate for the treatment of status epilepticus.

An aqueous suspension of carbamazepine, which also contained propylene glycol, sorbitol and sucrose, resulted in slow absorption of carbamazepine at a dose of 400 to 600mg, with a mean T_{max} of 6.3 h and C_{max} of 5.1 mg.L^{-1}. This can probably be explained by the poor water solubility of the compound. The bioavailability was 80% and 67% relative to oral tablets and oral suspensions respectively. Hence the rectal suspension was useful in maintaining administration in case of interrupted oral therapy. Unfortunately it was highlv irritant, indicating the need to optimise the formulation[127]. An aqueous suspension of 200 mg of carbamazepine containing 30% sorbitol showed a rectal bioavailability of 80% relative to the same suspension delivered orallv[128]. However, this formulation was difficult to retain, possibly because of a laxative effect of sorbitol.

Preopemtive medication and induction of anaesthesia

Preoperative medication is usually administered parenterally; however a more acceptable delivery route, particularly for children, is being sought. Rectal administration of midazolam produced a satisfactory sedative action 30 minutes after administration in children[129]. Rectal instillation of a solution of midazolam hydrochloride (5 g.L^{-1}:0.3 mg.kg^{-1}) in healthy volunteers produced a bioavailability of about 50%, however metabolic studies suggested that complete rectal absorption of the parent drug had occurred with substantial first-pass metabolism[130]. Absorption was rapid, the mean T_{max} being 31 min and C_{max} reaching 120 μg.L^{-1}.

Diazepam may also be used for preoperative medication. In adult patients, one study reported that premedication with a rectal diazepam solution was considered less effective than oral dosing. However the oral dose used was 50% higher than the rectal dose (15 vs. 10 mg)[131]. Rectally administered diazepam has been used in children for sedation for dental operations[132].

The use of rectal methohexital to induce anaesthesia in children has received considerable interest in recent literature. In children aged between 2 and 7 years, anaesthesia was induced with rectal administration of 15 mg.kg^{-1} of methohexital solution. Peak plasma concentrations ranged between 1 and 6 mg.L^{-1} and were reached in 7 to 15 min. indicating very rapid absorption[133]. Although the bioavailability ranged between 8 and 32%, satisfactory induction of anaesthesia was reached in 90% of children. It has been suggested that the variability in methohexital plasma levels is due the depth to which the drug is inserted, thereby altering the amount of drug which avoids first-pass metabolism. No clear correlation exists between rectal pH and absorption, suggesting that the variability in the extent of first-pass metabolism has a greater effect than the effect of luminal pH on drug uptake[134].

Atropine is administered prior to inhalation anaesthetics to reduce salivation and the production of bronchopulmonary secretions. Absorption from a rectal saline solution was slower and less complete than with intramuscular administration[135]. Atropine sulphate in a HPMC base had a bioavailability of approximately 30%, but absorption was fast, reaching a T_{max} after 15 minutes[136].

Analgesics and antiarthritics

Oral administration of narcotic analgesics in the treatment of postoperative and cancer pain is often limited by nausea and vomiting, or poor patient condition. Studies indicate that rectally administered morphine has a variable bioavailability compared to an intramuscular injection, 30–70% when administered in a starch-containing gel and 40–88% from a hard fatty suppository. Increasing the pH of a rectal morphine microenema from 4.5 to 7.4 significantly increased the extent of absorption[137]. Hydrogels have also been used to successfully deliver morphine, producing a lower and more sustained plasma concentration than intramuscular morphine given on demand[116].

Methadone administered rectally has a similar rate of uptake to an oral solution, but with a lower bioavailability. The use of the solvent glycofurol increased the rate and extent of absorption of methadone from a microenema (Figure 7.13)[138].

Rectal absorption of acetylsalicylic acid is strongly dependent upon the type of formulation in which it is administered, with an aqueous microenema (20 ml at pH 4) giving the best results. In contrast, the pH of the paracetamol microenema was unimportant. Paracetamol is well absorbed when administered intrarectally, although absorption is slower than from an oral solution.

Indomethacin is rapidly absorbed when delivered rectally, however the bioavailability is less than from oral capsules and there is great intersubject variation. Naproxen, ibuprofen and ketoprofen are all well absorbed when rectally delivered.

Diflunisal (Figure 7.14) had a bioavailability of 55% as a rectal suspension, but this could be inproved to 70–80% by either using a cosolvent (glycofural) or by buffering the

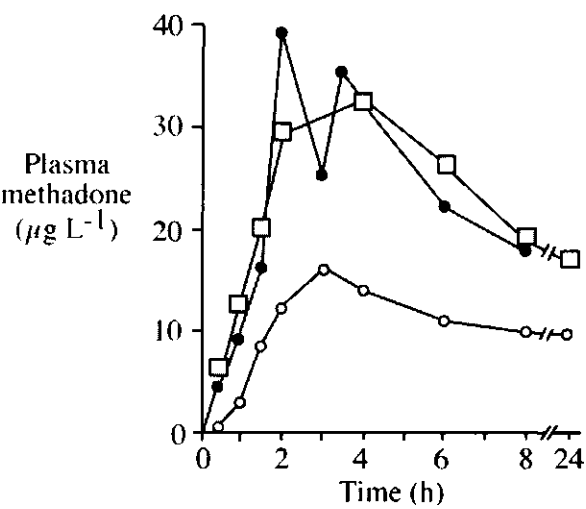

Figure 7.13 Plasma concentration of methadone after oral solution (●), Witepsol H-15 suppository (○) and PEG 1540 suppositoiy (□)

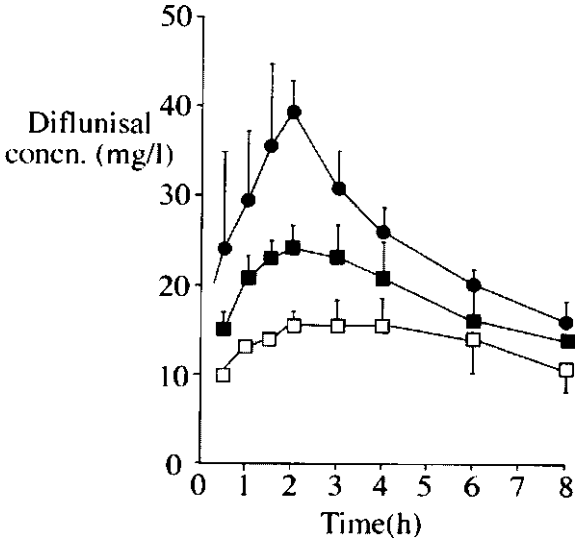

Figure 7.14 Plasma concentration versus time curves of 250 mg diflunisal after oral administration as a suspension in water (●) *and after rectal administration in methylcellulose solution at pH 4.5* (□) *and 7* (■)

pH to 7.0. Control of pH appears to be important to optimize the solubility of a number of drugs; for example codeine, when delivered in solution at pH 9, produced better absorption than at pH 4.3[139]. When delivered in 'Witepsol' H15, codeine phosphate can exhibit a plasma concentration profile almost identical to the oral formulation[140].

Natural or hydrogenated soya lecithin added to diclofenac suppositories prolonged absorption from about 1 h to 6 h in healthy volunteers, without affecting the extent of absorption[141]. Interestingly, this study reported that absorption was not affected by defaecation.

Antiemetics

Orally administered antiemetics suffer from quite obvious drawbacks and hence rectal administration of alizapride, promethazine and metoclopramide have been investigated. Rectal administration of alizapride as a suppository in an unspecified base resulted in a mean bioavailability of 61% relative to an intravenous bolus dose[142]. Both alizapride and promethazine have considerably slower absorption profiles from rectal administration compared to either oral or intramuscular administration. In addition, promethazine produces significant rectal irritation.

In human subjects, an aqueous microenema containing metoclopramide resulted in rapid absorption and complete absolute bioavailability. Another advantage of delivering metoclopramide rectally is that when given orally, it undergoes extensive first-pass metabolism.

Antibacterial agents

Metronidazole is used extensively in the prophylaxis and treatment of anaerobic infections. For practical and economical reasons, attempts have been made to develop rectal metronidazole formulations. It is absorbed rapidly but incompletely from aqueous suspension formulations.

Ampicillin is poorly absorbed from the rectum and despite many formulation attempts, currently the problem has not been overcome. In addition the drug can produce mucosal irritation and diarrhoea.

Xanthines

Theophylline absorption from a rectal solution is similar to absorption from oral solutions, and generally occurs rapidly and completely. However, absorption from suppositories may be variable and incomplete. Interestingly, theophylline was well absorbed when delivered in a rectal osmotic delivery device, despite the fact that the level of water available in the rectum is very low[143].

The absorption of enprofylline, a bronchodilating xanthine drug which is poorly metabolised, shows somewhat slow absorption from rectal administration of an aqueous solution compared with oral intake. Oral absorption was complete, whereas urinary data indicated an absolute rectal bioavailability of about 89%[144].

Drugs in inflammatory bowel disease

Mesalazine is the locally active moiety of sulphasalazine used in the treatment of inflammatory bowel disease. It is liberated from the orally administered parent drug in the colon by bacterial splitting of an azo bond. It is frequently delivered by enema, particularly in patients with ulcerative colitis of the distal colon. As the adverse effects of oral sulphasalazine are ascribed to the sulphapyridine moiety, colon specific formulations have been developed which have low systemic bioavailability without the sulphapyridine group.

Rectal instillation of corticosteroids is a well-established approach for the treatment of inflammatory bowel disease. Corticosteroids which show high efficacy and low systemic drug concentrations are preferred, in order to minimise adrenal suppression and other adverse effects inherent in steroid therapy. Rectal prednisolone, budesonide, tixocortol pivalate and beclomethasone diproprionate appear to interfere less with adrenocortical function than hydrocortisone acetate, prednisolone-21-phosphate and betamethasone. In clinical practice, steroid enemas prove to be difficult to retain because of their large volume, and hence foams are used.

Cardiovascular active drugs

Rate-controlled rectal drug delivery of nifedipine by an osmotic delivery device in healthy volunteers resulted in a steady-state plasma concentration, with the low input rate resulting in a lowering of blood pressure without concurrent reflex tachycardia.

Rectal irritation and damage

Long term rectal application of drugs has been reported to produce irritation, rectal bleeding pain and even ulceration. Ergotamine tartrate suppositories used at a dose range of 1.5 to 9 mg over a period of between 1 and 8 years can produce rectal damage, probably due to mucosal ischaemia produced by the alkaloid[145].

Rectal ulceration and stenoses have also been reported in patients using suppositories containing dextropropoxyphene[146], paracetamol, aspirin, caffeine, carbromal, bromisoval and codeine phosphate[147]. Rectal damage only appears to occur after long term daily suppository use and aspirin, ergotamine and paracetamol appear to cause the most common problems.

Local irritation can be elicited by rectal application of various drug in humans, for example oxprenolol solution, diazepam preparations, promethazine suppositories and carbamazepine suspension, hence tolerability represents an important consideration in the development of rectal formulations. Interestingly, epithelial cell loss and local inflammatory

reactions have been observed after administration of plain suppository bases, e.g. Suppocire AP, Witepsol H12, H15 and H19, and polyethylene glycols in rats[148 149]. However, since these materials are well accepted in clinical practice, the occurrence of mucosal damage does not necessarily preclude their use in humans, if the damage is reversible.

CONCLUSIONS

Reliable delivery of drugs to the proximal colon is one of the key areas of research in drug delivery at the present time. It is hampered by the relative inaccessibility and the difficulty in producing *in vitro* models which mimic the environment of the colon. Results from the studies of sustained release dosage forms using pharmacokinetic and scintigraphic techniques indicate that, for once a day dosing to be successful, the drug must be absorbed from the ascending colon to maintain therapeutic levels.

Oral dosing is the preferred route of administration for drug delivery to the proximal colon. Consequently the design of peroral controlled-release dosage forms has to take into account a plethora of factors which may influence the transit of the delivery system and the consequent degree of drug absorption.

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