

Chapter 2

The Organization of the Gut and the Oral Absorption of Drugs: Anatomical, Biological and Physiological Considerations in Oral Formulation Development

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Abstract Oral drug delivery remains the mainstay of patient treatment although the candidate drugs of the new millennium are becoming increasingly difficult to formulate for good systemic absorption. The area of oral delivery therefore represents an important area of innovation for pharmaceutical formulation including modulating solubility, exploiting windows of absorption and increasing bioavailability in a robust manner to attempt a more predictable outcome.

In order to deliver an active pharmaceutical ingredient to facilitate systemic exposure, the drug must be presented in a dosage unit that contains an accurate dose of a specified active pharmaceutical ingredient which remains intact to the point of administration. On dosing, the pharmaceutical phase must be undone appropriately: the drug must be liberated at the correct rate, escaping degradation and metabolism and reach sufficient concentrations in the target tissue. The exposition of the pharmacist's art is then completed in the lumen of the gut and therefore an understanding the organization of the organ system, at a macroscopic level, is of great relevance. In this chapter, the general integration of anatomy and motility with regard to the interaction of the dosage form will be considered. The biochemical and biophysical elements of absorption of the drug substance will not dealt with in detail in this chapter but by other books in this series.

2.1 Background

The gut is primarily designed for the absorption of nutrients which are presented in a complex and varied matrix comprising protein, carbohydrate, fat, minerals and vitamins in different proportions. The components must be extracted by batch

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processing, which involves fluid secretion of liquids providing an optimum milieu for the enzymes to work in a controlled sequence. If a foodstuff is energy rich but difficult to process, motility must be slowed to allow presentation at an appropriate rate with mixing patterns predominating over propulsive activity during digestion. This has to be achieved in the proximal regions of the gut, particularly the jejunum and ileum. At the end of the ileum, secretion is lower and assimilation is the main physiological activity. Finally in the colon water, salts and remaining nutrients must be extracted to conserve the ionic balance of cellular fluids.

The gut of mammals evolved into specialist herbivores, fairly inefficient carnivores and balanced omnivores who were able to take advantage of high calorific densities in flesh and nuts by processing in the fore-gut and to extract significant nutrients from pulverized and enzyme treated vegetables using bacterial populations of the hind-gut. This diversity required a range of enzymes to be available and control of exposure to allow efficient processing. The early diet contained seeds from berries which were poisonous, and nature has preserved protective functions throughout evolution of the mammals to man. Thus we recognize poisonous alkaloids as bitter by taste and have several protective mechanisms to avoid toxin exposure including, in the last resort, vomiting.

Our earliest medicines were derived from plant stuff, and of varied potency. The poor analytical techniques hampered quality control and thus the medicines were dangerous to use. The replacement of plant extracts by chemically synthesized drugs, which were obtained at high purity, and were single entities, made the materials easier to use as pharmacons. Doses of the chemically derived drugs could be relatively large (those which were more potent and hard to detect were still commonly referred to by the public as poisons) and although knowledge of the importance of hepatic metabolism and renal excretion was well established 60 years ago, we knew little of more subtle defense mechanisms. As pharmacological knowledge was refined and medicines became more potent, scientists became aware of protection at the prehepatic, intestinal level including efflux and drug metabolizing systems, which attempt to avoid exposure to xenobiotic materials.

These comments emphasize a couple of important principles which must be always considered. First, the gut is designed to process food and some component of the drug's absorption profile is likely to be affected by the sequence of meals. Second, if the drug concentration is sufficiently low, it may be processed by the protective guardians that reduce exposure.

The basic design of the gut is a long muscular tube with specialized areas for digestion and storage. The plan of the gut is illustrated in Fig. 2.1. As shown, the gut is a long tube supplied by arteries and drained by veins and a lymphatic trunk, all of which are supported in a mesentery, which are folds of the peritoneum attached to the abdominal wall. The small intestine is the major site of nutrient and anutrient absorption. Although uptake occurs in stomach tissue, the contribution of direct gastric absorption to bioavailability is small, and slow delivery into the upper gastrointestinal tract is far more important.

In adults the length of the gut is approximately 7 m and the large intestine 1.5 m in length. Differences in length are apparent at death, when inherent tone is lost.

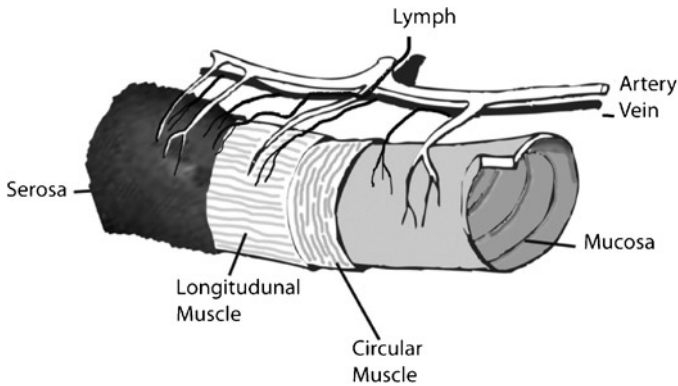


Fig. 2.1 Illustration of the plan of the gastrointestinal tract showing arrangement of mucosa and muscles

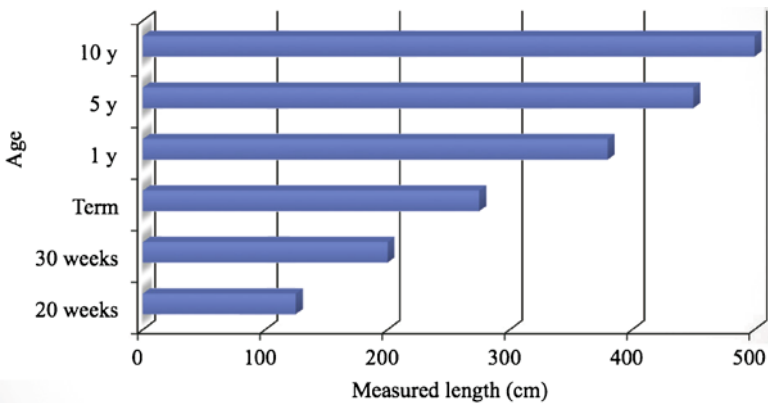


Fig. 2.2 The growth of the human intestine. Measurements made at necropsy. From data of [1]

A study of 1,010 small intestines at autopsy by Weaver, Austin and Cole was used to construct the data shown in Fig. 2.2 describing the growth of the small intestine to adulthood [1].

Functionally, the gut is divided into a preparative and primary storage region (mouth and stomach), a secretory and absorptive region (the midgut), a water reclamation system (ascending colon) and finally a waste-product storage system (the descending and sigmoid colon). The whole structure loosely fills the abdomen, with the esophageo-gastric junction just below the diaphragm. The pyloric sphincter area and the cardia provide points of attachment and help fix the ends of the stomach; however, when posture changes or the stomach is filled with food, organs such as the stomach can change shape and therefore their position in the abdomen. This generates potential differences in emptying patterns in supine, prone and upright positions.

2.2 Buccal Delivery

The first port of call to consider in oral drug delivery is the buccal cavity, and buccal delivery remains of interest for a small range of drugs used for cardiovascular control, smoking cessation and pain control. The primary function of the mouth is guarding of the gut by moistening the food to a soft, shaped bolus: the mucosa must therefore be tough and act as protective layer rather than an absorptive membrane. In areas of maximum abrasive stress, the mucosa will become keratinized. Prolonged exposure to tobacco smoke produces excess keratinization, as does poor dental hygiene. The water inlet channels, which hydrate the digesta, must have high capacity and react instantly: this is the function of the three main sets of glands assisted by minor glands.

Saliva is a viscous, watery fluid which is hypo-osmotic compared to plasma. One to two liters are discharged every day into the mouth and the composition and pH varies with the rate of secretion as illustrated in Fig. 2.3. The pH as shown varies from 7.4 and 6.2; however, the bacterial action can create local pockets where the pH falls below 5 and the tooth enamel starts to demineralize. Saliva acts as a diluent and the bicarbonate component raises pH. In addition, bacteria in the dental plaque metabolize components in saliva and raise the local pH: when this protection is lost a condition known as *xerostomia*, a diffuse and severe caries results.

The saliva produced by the glands varies. “Serous” saliva contains more protein particularly amylase, is watery and subserves the sense of taste by beginning digestion; the saliva stream also needs to produce mucins to resist drying at rest and to lubricate the structures to allow speech. Taste sensation in the tongue, palate and upper esophagus provide an input to the brain allowing involuntary responses such as gagging, retching and excess salivation to remove material. In the dog, the mouth is also used for thermo-regulation.

The classical routes of buccal delivery are summarized in Fig. 2.4 and specific examples are given in Chap. 16. The access to saliva, the variation in patterns of keratinization and squamous cell thickness, and the abrasive forces associated with speech and chewing are important factors in variation in performance.

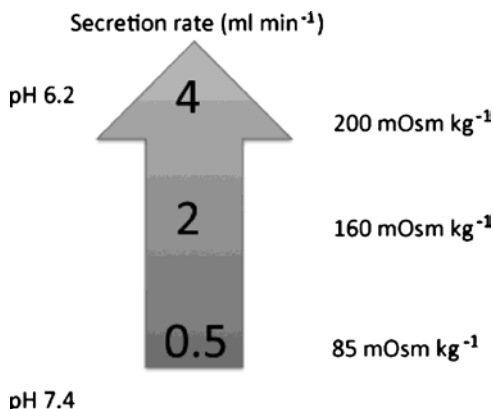
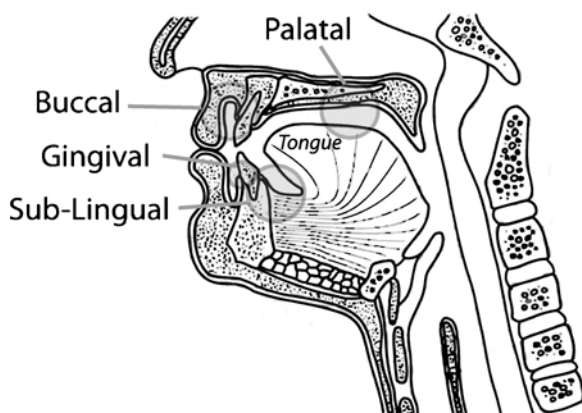


Fig. 2.3 The change in saliva pH and osmolality with increasing flow

Fig. 2.4 Buccal routes of delivery



The mucosa or inner lining of the mouth is divided into four zones. The first part of the gut has a lining of the squamous epithelium which extends from the mouth to the stomach. The many layers of cells are analogous to dermal tissue and drugs will only penetrate if residence is prolonged. The exception is the tissue under the tongue, as used in sublingual delivery, where the epithelium is thin. The vessels of the face drain directly to the heart and thus avoid the hepatic portal system, which provides a number of obvious advantages.

An important property is mouth feel and taste, since the released drug will be in intimate contact with the tongue. Variability in performance may be associated with changes in saliva flow and movements of the mouth when talking. The marked variation in the thickness and keratinization of the epithelial lining is also exaggerated in rodents, and pig and dog are more suitable models for human buccal tissue. The characteristics of buccal delivery are summarized in Fig. 2.5.

2.3 The Esophagus

The esophagus is approximately 40 cm long in the adult, passing through the diaphragm at approximately 38 cm. The surface of the esophagus is a squamous epithelium with a protective function as in the mouth and has few if any glands. The morphology changes sharply at the junction with the stomach into secretory epithelium.

After the dosage form leaves the buccal cavity, movement through the esophagus is normally complete within 10 s. The voluntary maneuver is handed over to a complex autonomic sequence in the cricopharynx, followed after swallowing by short secondary peristaltic waves, which serves to attempt to clear the esophagus. The efficiency of clearance may be influenced by several factors, including the outside surface of the dosage form, the age of the subject and pre-existing disease. Conditions such as type 1 diabetes reduce the amplitude of peristaltic waves and further exacerbate the problems of esophageal clearance, particularly for solid swallows [2]. The elderly often report problems in attempting to swallow

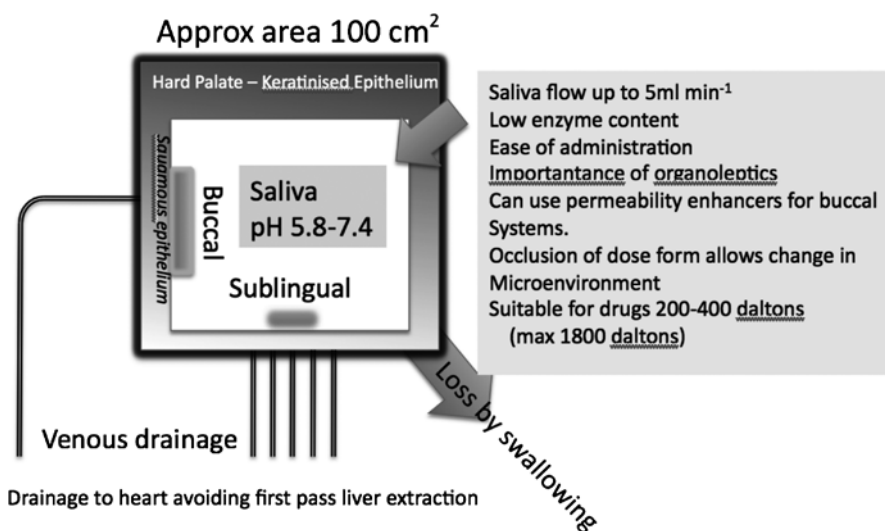


Fig. 2.5 General plan of buccal physiology. Note that the tissues at the top of the mouth are much less permeable than the sublingual area. Buccal systems are used along the gum margin and cheeks and are generally sustained delivery systems, whereas sublingual systems are fast release, as they cannot be anchored

large objects, in part influenced by previous unsuccessful attempts but influenced by the increased stiffness and lower muscle compliance. The elderly have little “swallowing reserve” but experience fewer problems in clearing a liquid bolus compared to a solid mass. It is a common practice in nursing homes to crush medications for dysphagic patients, despite the fact that controlled release formulations are specifically designed not to be damaged prior to ingestion. Although, large tablets are commonly identified as problematic, small flat and buoyant dosage forms are particularly likely to cause problems in the elderly because of the inability to complete the swallowing maneuver.

The coating of tablets to identify the product, to protect the integrity of the dose or to mask bitterness or appearance is a principal activity in the manufacture of oral formulations. The film coat can be functional as for enteric release products or esthetically pleasing and the mouth feel emphasizes the “swallowability” of the product. Channer and Virjee (1985) showed that the clearance of plain, sugar-coated, enteric-coated and film coated tablets in 34 patients was strongly influenced by coating and by posture [3]. The authors reported 100% clearance of film coated tablets in 13 s; for the plain uncoated formulation full clearance was observed in only 60% of subjects at this time. The findings also confirmed their earlier report that oval coated tablets showed the fastest esophageal transit in the erect position, even when swallowed with low volumes of water [4]. A recent interesting article nicely illustrates the importance of shape factors and organoleptic issues on the swallowing of large dosage forms [5].

2.4 The Stomach

The gut contains two reservoirs, in which the tube structure of the gut is modified to accommodate gut contents for longer periods of time. The first, the stomach, allows a regulated supply of calories to the small intestine by control of rate of emptying according to food type. The arrangement of the human gut is illustrated in Fig. 2.6, with the stomach sitting below the diaphragm, nestled by lobes of the liver (removed from the illustration) and the greater curvature of the stomach placed just above the transverse colon. The position of the cardia and the pyloric sphincter are usually fixed but as the stomach is filled, the fundus changes shape by receptive relaxation and on lying down, the proximal stomach falls into the abdomen cavity remaining lower than the distal stomach.

The stomach is lined by a secretory epithelium which is covered by a thick, relatively impermeable layer of gastric mucus. This is the second type of mucosal structure with a longitudinal cell structure; however, the tightness of the intercellular junctions restricts significant passive diffusion, even for small well-absorbed molecules such as ethanol. At the epithelial surface, cells secrete bicarbonate such that a pH gradient is created across the strongly adherent mucus, produced by goblet cells.

2.4.1 Gastric pH

In compendial terms, the pH of the stomach contents is mimicked as a hydrochloric acid solution of 1.0, 1.2 or 1.8. At rest, the stomach pH varies: in a large study of

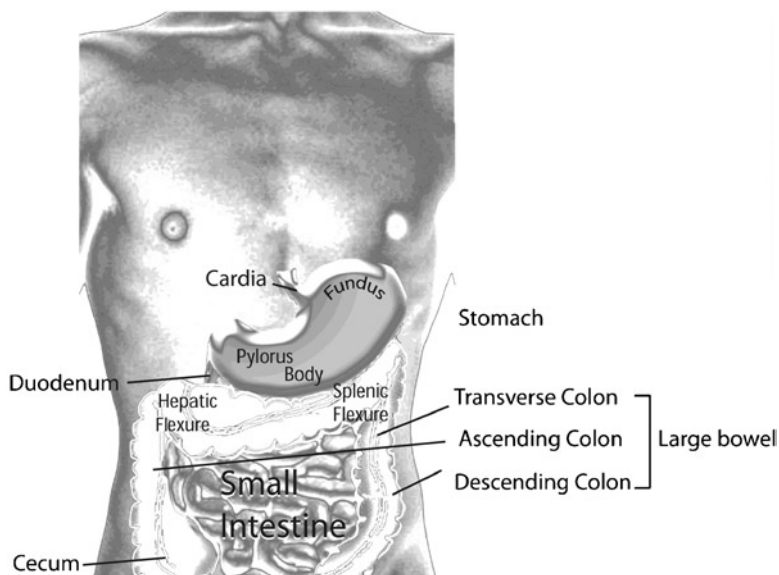


Fig. 2.6 Diagram of the features of the gastrointestinal tract showing location in the abdomen

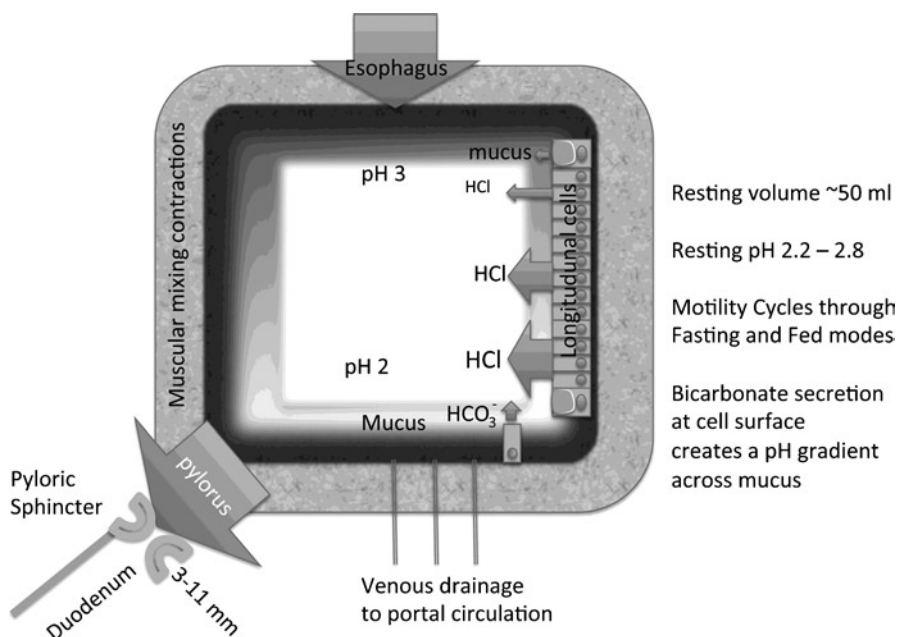


Fig. 2.7 Key gastric features

685 volunteers, Feldman and Barnett reported that the median basal pH for females was 2.79 ± 0.18 and that for males was 2.18 ± 0.18 [6]. In adults, the population of parietal cells is decreasing which will lead to elevated pH in the elderly. As the drugs encountered for oral medication are often weak electrolytes and many are salts of bases, the pH change between the stomach and the small intestine will exert important effects on systemic exposure. Moreover, differences will emerge when considering absorption from the fasted compared to the fed state. If a medication is taken with water, the pH will be elevated temporarily by dilution, returning to baseline at around 20 min post-imbibing. Intake of the meal will cause acid secretion but meal components dictate the magnitude of the response. Food processing acts as a sustained delivery mechanism regulating the supply of materials by controlling gastric emptying. Backwash of duodenal contents into the stomach will cause decrease in surface tension, which can further aid solubilization, which may either subsequently increase absorption or the rate of compound degradation.

The change in pH environment of the upper gastrointestinal tract is very important in oral drug delivery, although the import of regional variations both within the stomach as an organ and between the lumen and unstirred water layer is sometimes not appreciated. A current research direction is the preservation of the super-saturated state to avoid precipitation, particularly of bases, on change of media from the gastric milieu to intestinal fluid.

The pH gradients within an organ and between the lumen and the unstirred water layer next to epithelium can vary by at least a pH unit (Fig. 2.7). In the stomach,

such differences are very large as the parietal cell mass decreases in the fundus raising the pH. In the stomach, such differences are very large as the parietal cell mass decreases in the fundus raising the pH.

The volume of the stomach swells by relaxation of the fundus to accommodate a meal and food layers without significant mixing if the viscosity is high enough. The resting volume is very low – around 50–100 ml but intake of food causes it to relax to accommodate between 1 and 1.5 L. The maximum volumes recorded are around 4 L in man.

2.4.2 *Regulating Gastric Emptying*

The duodenum regulates the supply of material from the stomach to the small intestine. Fat, high salinity and highly acid solutions cause the duodenal wall pressure to increase and slow down the exit of the gastric contents. Because the gastroduodenal system regulates the exit of the slurried contents from the stomach, the transit time from duodenum to the caecum is relatively constant. The diameter of the pyloric opening varies according to the nature of the gastric contents. When taken with water in a fasted individual, the time of tablet emptying will be highly variable. Tablets will be emptied at various times after ingestion according to posture, volume of fluid taken and the calorific value of food taken before or with the dosing. If they disintegrate and dissolve, pulses of material will appear regularly in the small intestine at a rate determined by the meal, with the rise to intestinal pH (Fig. 2.8).

Pellets and disintegrated dosage forms empty from the stomach as either a series of pulses when fasted or distributed in the meal when fed [7]. The emptying of pellets is much more predictable in the fasted state as illustrated in Fig. 2.9. Tablets that remain intact will empty at very variable times when fasted but eating a light meal reduces the variability in emptying as illustrated.

Large tablets will stay in the stomach for prolonged periods of time especially in the more elderly subject where the laxity in stomach becomes predominant.

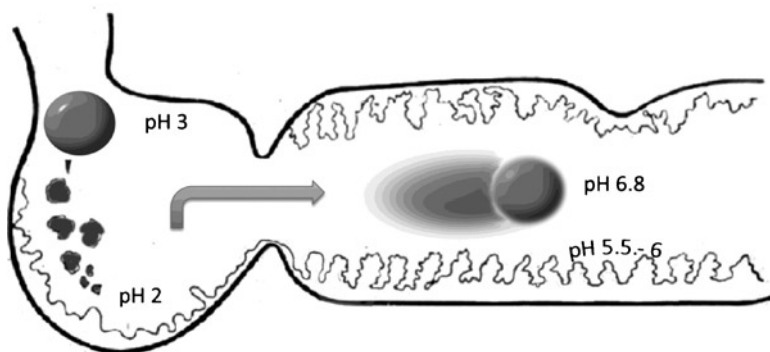


Fig. 2.8 pH and motility in the upper gastrointestinal tract

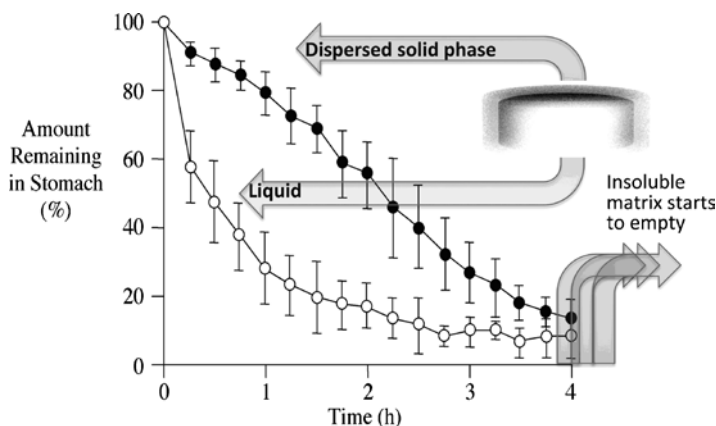


Fig. 2.9 Emptying of tablet components with a meal. Dissolving drug will follow the liquid emptying curve, disintegrated API the disperse phase. Any large fragments or intact tablets will exit with the housekeeper sequence

When food is taken, this discrimination is more extreme as the effective diameter of the pylorus decreases and large tablets are retropulsed back into the body of the stomach at the end of a gastric contraction. Smaller particulates are emptied in the mass of the food and the presentation of the dose in a dispersed system is a function of calorific load and mass of the gastric contents [8]. If food is eaten throughout the day after a heavy breakfast and subsequent meals, then in some individuals a conventional enteric-coated ibuprofen will remain intact up to the end of the day having neither disintegrated nor emptied [9].

Drug, ejected with chyme from stomach will be absorbed in the first highly permeable part of the intestine; however, transit through this region occurs rapidly. Thus, whilst high drug absorption can be demonstrated under *in vitro* conditions, it is most probable that duodenal absorption occurs when the dose remains in the body of the stomach. When recumbent, the fundus or first part of the stomach is positioned lower in the abdomen than the pyloro-duodenal sphincter. As a consequence, drug released in the upper stomach may not appear in the systemic circulation until a postural movement allows flow through to the distal stomach and out into the intestine.

Once the intake of food stops and blood sugar and free fatty acids decrease, the “housekeeper sequence” (migrating myoelectric complex) is initiated which serves to remove debris. This powerful peristaltic wave causes powerful contractions against an open pylorus. In scintigraphy studies, in young people who have fasted, this is evident about 2 h postdosing (i.e. around 10 a.m.). As tablets travel down the gut, the movement slows and periods of stasis are common just before the tablet leaves the ileum and enters the large intestine. Eating food later on will cause a gastrocolic reflex (see Sect. 2.6.2), enabling the contents to move from small intestine to large bowel.

This mechanism, colloquially known as the housekeeper sequence or more properly as the migrating motor complex (MMC) can be recorded externally with

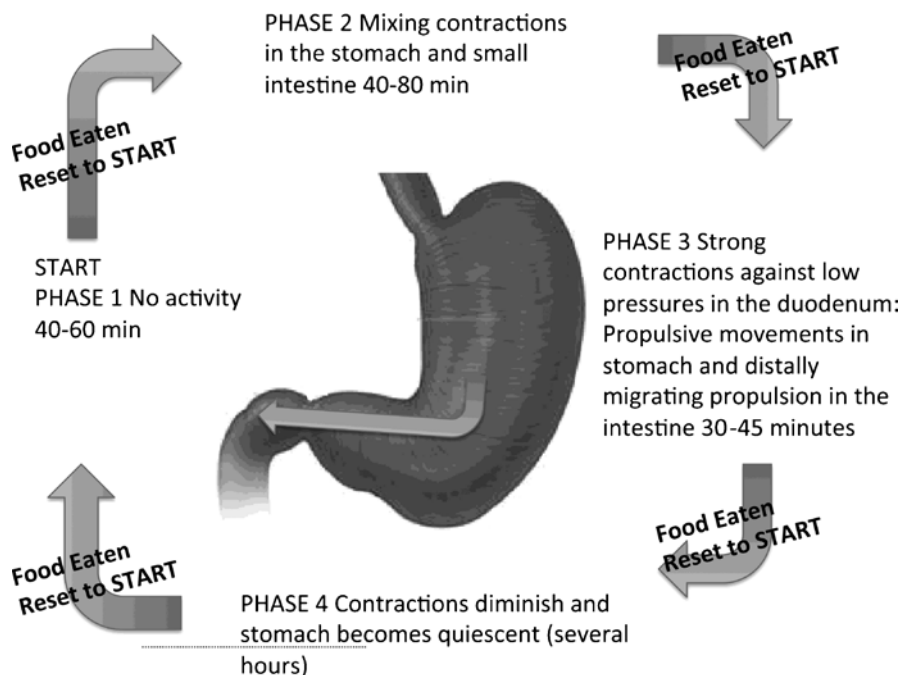


Fig. 2.10 The migrating myoelectric complex or housekeeper sequence

electrodes on the abdomen (Fig. 2.10). This was first described in the literature following the first experiments described by Code and Martlett and by Bull and colleagues [10, 11]. The mixing activity gives way to strong propulsive waves, which migrate through the small intestine. The strong contractile activity during phase III of the MMC is an important factor limiting the retention of dosage forms, but the cycle may be interrupted and reset by the intake of food.

2.4.3 Utilization of Upper Windows of Absorption

Exploitation of areas of the gastrointestinal tract where maximum absorption occurs by deliberate formulation efforts has been attempted using several mechanisms including ligand association, bioadhesion and physical properties (gastroretention). It was thought that prolonged positioning of a dose form within a specific area of the intestine would allow exploitation of transporter populations expressed differentially along the length of the gut. Although binding to the small intestine in vitro is readily achieved using a variety of ligands, the motility and pattern of luminal flow may restrict access, except in the distal gut during periods of stasis. The relative importance of pH effects versus differential transporter expression has often been a subject of debate. Woodley has commented that using everted sacs, his group has

noted marked differences in the pattern of absorption of xenobiotic compounds along the gastrointestinal tract but he suspected that so-called “windows of absorption” are largely a phenomenon related to solubility and pH [12]. Any attempt to modulate the point or time of release is, however, still a useful endeavor as it may result in increased patient benefits. It relies on construction of a dosage form utilizing a controlled release technology.

A few important drugs show an apparent window of absorption, with best permeability in the duodenal segment. Since transit through this region of the gut is very rapid – typically less than 5 min – the formulator must attempt to keep the delivery device for a prolonged period of time in the stomach such that the first segment of intestine is continually bathed in drug. A simple test was proposed to test the usefulness of gastroretentive devices – simply sipping a formulation over a prolonged period to examine a change in the pharmacokinetic parameters [13]. Lewis describes an example of this maneuver and compared the exposure following an oral IR formulation of acyclovir with a solution of the drug sipped over 4 h [14]. The $AUC_{0-\infty}$ was doubled for the sipping administration compared to the simple tablet administration.

Floating systems are therefore most successful if the patient is fed and upright. A general strategy is to float or to expand due to the liberation of gas into a gelling structure such as alginic acid. There are problems if the subject is recumbent and turns onto the left as the floating layer will empty out of the stomach ahead of the rest of the gastric contents [15].

2.5 The Intestine

The third type of mucosa is the secretory/absorptive mucosa of the intestine, designed for the digestion of food and assimilation of smaller building blocks of fats, proteins and carbohydrates. Materials such as glucose, vitamins and essential amino acids must be actively scavenged from the intestine by active transport processes. Some drug absorption routes can utilize these pathways, such as valine-based prodrugs, but most drug absorption occurs at least in significant part by passive or facilitated diffusion (Fig. 2.11).

The small bowel is divided into three parts, the first 20–30 cm is termed the duodenum, the second 2.5 m the jejunum and the final 3.5 m the ileum. The mucosa of the small intestine has a surface area which is greatly increased by the folds of Kerckring, villi and microvilli (brush border) and is about 200 m² in an adult. The surface of the mucous membrane of the small intestine possesses about 5 million villi, each about 0.5–1 mm long. Although the villi are often described as “finger-like,” their shape changes along the gut and duodenal villi are shorter and broader than those found in the jejunum. Further down the gut the villus height decreases. Diet and environment markedly affect mucosal morphology.

The epithelium, which covers the intestinal villi, is composed of absorptive cells, goblet cells, a few endocrine cells and tuft or calveolated cells. The absorptive cells or enterocytes are tall, columnar cells, with their nuclei located close to their base.

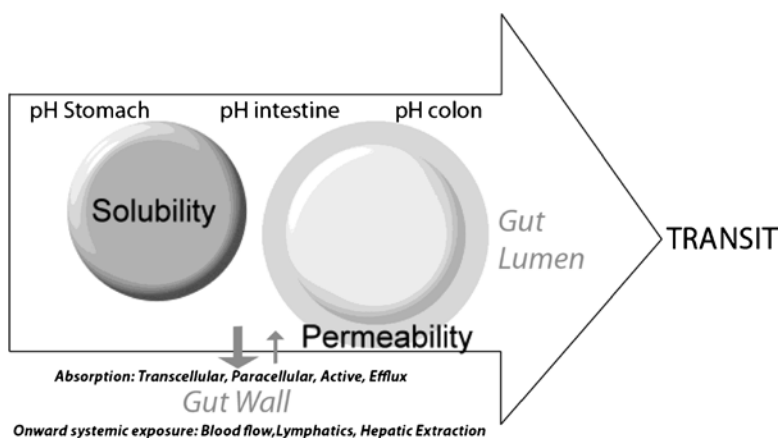


Fig. 2.11 Summary of the transit, solubility and permeability interactions

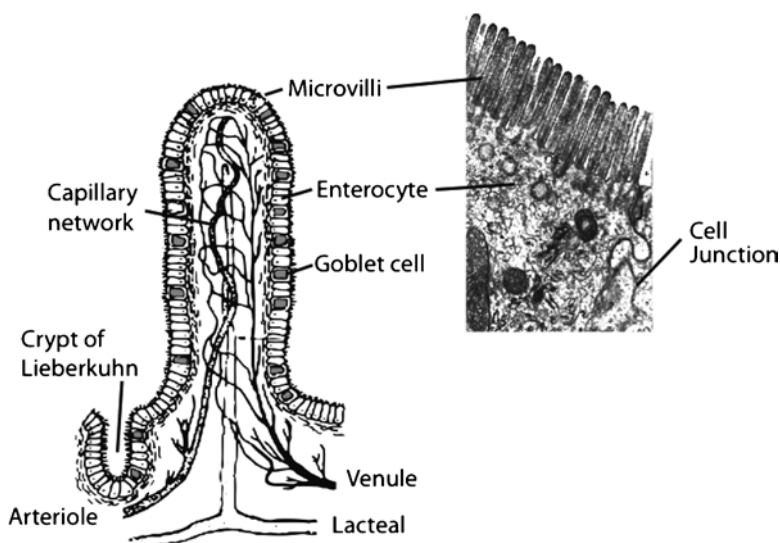


Fig. 2.12 Structure of intestinal villus, showing microstructure of villus surface and enterocyte junctions

The principal permeability barrier is represented by the luminal surface of the brush border, or microvilli as shown in Fig. 2.12. Most drugs are absorbed by passive diffusion in their unionized state. The pH of the small intestine determines the degree of ionization and hence controls the efficiency of absorption; this is the basis of the pH-partition theory of drug absorption. Protein binding at the serosal side of the epithelium helps maintain a concentration gradient by binding the absorbed drug, which is then removed by blood flow from the absorption site.

Between cells epithelial brush borders come into close contact and under the electron microscope it appears as if the membrane is fused. However, functionally

the tight junctions are not sealed but are permeable to water, electrolytes and other charged or uncharged molecules up to a certain size. The size of the “pore” varies along the length of the gastrointestinal tract and can be calculated from recoveries of polyethylene glycols of various molecular weights. Intercellular transport may be important for oligosaccharides and small peptides, which is an area of considerable current interest.

There is a special mode of permeation across the intestinal wall in which the cell membranes are not involved. Intestinal cells are continuously produced in the crypts of Lieberkühn and migrate towards the tip of the villus. During digestion the cells are sloughed off leaving a temporary gap at the cell apex and through this gap large particles can slip into the circulation. This has been termed “persorption.” The observation that large objects such as starch grains can be found in the blood after a meal of potatoes or corn is often quoted as the *prima facie* evidence of persorption or phagocytosis.

Although the absorption of most drugs can be explained by passive diffusion, some compounds have specific transport mechanisms. An example is the absorption in the intestine of some penicillin derivatives, e.g. cyclacillin (1 aminocyclohexylpenicillin). This process is saturable, proceeds against an unfavorable concentration gradient and shows temperature dependence. Transport of amoxycillin is also carrier mediated but it is not an active process. Since these materials are xenobiotics, the transport mechanism is probably one which serves some other function in the body. The two penicillins probably share the same carrier since they are mutually competitive. Digitalis and other cardioselective glycosides also demonstrate a behavior not compatible with simple partition theory which suggests carrier-mediated transport.

2.5.1 Movement of the Dosage form Along the Gut

Muscular contractions in the wall of the small intestine have to achieve two objectives: first, stirring of the contents to increase exposure to enzymes and second, to bring the lumenally digested products close to the wall, propelling indigestible material towards the distal gut. To accomplish this, movements of the gut consist of a mixture of annular constricting activity (segmentation) together with peristaltic movements, which are of both long and short propagation types. Measurements indicate that there are only small perturbations caused by meal components such as fat. Early emptying of partially digested lipid, initiated by gastric lipase and perhaps backwash of proximal intestinal contents into the stomach, initiates the ileal brake, which is discussed later in the book by Boyd and colleagues.

The pattern of movement through the small intestine was first nicely illustrated by the work of Lydia Kaus and the Manchester team of Fell, Taylor and colleagues [16]. Progress in this area has been facilitated by techniques including scintigraphy but more significantly by magnetic moment monitoring. Small intestinal transit of magnetized units in the small intestine is characterized as a series of rapid movements

in the proximal intestine, becoming more quiescent in the distal intestine. Scintigraphy shows a plug flow of pulses through the small intestine, stopping occasionally and bunching of material at the ileocaecal junction with a reduction in the dispersed volume.

The extent to which shape controls gastrointestinal transit is important as illustrated for pellet and single unit emptying of the stomach; however, in the small intestine formulations appear to travel at approximately the same rate. Measurements indicate that there are only small perturbations caused by meal components such as fat. Early emptying of partially digested lipid, initiated by gastric lipase and perhaps backwash of proximal intestinal contents into the stomach, initiates the ileal brake. Following administration of a light meal, movement through the proximal gut is rapid and longer periods of stasis become evident as the formulation enters in the terminal ileum. Bunching of the formulation label is noticeable at the ileocaecal junction, immediately before entry into the caecum. Eating initiates propulsive activity and approximately 15 min after a meal, pulses of activity can be recorded in the sigmoid colon. Essentially, material is swept forward from the small intestine to clear a path for gastric effluent. The ability to small intestinal transit time remains annoyingly elusive and therefore attempts at extending the therapeutic time window after a single dose focus on gastric residence and retention in the ascending colon. Both factors appear to be influenced by bowel habit and in very young children, there is evidence that establishing a normal microflora has an action on gastric emptying and colic of the new born [17]. In nonulcer dyspepsia, constipation is a common observation [18].

2.5.2 Intestine: Can Transit Be Modulated?

The primary area of the gut for drug absorption is the small intestine; with an absorptive flux around 10–20 times that of the large bowel [19]. The slow absorption associated with those compounds with poor solubility or intrinsic slow dissolution in Class 2 of the BCS classification still prompts scientists in biopharmaceutics to look for methods of increasing small intestinal transit time. Although binding to the small intestine *in vitro* is readily achieved using a variety of ligands, the motility and pattern of luminal flow may restrict access, except in the distal gut during periods of stasis. Small studies in dogs have suggested that carbomer 934 may achieve bioadhesion in the intestine but there is an important methodological problem in that a prolongation of gastric emptying time will result in later (clock) arrival at the end of the small intestine [20]. The material presented at the end of the intestine will be retained until the next large migrating movement of the bowel.

Using imaging techniques including gamma scintigraphy and magnetic moment imaging show that movement gradually slows as the dosage form moves from duodenum to ileum, with periods of stasis and sluggish movement [21]. The movement is an inherent feature of the gastrocolic reflex and appears to be difficult to modulate. Sluggish movement in the gastrointestinal tract is associated with

blockages-bezoars, due to ingestion of fruit (especially unripe persimmons, phytobezoars), hair (trichobezoars) and mixtures of tablets with an anticholinergic effect (pharmacobezoars).

The opposite extreme – fast transit – is also evident. In volunteer studies with the drug gefitinib, the pharmacokinetics was shown to be highly variable [22]. Subsequently, it was appreciated that there was a subgroup of about a fifth of the whole panel who displayed a pharmacokinetic profile following single oral dose that was significantly different to their peers. The shape of the elimination profile in this subset was also different, showing a monophasic elimination pattern rather than the biphasic pattern observed in the majority of subjects. A study was conducted using radiolabeled tablets to examine the relationship of gastrointestinal transit and drug absorption in the subgroup and matched normal volunteers [23]. The rapid clearance cohorts were shown to have a faster mean gastric emptying T90% (37 min vs. 74 min) and shorter small intestinal transit time (156 min vs. 204 min). Mean plasma C_{\max} was lower (99.2 ng/ml vs. 116 ng/ml) and AUC almost half in the rapid clearance group ($2,162 \pm 81$ ngh/ml vs. $4,996 \pm 64$ ngh/ml).

Overall, using a wide range of markers, meals, tablets and pellets, the small intestinal transit time in normal, healthy volunteers is between 3 and 4 h. As might be expected, the presence of nutrients in the gut alters motility – drinking glucose solutions or Intralipid® increases contraction of the gut significantly. Both increase contractions to the same extent, with the duration of the increase dependent on caloric activity [24]. Modulation of transit by food produces relatively modest effects in xenobiotic absorption and it is unlikely that this is a fruitful area for consideration.

2.6 The Colon and Drug Delivery

The importance of the colon varies in mammals according to the nature of their diet. Thus true carnivores have a short colon with a small caecum, whereas large ruminants have a high capacity rumen for fermentation. The appendix in humans is vestigial and apparently unimportant in the human nutritional process. On opening the abdomen, the large colon is usually easily visible because the transverse loop has a very antral position in the abdominal cavity and may contain gas. Figure 2.13 illustrates the main physiological features of the colon. The bacterial fermentation of ingested soluble carbohydrates yields carbon dioxide, and in some individuals if the redox potential is low enough, hydrogen and methane.

Compared to the small intestine it is shorter – 1.5 m rather than 5 m – and the lumen is wider, without the extra surface area provided by the folds of Kekring and the villi. The absorptive capacity for drugs is therefore markedly reduced but this can be balanced by the long periods of residence in the ascending colon. The major regions of the colon are the right or ascending colon; the transverse colon which is folded in front of the ascending and descending arms by the hepatic and splenic flexures; the descending colon which stores feces and finally the rectum and anus. Overall the length of the human colon is approximately 150 cm, but only the last

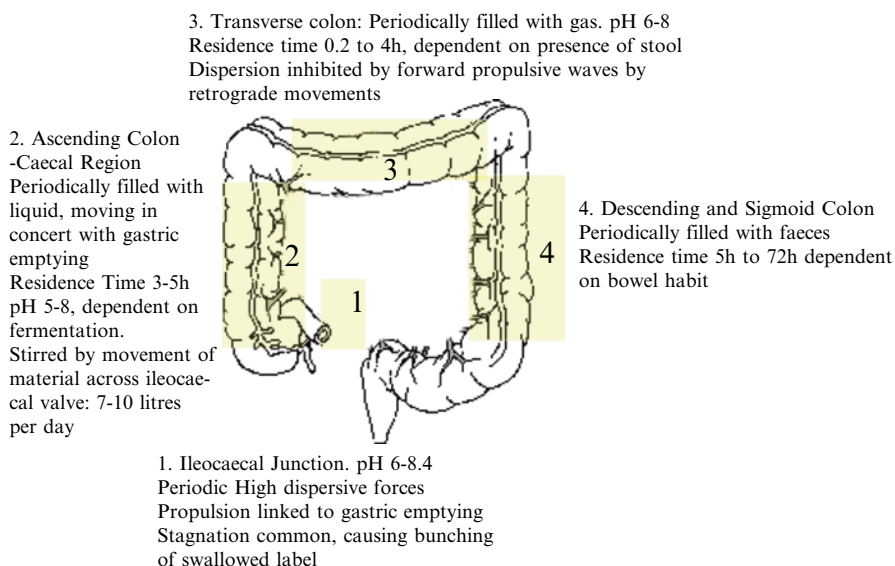


Fig. 2.13 Schematic of colon transit. From [25]

30 cm is accessible from the anus, since the folding of the splenic flexure resists material entering the transverse colon if rectal delivery of large volume enemas is attempted. Targeting the first half of the colon is therefore difficult from a physiological perspective; however, the bacterial population provides a step change in luminal environment with a different set of metabolic enzymes to aid selective release. As an incentive, drug delivery to the colon has often been an attractive goal for peptide delivery as it is supposed that the lack of digestive enzymes would facilitate absorption. A drawback is the lack of fluid for dissolution and the environment is moist rather than full of fluid, with normal maximal water content of 30 ml recoverable postmeal from the caecum [26]. When empty, the colon is collapsed with little motility but the transverse section may extend with gas following fermentation of the carbohydrate. The terminal segments may be occupied by stool and little drug absorption can occur from the distal regions under these conditions.

The wall of the ascending colon when scraped with a pH electrode gives an alkaline reading as high as pH 8, caused by secretion of bicarbonate by a sodium-dependent bicarbonate secretion which is non-chloride ion dependent [27]. This secretion of the bicarbonate would be expected to render the colon alkaline, but this is balanced by the bacterial fermentation of carbohydrate to short chain fatty acids, particularly in the caecum and right colon. Studies with reliable pH electrodes implanted on the colon wall during colonoscopy in areas free of debris indicate that patients with a normal bowel have a more acidic right colon (pH 7.05 ± 0.32), followed by a more alkaline transverse colon (pH 7.42 ± 0.51), becoming more acid moving towards the rectum (pH 7.15 ± 0.44). The lumen pH mirrors the changes of the wall, but remains consistently more acidic [28]. Press and colleagues (1998) report values illustrated in Fig. 2.12 [28, 29].

2.6.1 Regional Transit Through the Colon

The environment of the large bowel differs along its length and it is only in the right colon where conditions are sufficiently favorable to allow drug absorption. In the clinic, the first measurements of ascending colon transit times were performed by long tube studies, in which the subject was encouraged to swallow a dosing tube orally, down to the caecum. Under these conditions, very short proximal ascending loop transit times, 87.6 ± 27.0 min were observed following the instillation of a liquid bolus into the caecum. Intubation and the CCK administered to accelerate transit were probably significant influences on this procedure [30].

The transverse colon is frequently full of gas, and access to water is extremely limited. In the descending colon, the consolidation of fecal matter would inhibit dissolution and absorption of drug through the gut wall. The division of colonic transit into regional areas is therefore important in describing the transit of dosage forms through the colon and the possible impact on drug absorption. Targeted delivery of drugs to the terminal gut has been employed to achieve a variety of therapeutic objectives including to delay delivery to the colon to achieve high local concentrations in the treatment of diseases of the distal gut; to delay delivery to treat acute phases of disease at the appropriate time of day (chronotherapy or chronopharmaceutics); to utilize sustained delivery to reduce dosing frequency and historically, in the hope that compliance would improve.

2.6.2 The Gastrocolic Reflex

It has been noted in scintigraphic studies that ingestion of food whilst a tablet was in the ascending colon tended to move the unit into the transverse colon, or if the tablet was in the transverse colon, it moved it further along [31]. This provided a good illustration of the propulsive ileocolic reflex, sometimes mistakenly termed the gastrocolic reflex. Misiewicz, in a classical paper on colonic motility, referred to his earlier study [32, 33] and pointed out that this phenomenon occurs in patients who had undergone a total gastrectomy and therefore gastrin is unlikely to be involved.

2.6.3 Problems of Low Motility and a Lack of Water

In the colon, only the first parts of the colon (ascending and transverse loops) contribute to drug absorption when the drug is delivered from the oral end and fluid levels are very restricted. Both Reppas and Weitschies estimate, by different methods, about 20–30 ml of liquid is available for dissolution (Weitschies W. and Reppas C. Personal communications). Disease states such as diarrhea associated with hypersecretion of

fluid by the small intestine can be simulated by administering 20 g of lactulose for 3 days. When a capsule containing tablets and beads is then given to young volunteers, there is a marked increase in the dispersion and dissolution in the transverse colon [34], suggesting that lack of water usually restricts the surface area following release in the distal gut.

Pulsincap® represented an interesting concept in the delivery in which a swellable plug hydrated and ejected from the delivery device exposing the contents with remarkable accuracy in vitro. It seemed to be the ideal solution to targeting the proximal and mid colon, a region which is not accessible from the anus as the splenic flexure prevents ingress of enemas. It proved a good tool for illustrating the problems of colonic drug delivery. Studies using the Pulsincap system [35] were carried out with the objective of targeting the distal colon with a pulsed delivery of a transcellular probe (quinine) and [⁵¹Cr]-EDTA, a paracellular probe. In these studies, subjects were dosed at 10 p.m. to ensure delivery to the descending colon by lunchtime the following day. The site of release was identified by incorporating [¹¹¹In]-labeled resin into the unit and imaging the subjects by scintigraphy. Fifteen hours after nocturnal administration, the majority of the delivery systems were situated in the proximal colon at their predicted release time and had not advanced further than a similar set of systems viewed only 6 h after dosing. This relative stagnation appeared to reflect the lack of propulsive stimuli caused by the intake of food, and the effect of sleep in reducing colonic electrical and contractile activity. A further problem was the poor ingress of water into the system.

Eventually this system was abandoned and the only device of this type in development was the Egalet® system. This had two end plugs at end and the earliest iteration had similar problems to the Pulsincap®. By changing the dimensions of the device, the problem of water access was overcome [36].

2.6.4 The Bacteria of the Colon

At birth, the colon is sterile but gradually becomes populated with microbes from maternal supply and the environment, dominated by species acquired from the mother's vaginal microbiota including *Lactobacillus*, *Prevotella* or *Sneathia* spp, whereas C section babies show those of the skin surface, including the *Staphylococcus* genus [37]. The thick mucus lining of the colon provides a structural and metabolic support for the bacteria, partitioning the microbiota from the underlying epithelium. In diseases of the colorectal mucosa, the normal biochemistry of this human-bacterial balance is lost and is difficult to re-establish [38].

The colonic microflora secretes a number of enzymes which are capable of hydrolytic cleavage of glycosidic bonds. These include β -D-glucosidase, β -D-galactosidase, amylase, pectinase, xylanase, α -D-xylosidase, and dextranases. In addition, there are scission reactions catalyzed azo-reductases secreted by the anaerobes but these are more generally used in a prodrug approach for example 5-ASA adducts such as balsalazide and olsalazine. The biodegradable polysaccharides can

be employed (1) in the formulation matrix, or (2) as a coat, alone and in combination. Many of these polysaccharides have limited release control properties due to high water solubility. Hence, they are employed in formulations in two ways (1) combination with synthetic nonbiodegradable polymers, especially acrylates or (2) synthetic modification such that solubility is decreased [23].

2.7 Disease and Gut Transit

An issue for all systems relying on consistent transit times is the issue of diseases affecting gastrointestinal motility. The change produced by increased hydrodynamic action – conditions such as diarrhea – will impact on sophisticated zero-order release formulations such as osmotic pumps. For the pumps inadequate retention may occur in some patients, leading to less optimal clinical outcomes. For example, the median GI transit time for both oxprenolol and metoprolol Oros drug delivery systems has been reported as 27.4 h, with individual times ranging from 5.1 to 58.3 h [39]. The possibility of inadequate GI retention of the nifedipine GITS is perhaps more likely in patients who have pre-existing GI motility disorders or who are taking other medications that enhance GI motility. In many patients who are hospitalized, slow transit is often a problem, usually associated with gastric stasis or intestinal trauma. Clearly, any strategy based on control within the formulation will be susceptible to intrinsic factors based on the characteristics of the patients receiving treatment.

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<http://www.springer.com/978-1-4614-1003-4>

Controlled Release in Oral Drug Delivery

Wilson, C.G.; Crowley, P.J. (Eds.)

2011, XIV, 414 p., Hardcover

ISBN: 978-1-4614-1003-4