Chapter Five

The Stomach

ANATOMY AND PHYSIOLOGY

The stomach has several functions:

1. it acts as a reservoir for food,
2. it processes it into fluid chyme which facilitates the absorption of nutrients from the small intestine,
3. it regulates the delivery of food to the small intestine where the nutrients are absorbed,
4. it produces acid which is bacteriostatic, since ingested food is not sterile, and it also produces the correct pH for pepsin to function.

The stomach is located in the left upper part of the abdomen immediately below the diaphragm. In front of the stomach are the liver, part of the diaphragm, and the anterior abdominal wall. The pancreas, the left kidney, the left adrenal, the spleen and the colon are located behind it. When the stomach is empty, it contracts, and the transverse colon ascends to occupy the vacated space. The size, shape, and position of the stomach can vary quite considerably depending upon the extent of its contents as well as upon the tension in the muscles of its walls. The opening from the oesophagus into the stomach is the gastrooesophageal sphincter or junction. It is also known as the cardia. The pylorus is the outlet from the stomach into the duodenum.

Organisation of the stomach

The stomach can also be divided into three anatomical regions (Figure 5.1). The uppermost part is the *fundus,* which after a meal is often seen to contain gas. It also produces slow sustained contractions which exert a steady pressure on the gastric contents gradually pressing them in an aboral direction. The largest part of the stomach is the *body* which acts as a reservoir for ingested food and liquids. The *antrum* is the lowest part of the stomach. It is almost funnel-shaped, with its wide end joining the lower part of the body of the stomach and its narrow end connecting with the pyloric canal. The pyloric portion (the antrum plus the pyloric canal) of the stomach tends to curve to the right and slightly upward and backward and thus gives the stomach its J-shaped appearance.

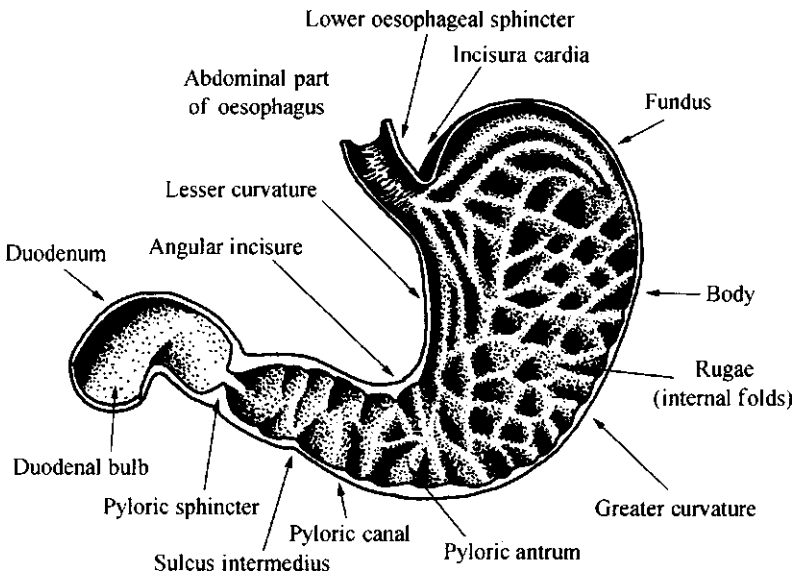

Figure 5.1 Structure of the stomach

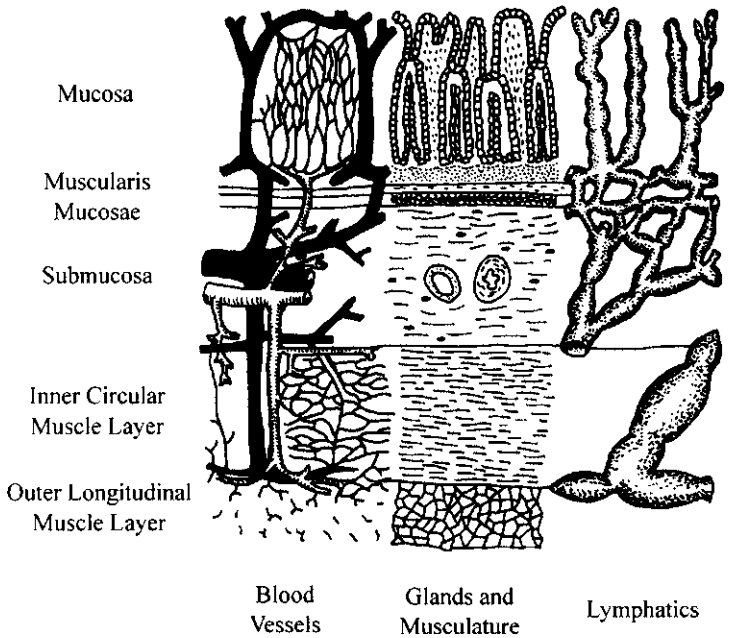

Figure 5.2 Structure of the stomach wall

The stomach adapts to increasing volumes of food by receptive relaxation, which allows the stomach to expand with little variation in intragastric pressure. The distal or antral portion of the stomach has a wall composed of thicker muscle and is concerned with regulation of emptying of solids by contraction, and by acting as a gastric homogenizer and grinder. It is co-ordinated with the body in the propulsion of gastric contents towards the pylorus. The pyloric sphincter has two functions. It sieves the chyme and prevents large particles of food from being emptied from the stomach before solid masses have been sufficiently reduced in size. It also prevents reflux of duodenal material containing bile and pancreatic enzymes which may damage the gastric mucosa.

Mucosa

The mucosa of the stomach (Figure 5.2) is thick, vascular and glandular and is thrown into numerous folds or rugae, which for the most part run in the longitudinal direction, and flatten out when distended. The mucosal surface of the stomach is lined by a single layer of simple columnar epithelium, 20 to 40 μm in height. Approximately 3.5 million gastric pits (foveolae) puncture the lining, each of which serves approximately 4 gastric glands (Figure 5.3). The distribution of gastric glands varies throughout the stomach. The first region, 1.5 to 3 cm in length, around the gastric cardia or gastro-oesophageal junction, contains the cardiac glands. The second region, the fundus and body, contains the acid-secreting glands. The third region, which contains the pyloric or antral glands, includes the pylorus and extends past the antrum to the lesser and greater curvatures.

Gastric mucus

The surface of the mucosa is always covered by a layer of thick tenacious mucus that is secreted by the columnar cells of the epithelium. Gastric mucus is a glycoprotein which lubricates food masses, facilitating movement within the stomach, and forms a protective

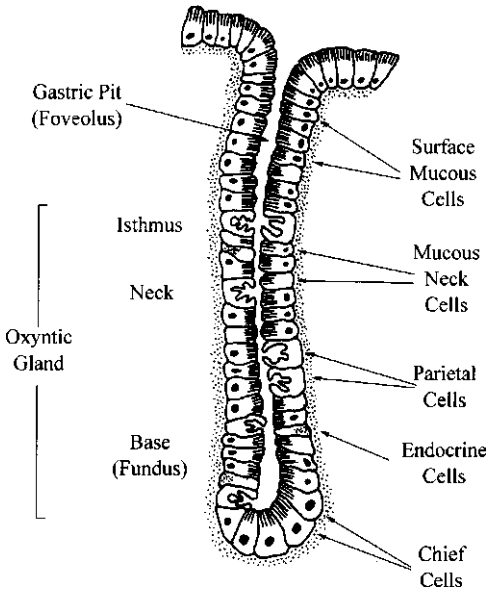

Figure 5.3 Structure of a gastric pit

layer over the lining epithelium of the stomach cavity. This protective layer is approximately 140 μm thick in humans and is a defence mechanism to prevent the stomach from being digested by its own proteolytic enzymes (Figure 5.4). The barrier is enhanced by the secretion of bicarbonate into the surface layer from the underlying mucosa. As the hydrogen ions diffuse across the mucus layer from the lumen, they meet bicarbonate secreted from the underlying mucosa, thus setting up a pH gradient. The mucus is continually digested from the luminal surface and is continually being replaced from beneath. It has been estimated that the turnover time of the mucus layer, i.e. from production to digestion, is in the order of 4 to 5 hours. However, it may be slower since any interaction with the mucosa causes it to secrete copious amounts of mucus, making accurate measurements problematic.

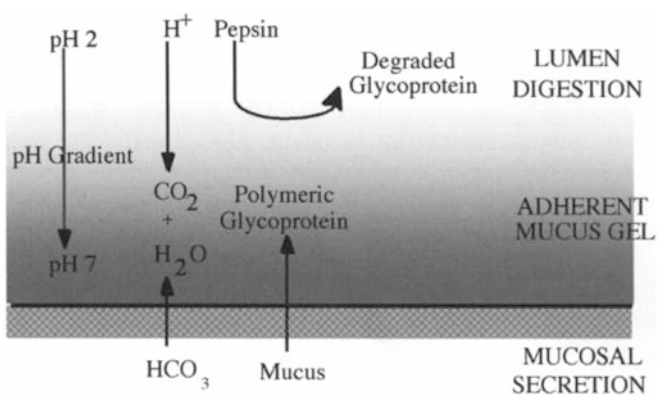

Figure 5.4 Mucus degradation in the stomach

Gastric glands

The gastric glands are located beneath the surface epithelium and open into small pits or foveolae gastricae. There are approximately 100 gastric pits per square millimetre of surface epithelium. Between three and seven glands open into each pit.

The gastric mucosa contains five different types of cells. In addition to the tall columnar surface epithelial cells mentioned above, the other common cell types found in the various gastric glands are:

(1) Mucoid cells which secrete mucus and are found in all the gastric glands. They predominate in the gastric glands in the cardiac and pyloric areas of the stomach. The necks of the glands in the body and fundus are also lined with mucoid cells.

(2) The chief or zymogen cells are located predominantly in the gastric glands in the body and fundus. These cells secrete pepsinogen, the precursor for the enzyme pepsin.

(3) Hydrochloric acid is secreted by the parietal or oxyntic cells which are mainly located in the body and fundus of the stomach (Figure 5.5). They are also responsible for secreting most of the water which is found in the gastric juice and a protein called intrinsic factor. Parietal cells are almost completely absent from the antrum.

(4) Endocrine cells or endocrine-like cells. The endocrine cells throughout the antrum secrete the acid-stimulating hormone gastrin. The endocrine cells are scattered, usually singly, between the parietal and chief cells.

Blood and nerve supply

Arterial blood is brought to the stomach via many branches of the celiac trunk. The celiac trunk is a short, wide artery that branches from the abdominal portion of the aorta, the main vessel conveying arterial blood from the heart to the systemic circulation. Blood from the stomach is returned to the venous system via the portal vein, which carries the blood to the liver.

Both parasympathetic and sympathetic divisions of the autonomic nervous system supply the stomach. The parasympathetic nerve fibres are carried in the vagus (10th cranial) nerves. As the vagus nerves pass through the opening in the diaphragm together with the oesophagus, branches of the right vagus nerve spread over the posterior part of the

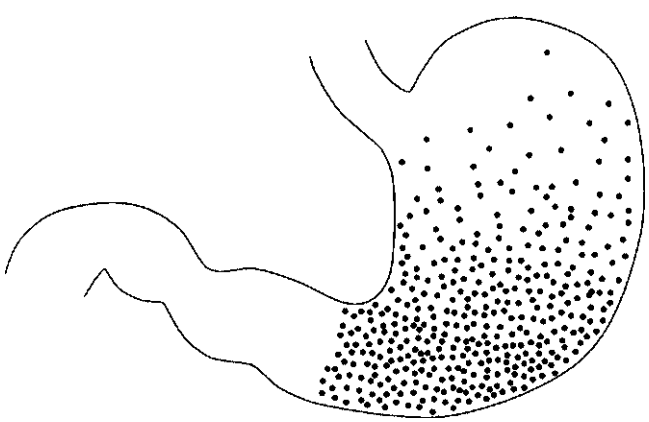

Figure 5.5 Distribution of parietal cells in the stomach. Note their absence in the antrum

stomach, while the left vagus supplies the anterior part. Sympathetic branches from a nerve network called the celiac, or solar plexus accompany the arteries of the stomach into the muscular wall.

Gastric secretion

The human stomach secretes between 1.0 and 1.5 litres of gastric juice per day. This juice is highly acidic because of its hydrochloric acid content, and it is rich in enzymes. Gastric juice provides a medium for soluble food particles to dissolve and it initiates digestion, particularly for proteins.

Acid secretion

The composition of the gastric juice varies according to the stimulus and the secretion rate (Figure 5.6). It is a mixture of water, hydrochloric acid, electrolytes (sodium, potassium, calcium, phosphate, sulphate, and bicarbonate) and organic substances (mucus, pepsins, and protein). Parietal cells can secrete hydrogen ions at a concentration of 150 mmolar. In comparison, the hydrogen ion concentration in the blood is 40 nmolar. Pure parietal cell secretion is diluted to between 20 and 60 mmolar by non-parietal cell secretion. Normal adults produce a basal secretion of up to 60 ml per hour containig approximately 4 mmoles of H^+. This can rise to more than 200 ml, and between 15 and 50 mmoles per hour, when maximally stimulated.

Hydrogen ions are produced by metabolic activity in the parietal cells (Figure 5.7). The key reaction between water and carbon dioxide is catalysed by carbonic anhydrase. The bicarbonate produced diffuses back into the bloodstream and after a meal, its concentration is sufficient to produce a marked alkalinity in the urine called the "alkaline tide". The hydrogen ions are actively pumped into the stomach lumen in exchange for potassium ions. Potassium also diffuses passively out of the cell, hence pure parietal secretion is a mixture of hydrochloric acid and potassium chloride.

Hydrochloric acid is produced by the parietal cells in response to histamine, gastrin or acetylcholine stimulation. Histamine is released from gastric mast cells in response to food ingestion, and acts on the H_2 receptors in the parietal cells, directly causing acid secretion. Gastrin is released in response to reduced acidity of the gastric contents when food enters the stomach, and in particular by the presence of peptides. Acetylcholine is

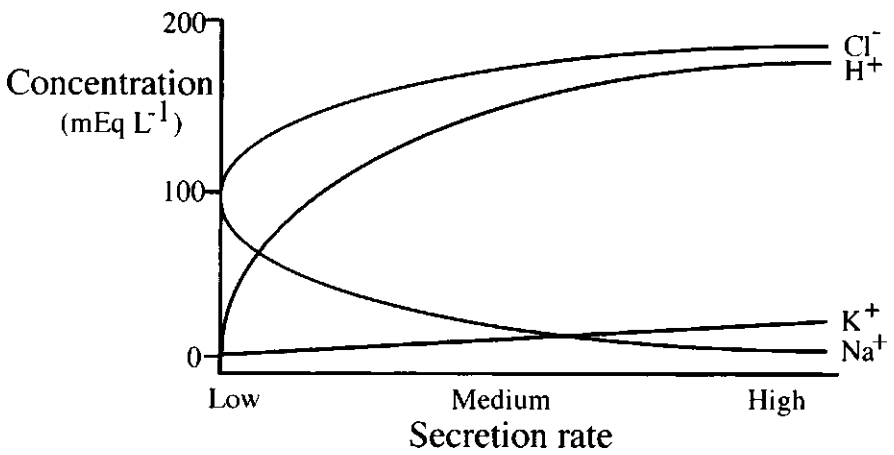

Figure 5.6 Variation in composition of gastric juice with secretion rate

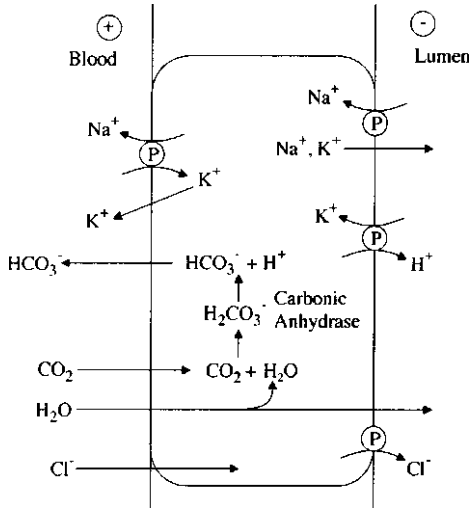

Figure 5.7 Mechanism of acid production by the parietal cell

released when stimuli descend the vagus nerve in response to the sight, smell and taste of food and to the physical effects of chewing and swallowing. It is likely that acetylcholine and gastrin may operate by activating the mast cells which then release histamine, so that histamine is the final common pathway by which the parietal cell is activated.

The process of gastric secretion has been divided into three phases: cephalic, gastric and intestinal, which have different primary mechanisms. The phases of gastric secretion overlap, and there is an interrelation and some interdependence between the neural and humoral pathways.

The cephalic phase of gastric secretion occurs in response to stimuli received by the senses; that is, taste, smell, sight, and sound. This phase is entirely reflex in origin and is mediated by the vagus nerves. The gastric juice that is secreted in response to vagal stimulation is rich in enzymes and is highly acidic.

The gastric phase is mediated both by the vagus nerves and by the release of gastrin. Acid continues to be secreted during the gastric phase in response to distension, and to the peptides and amino acids liberated from food as protein digestion proceeds. The free amino acids and peptides liberate gastrin from the antrum into the circulation. When the pH of the antral contents falls below 2.5, a feedback mechanism inhibits the release of gastrin, thus the system is self-limiting. The gastric phase continues until the food leaves the stomach.

During the intestinal phase the chyme in the small intestine continues to elicit acid secretion for many hours, although the amount of acid released diminishes progressively during the digestion and absorption processes in the small intestine. Some of the actions of the intestinal phase are due to gastrin released from the duodenum, but there is evidence that another hormone-like substance not yet characterised may be responsible. Finally, as certain amino acids and small peptides are infused into the circulation during this phase, they also promote gastric acid secretion. It is possible, therefore, that the absorption of the products of protein digestion also may have a role in the intestinal phase.

Once food reaches the small intestine, it stimulates the pancreas to release fluid containing a high concentration of bicarbonate. This neutralizes the highly acidic gastric juice, which would otherwise destroy the intestinal epithelium, resulting in a duodenal ulcer. Other secretions from the pancreas, gallbladder, liver, and glands in the intestinal wall add to the total volume of chyme.

Pepsin

Pepsinogen is converted to the active enzyme, pepsin, by hydrolysis of the precursor by hydrochloric acid. The hydrochloric acid present in the stomach provides the correct pH for the pepsins to act, i.e. between 1.8 and 3.5; above pH 5 they are denatured. Human pepsins are endopeptidases which hydrolyse several peptide bonds within the interior of ingested protein molecules to form polypeptides, but little free amino acid. The susceptible bonds involve the aromatic amino acids tyrosine or phenylalanine. The polypeptides produced have N-terminal amino acids with lipophilic side chains which facilitate absorption.

Other enzymes

Some other enzymes, including gastric lipase and gastric amylase and gelatinase can be found in gastric juice. Gastric lipase is highly specific tributyrase acting solely on butterfat which is largely tributyrin. It is not capable of digesting medium- and long-chain fatty acids, but since there is only a small proportion of short-chain fatty acids in food, little fat digestion proceeds in the stomach. Gastric amylase plays a minor role in the digestion of starches and the enzyme gelatinase helps liquefy some of the proteoglycans in meats.

Intrinsic factor of Castle

Parietal cells also secrete a glycoprotein known as intrinsic factor of Castle (m. w. 1350 Dalton) which is required for the absorption of vitamin B_{12}. It is continuously secreted, even in the absence of any gastric secretory stimulus in man. Its basal secretion greatly exceeds the minimum amount required for normal vitamin B_{12} absorption.

Prostaglandins

Prostaglandins are hormone-like substances which are derived from dietary lipids. They are present in virtually all animal tissues and body fluids, and are involved in the contraction and dilatation of blood vessels, the aggregation of platelets (clotting), and the contraction and relaxation of the smooth muscle of the gastrointestinal tract. Prostaglandins also inhibit the secretion of hydrochloric acid by the stomach in response to food, histamine, and gastrin. They also protect the mucosa from damage by various chemical agents. This protection is not related to their ability to influence acid secretion. Prostaglandins increase the secretion of mucus and bicarbonate from the mucosa, and they stimulate the migration of cells to the surface for repair and replacement of the mucosal lining.

Digestion and absorption

Salivary amylase acts on food starch while the acidity of the mixture is low, around pH 6, but ceases when the acidity of the mixture increases with greater acid secretion. Gastric pepsins account for only about 10 to 15 percent of the digestion of protein and are most active in the first hour of digestion. The stomach is primarily a processing organ and not an absorptive one and is not essential to life. It is possible, for example, after total gastrectomy (the complete removal of the stomach) for a person to remain, or to become, obese because most of the digestion and absorption of food takes place in the intestine. The stomach can absorb some substances, including glucose and other simple sugars, amino acids, and some fat-soluble substances. A number of alcohols, including ethanol, are readily

absorbed from the stomach. The pH of the gastric contents controls the absorption of certain ionizable materials such as aspirin, which is readily absorbed in its unionized form when the stomach is acidic, but more slowly when the gastric contents are neutral. The absorption of water and alcohol can be slowed if the stomach contains food, especially fat, probably because gastric emptying is delayed and most water in any situation is absorbed from the jejunum.

Water moves freely from the gastric contents across the gastric mucosa into the blood. The net absorption of water from the stomach is small, however, because water moves just as easily from the blood across the gastric mucosa to the lumen of the stomach. In tracer experiments using deuterium oxide, about 60 percent of the (isotopic) water placed in the stomach is absorbed into the blood in 30 minutes.

GASTRIC pH

Gastric pH is primarily influenced by two factors; acid secretion and gastric content. In a 24 hour period, the median daytime pH for eight subjects was 2.7 (range 1.8 to 4.5) in the body and 1.9 (range 1.6 to 2.6) in the antrum of the stomach[1]. Food buffers and neutralizes gastric acid, producing an increase in pH. The pH is not uniform in the stomach, due to the differences in the distribution of parietal cells, and the different patterns of motility in various regions of the stomach. These effects are illustrated by the experiment shown in Figure 5.8, in which pH electrodes were placed 5 cm, 10 cm and 15 cm below the gastrooesophageal junction prior to administering a test meal. Initially all electrodes showed a low basal pH. The meal raised the pH in the fundus to approximately 4.5, but this rapidly began to decline, returning to baseline after 2.5 h. The pH in the body of the stomach was slower to respond, again increasing to about 4.5, 15 minutes later than the fundus. This region returned to basal pH 3.5 h after meal ingestion. The magnitude of the change in pH in the antrum was much smaller, indicating that in this region the food is acidic for the majority of the time. In the body of the stomach, the large concentration of parietal cells

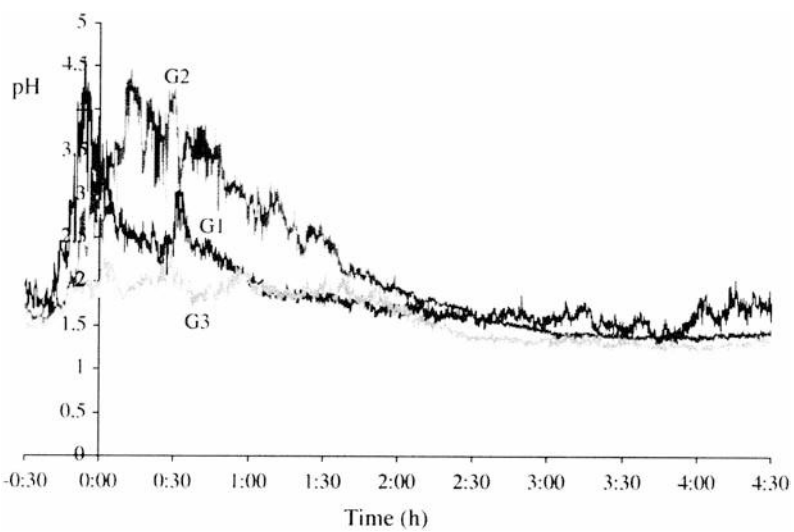

Figure 5.8 Gastric pH after a meal. Electrode positions are G1=5 cm, G2=10 cm and G3=15 cm below the gastro-oesophageal sphincter

causes rapid acid production, but mixing in this region is poor, so that the extended buffering effect of the food is observed. As the food moves into the antrum, the vigorous mixing not only reduces particle size of the food, but mixes it with the gastric acid which was produced higher in the stomach. The pH in the antrum remains low, despite the fact that there are no parietal cells in this region, since much of the food has been neutralized while stored in the body of the stomach (note: the small peak seen after 30 minutes was due to the administration of 50 ml of water for a separate phase of the experiment, and should be ignored).

Acid secretion is increased after hot or cold meals even though temperature of the meal per se does not alter gastric emptying. It takes significantly longer for cold meals to be brought to body temperature than hot meals[2]. Content of the meal also affects gastric pH; for example, a pure carbohydrate meal given as a pancake has no detectable effect on acidity[3], while a protein meal of similar calorific value has a significant buffering effect[4]. A liquid meal, rather than a mixed phase meal, with a balance of carbohydrate and protein has a strong buffering effect but the pH rapidly returns to basal levels as the liquid is emptied. The situation is complicated by feedback effects; for example pepsin normally hydrolyses proteins to peptides and amino acids, which are potent secretagogues, and increase the acidification of gastric contents. However pepsin is inactivated above pH 5, so a large meal which raises the pH above this value will prevent the production of these substances, and peak gastric acid secretion will be reduced.

Circadian rhythm of acidity

A circadian rhythm of basal gastric acidity is known to occur with acid output being highest in the evening and lowest in the morning (Figure 5.9)[5]. The daytime patterns of gastric pH vary greatly between individuals, in part due to the differences in the composition of meals and the variable responses of acid secretion and gastric emptying. However, nocturnal patterns of gastric acidity are very similar with very low pHs between midnight and early morning[3]. The later in the day the evening meal is taken, the later the nocturnal peak of acidity occurs[6]; it is therefore important to standardise the time for the evening meal when comparing the nocturnal effects of anti-secretory drugs.

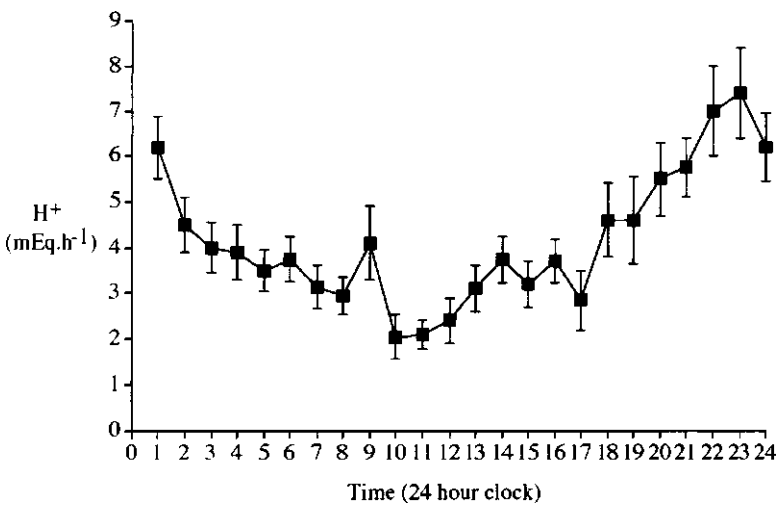

Figure 5.9 Circadian variation in gastric acidity

Night-time transient increases in pH can be detected by electrodes placed in the antrum and body of the stomach. They have been interpreted as evidence of duodeno-gastric reflux flowing from the antrum into the body[7] since the increase often occurs in the fundus before that in the body. The same phenomenon may explain the observation that if a group of subjects are kept awake at night, the pH of the gastric juice is observed to rise compared to sleeping levels, which may be due to increased duodeno-gastric reflux in subjects who are denied sleep.

pH and gender

Healthy women secrete significantly less basal and pentagastrin-stimulated acid than men with a median 24 h integrated acidity of 485 $mmol.h^{-1}$ versus 842 $mmol.h^{-1}$. In a sample of 365 healthy subjects, the average basal pH was 2.16±0.09 for men and 2.79± 0.18 in women[8].

pH and age

It has always been assumed that gastric acid secretion decreases with age, however this has shown not to be true. A group of healthy subjects with a mean age of 51 years (range 44–71 years) had a higher basal acid production than a group with a mean age of 33 years (range 23–42 years)[9]. The age related increase in secretion was greater in men than women and was not correlated with height, weight, body surface area or fat-free body mass, or by the increased incidence of *Helicobacter pylori* infection.

Occasionally, babies are intubated for the purposes of investigating oesophageal reflux, but results are sparse in older children. In twelve healthy children aged 8–14 years, the mean fasting gastric pH was 1.5 and the duodenal pH was 6.4. The pH gradually rises down the small intestine reaching a peak value of 7.4 in the distal ileum[10]. The pH dropped to 5.9 in the caecum but increased to 6.5 in the rectum. In 11 healthy adults, the median pH was 7.0 in duodenum, dropped to pH 6.3 in the proximal part, but rose to 7.3 in the distal part of the small intestine[11]. These values are quite similar and allay fears that, for example, sustained-release or enteric coated dose forms evaluated in adults may not work correctly in children.

pH and smoking

Daytime intragastric acidity is higher in smokers (median pH 1.56) compared to non-smokers (median pH 1.70); however, there is no significant difference in 24 hour or night time pH[12].

GASTRIC MOTILITY

The fasted state

The stomach will revert to the fasted pattern of motility in the absence of digestible food, or when it is empty (Figure 5.10). After a meal, the digestible food will have been processed to chyme and passed to the small intestine leaving a residue of mucus and undigested solids. These remain in the stomach until the small intestine has finished absorbing nutrients from the chyme i.e. approximately 2 h after the last of the digestible food has left the stomach. At this point the digestive phase of activity ceases and is replaced by the interdigestive phase, which is also the normal resting condition of the stomach and small intestine. All gastric residues which the stomach has failed to process to chyme are removed in this phase, the migrating myoelectric complex (MMC) or so-called 'housekeeper contractions'. The MMC removes debris from the stomach by strong contractions against an open pylorus.

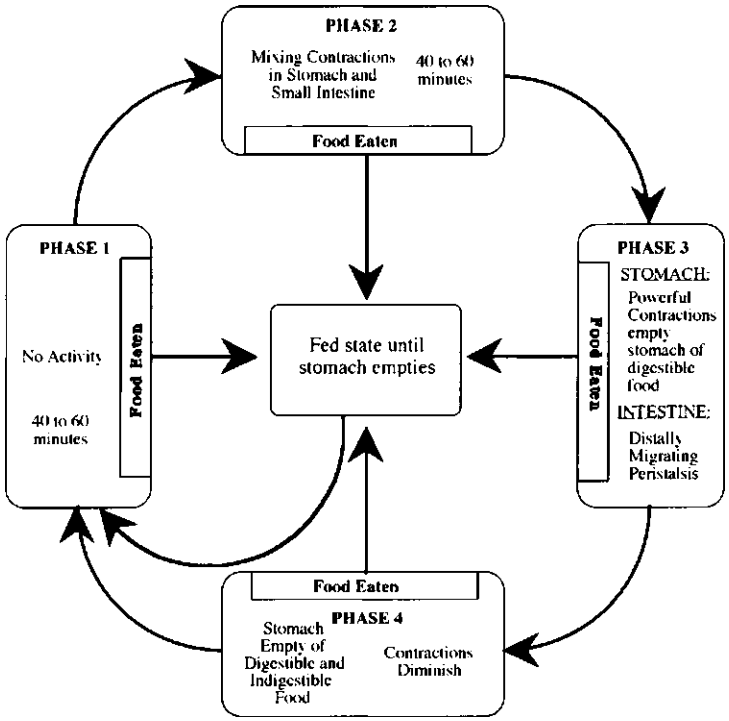

Figure 5.10 The migrating myoelectric complex

Starting from a state in which the stomach and small intestine show no motor activity (Phase I), the activity front begins simultaneously in the antrum and duodenum producing a series of mixing contractions which build up over a period of 60–90 minutes (Phase II). These end in a series of powerful circular peristaltic waves which sweep from the site of origin down the entire small bowel to the caecum emptying all the large solid particles from the stomach and small intestine (Phase III). The waves then subside to the resting phase. The whole cycle repeats every two hours until a meal is eaten, when they are immediately interrupted to initiate the digestive phase of motility. The peristaltic waves can also be halted by an intravenous infusion of a hormone, motilin.

Gastric emptying of the basal gastric secretion occurs even during fasting to prevent accumulation of fluid, as there is very little net absorption by the gastric mucosa.

The fed state

The adult capacity of the stomach is about 1500 ml. The average (western) daily intake of food and drink is 3 to 4 kg, and it is estimated that another 5 litres of fluids such as saliva, gastric juice, pancreatic juice and other body liquids are added to this. The greatest secretory activity occurs in the stomach within the first hour of eating and the volume of gastric juices produced may be up to twice that of the meal.

The uppermost third of the stomach, or fundus, adapts to the varying volume of ingested food by relaxing its muscular wall, holding the food while it undergoes the first stages of digestion. The adaptive process allows it to accommodate the ingested food without increasing intragastric pressure.

The stomach not only elicits a fed pattern of motility in response to the presence of food with calorific value, but it will also respond to the presence of a large quantity of small

particle size indigestible material, suggesting that gastric distention is also a contributory factor[13]. Indigestible material of small diameter (1–3 mm) will elicit the fed pattern of motor activity in dogs, and the duration of postprandial antroduodenal motility patterns can be influenced solely by the size of a meal which comprises only of indigestible material.

The mixing, grinding and emptying of food all occur together. The dispersion of food is more a mechanical process than an enzymatic one. Mixing and grinding are carried out by a series of peristaltic waves which originate in mid-body as a shallow indentation and gradually deepen as they progress toward the duodenum. The velocity of the wave increases until the final 3 to 4 cm of the antrum are reached, at which stage the antrum and pylorus appear to contract simultaneously. This is often called antral systole. Liquids and solids within the distal antrum are compressed as the antral wave deepens. The wave does not occlude the lumen and hence liquid and suspended particles are retropelled through the wave, but larger and denser solids are trapped ahead of the constriction. Once the pylorus has closed, the antral systole grinds and then retropels the solids into the proximal antrum (Figure 5.11). The grinding action, combined with the shear forces produced during retropulsion, reduce the particle size and mixes the particles with gastric juice. The motion and acid-pepsin digestion accounts for the physical breakdown of solid food in this region. The rate of emptying from the human stomach decreases if the ingested solid food is composed of larger masses. Solids are only emptied after they are ground to particles smaller than approximately 1 mm, and the larger, harder particles will take longer to reach this size.

Tonic or sustained motor activity decreases the size of the lumen of the stomach, as all parts of the gastric wall seem to contract simultaneously. It is this type of activity that accounts for the stomach's ability to accommodate itself to varying volumes of gastric content. Mixing contractions and peristaltic contractions are superimposed upon the tonic contraction, which is independent of the other contractions. Both the mixing and the peristaltic contractions occur at a constant rate of three per minute when recorded from the gastric antrum. This rate is now recognised as the basic rhythm, although some drugs are capable of abolishing both types of contractions or of stimulating the strength of contractions. The distension of the body of the stomach by food activates a neural reflex that initiates the activity of the muscle of the antrum.

About twice per minute between 1 and 5 ml of antral contents escape into the duodenum, and decrease the duodenal pH. Emptying from the pylorus occurs in discrete episodes of 2 to 5 seconds only, and the majority of these occur as the terminal antrum,

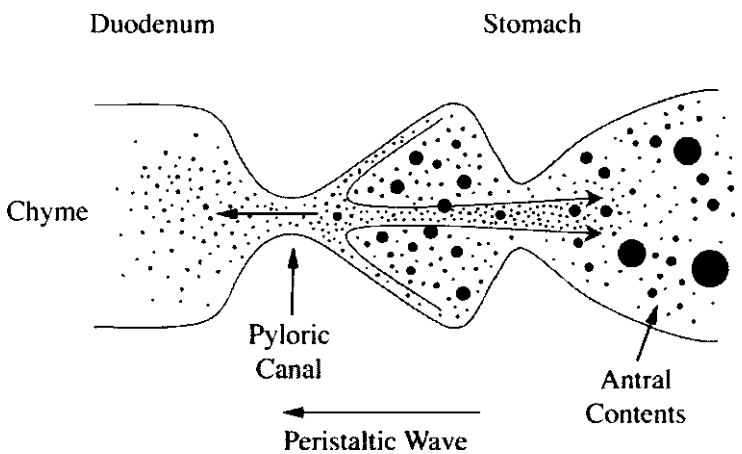

Figure 5.11 Grinding and mixing action of the antral mill Note retropulsion of large particles i.e. sieving

pylorus and duodenum relax at the start and end of each peristaltic cycle[14]. Transpyloric flow ceases approximately 2 seconds before the antral systole occurs[14 15]. It was assumed that the particle size cut-off was produced by the narrow pyloric diameter, but neither pyloroplasty nor pylorectomy alters the size distribution of food passed into the duodenum[16] and the antrum alone can selectively retain solids in the absence of the pylorus. The pylorus appears to be wide open, having an aperture larger than 5 mm, for approximately 15 to 20% of the time[17]. The length of time for which the pylorus is wide open does not completely determine the emptying rate of liquids because the duodenum also seems to apply a braking mechanism. The periodic opening of the pylorus during the fed phase of motility can explain how some large particles, including intact large fragments of tablets, can be emptied during this cycle.

Solids and liquids do not empty from the stomach together as a homogeneous mass. Liquids empty according to the pressure gradient between the stomach and duodenum, with isotonic liquid meals emptying more rapidly than hypotonic or hypertonic mixtures. The liquid component of a meal empties exponentially, but the emptying of solids is linear after a variable lag time (Figure 5.12). The lag phase is dependent upon the size of the food particles in the stomach. Larger particles require a longer period of digestion to break them down into a size suitable to exit through the pylorus. Small indigestible solids of between 1 to 5 mm in diameter are progressively emptied during the whole postprandial period even before liquid emptying is completed. Certain liquids and solids can be clearly seen as two separate layers on magnetic resonance images (Figure 5.13). Interestingly, during episodes of heartburn or gastro-oesophageal reflux, food and acid are refluxed into the oesophagus independently of each other[18]. It is likely that this occurs because the food forms a central core in the body of the stomach. As gastric acid is secreted around the outside of the food mass, it is only mixed effectively with the food in the antrum. Refluxed material originates largely from the upper part of the stomach where mixing is irregular.

Receptors in the duodenal bulb detect the calorific value and hydrogen ion concentration of the chyme causing relaxation of the lower part of the duodenum, and allowing gastric emptying to start. During a duodenal contraction, the pressure in the

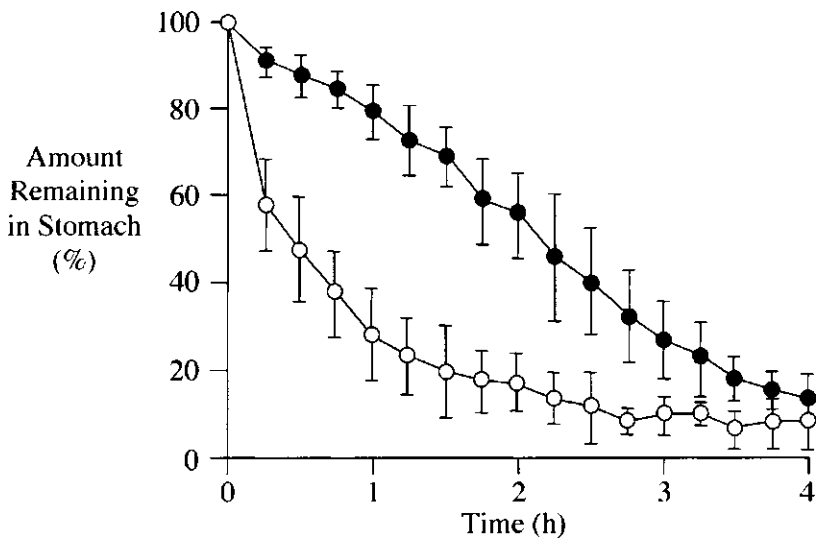

Figure 5.12 Gastric emptying of liquid (○) and solid (●) components of a meal

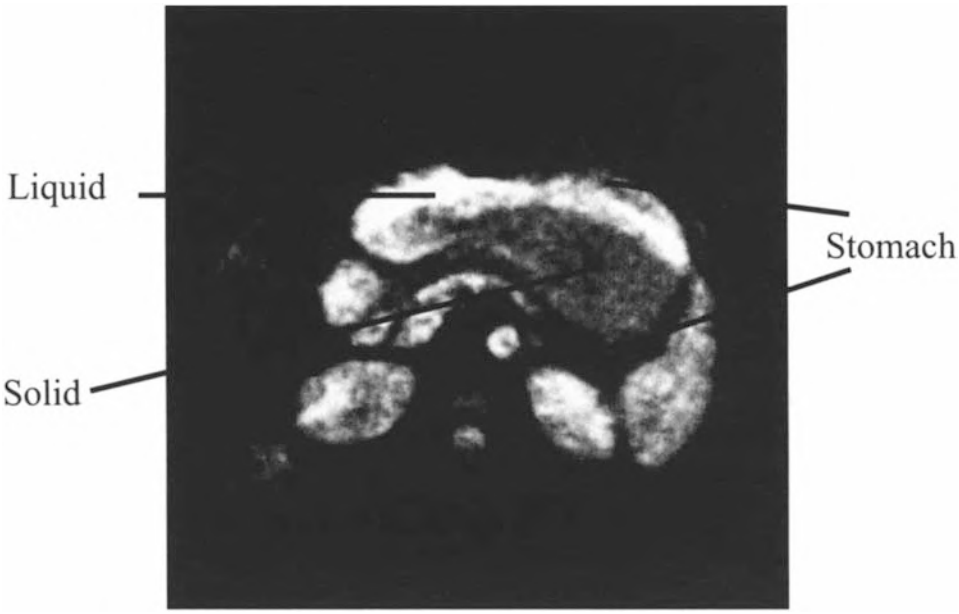

Figure 5.13 MRI cross section through the body. The large organ at the top is the stomach, which clearly shows the liquid layer (white) floating on the solid (grey) matter

duodenal bulb rises above than that in the antrum, and the pylorus prevents reflux by closing. The vagus nerve has an important role in the control of emptying, but studies on paraplegia caused by injury to the spinal cord indicate that the sympathetic division of the autonomic nervous system is also involved.

Effect of meal size and composition on gastric emptying

The empty stomach has a volume of approximately 50 ml which increases to over 1 litre when full. The stomach empties the three different components of the meal, liquid, digestible solid and indigestible solid, at different rates. For example, in a study of the emtying of a mixed meal consisting of soft drink, scrambled egg and radioopaque markers, the separate components had T_{50}'s (the time or half the component to be emptied) of 30±7 minutes, 154±11 minutes and 3 to 4 hours respectively[19].

In general, the larger the amount of food ingested, the longer the period of fed activity; large meals tend to empty more slowly in the first hour and then more quickly compared to a small meal. Gastric emptying rates correlate with the nutritive density of the meal; foodstuffs slow gastric emptying equally when their concentration is expressed as kilocalories per milliliter. It is now believed that two types of receptors exist which control the rate at which the energy density is delivered to the duodenum. Two sets of duodenal receptors are involved, one stimulated by the osmotic properties of the digestion products of carbohydrate and protein, and one by the digestion products of fat. Energy is not actually sensed, but the two sets of receptors behave in tandem to control the delivery of the chyme to the duodenum by energy density.

The emptying of amino acids appears to be solely dependent upon their osmolarity, except for L-tryptophan which delays gastric emptying in concentrations which can be obtained from normal protein digestion[20]. Fatty acids, monoglycerides and diglycerides all

delay gastric emptying, but the greatest delay is produced by fatty acids of chain lengths of 10–14 carbon atoms[21]. The slowing of gastric emptying produced by triglycerides depends upon their rate of hydrolysis to long-chain fatty acids.

Manometric and scintigraphic studies indicate that bland liquids such as water and saline empty from the stomach in gushes associated with co-ordinated contractions of the antrum and duodenum[22]. For example, during the emptying of 600 ml of a bland liquid, 1–3% passed into the duodenum very quickly, followed by a lag phase of 4–6 minutes, with the overall emptying having a T_{50} of only 15 minutes[23].

Food was believed to form layers in the body of the stomach in the order in which it was swallowed, since for the first hour after ingestion of a meal peristalsis is weak, allowing the food to remain relatively undisturbed[24], with the food ingested first being closest to the stomach wall. This data was generated from a study in which rats were fed successive portions of bread, each coloured with a different dye. The animals were killed, the stomachs removed, frozen and sectioned. The portions were found to be separate[25]. This is a simplified case which bears little resemblance to a typical human meal, which consists of a mixture of components of varying density. The human stomach is of course much larger than the rat stomach, so that the effects of sedimentation and stratification are likely to be very different. Pellets with a density of 1.2 g cm^3 sink through food to the base of the greater curvature and are emptied after the majority of food (Figure 5.14). Increasing the viscosity of the gastric contents increases the rate at which dense spheres will empty from the stomach[26]. This suggests that the high viscosity of the medium prevents the spheres from settling into the base of the greater curvature, away from the mixing, grinding and emptying function of the antrum. Materials which have been demonstrated to float *in vivo* can be refloated from the antrum of the stomach to the fundus by the subsequent intake of food[27] thus casting doubt on the theory of stratification.

The effects of fats and oils on gastric emptying

Although it is widely recognised that the fat content of food is the most important factor controlling gastric emptying, the majority of studies over the past 15 years have been carried out in animals such as rats, mice and dogs. The fundamental difference between these

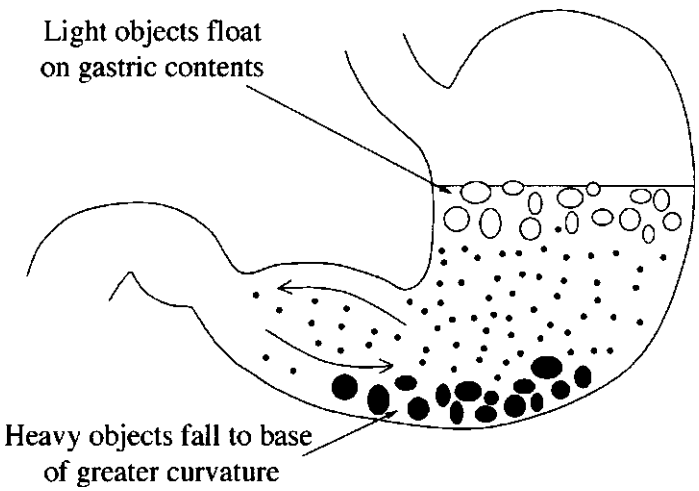

Figure 5.14 The effect of density on gastric distribution

species and man is posture, and since certain types of fat will layer in the stomach, their presentation to the pylorus and duodenum naturally will be different in relation to other components of the meal. This is due to the effect of gravity. This effect can be demonstrated in man since olive oil empties more slowly than an aqueous component of a meal when subjects are seated whereas, in the decubitus position (lying), it empties faster[28 29].

The delayed emptying of fat is not just due to the fact that it floats on the meal, and hence emptyies last when subjects are upright, but the presence of fat in the intestine causes the fundus to relax. This lowers the intragastric pressure, increasing the reservoir function of the stomach. It also inhibits antral contractile activity, increases pyloric contraction and narrows the pyloric lumen[15]. This has the effect of significantly increasing the lag phase of the meal after an initial amount has entered the small intestine[23]. The movement of food from the proximal to the distal stomach still occurs; however, it is followed by a retrograde movement of food back to the proximal stomach, and this may also contribute to the increased lag phase. This redistribution of food in the stomach is also seen after intraduodenal infusion of lipid[30]. Interestingly, the emptying of the oil follows a linear pattern rather than the expected monoexponential emptying typical of liquids.

Dietary fat is ingested in three forms: 1) in solid food, 2) as aqueous emulsions, and 3) as unemulsified, liquid oil. To complicate matters, the gastric residence of a meal with identical composition will be prolonged if the fat content is used to fry the food rather than ingested as the cold oil[31]. Ingestion of a high fat meal increases satiety and a feeling of epigastric fullness for a longer period than an energy-matched low fat meal. It will influence the amount of food taken at the next meal even though the amount of food remaining in the stomach from the first meal is approximately the same[32]. The addition of fat to a meal will also prolong the time for which the meal elevates gastric pH[33].

The behaviour of oils within the stomach is also affected by the other constituents of the meal. When 60 ml of ^{99m}Tc labelled oil was given to subjects with 290 ml of ^{113m}In-labelled soup, gastric emptying of the oil was significantly slower than the soup (time to 50% emptying 139 versus 48 min)[34]. Oil was retained in the proximal stomach and retrograde movement of oil from distal into proximal stomach was noted. The second arm of this study investigated the relative gastric residence time of ^{113m}In-labelled minced beef, ^{99m}Tc-labelled oil and non-labelled soup. In this case, there was no difference in emptying of oil and beef from the stomach, but again more oil was retained in the proximal stomach whereas more beef was retained in the distal stomach. In another study[35] the effect of adding 60 g of margarine into either the soup or mashed potato component of a meal was investigated. The addition of margarine to either component significantly delayed the gastric emptying of the mashed potato, but the pattern of emptying of the potato varied depending which component was fat-enriched. Incorporation of fat into the soup increased the lag phase but did not influence the slope of emptying of the mashed potato, while incorporation of fat into the mashed potato reduced the slope of emptying of the mashed potato but did not influence its lag phase.

When ingested as part of a mixed meal, water invariably leaves the stomach faster than fat[36]. Solid fat, extracellular fat, and intracellular fat phases of a meal empty together, in parallel, after an initial lag[26]. The way in which fat is emptied from the stomach is species dependent. In humans, significantly less extracellular fat than intracellular fat empties from the stomach on or in solid food particles (22% versus 51%). In dogs, 81% of the extracellular fat empties as an oil, 13% empties on the solid particles, and only 6% empties as a stable, aqueous emulsion. Sixty-six percent of the intracellular fat emptied in the solid food particles, 20% as a stable, aqueous emulsion, and 14% as an oil. The conclusion from this study was that the majority of the intracellular fat empties within the solid food phase, whereas most of the extracellular fat empties as an oil phase[26].

Dietary fats leave the stomach faster, but are absorbed less efficiently, after homogenised meals, compared to being given as a mixed phase meal[37]. Co-ingestion of fat with carbohydrate results in a significant flattening of the postprandial glucose curves, the effect being more pronounced for carbohydrates such as mashed potatoes which are more rapidly absorbed than carbohydrates such as lentils[38].

In humans, duodenogastric reflux occurs both after meals and under fasting conditions. The reflux rate is on the average 13 times smaller than the emptying rate, but is higher with a lipid than with a protein meal, and is independent of the rate of gastric emptying. The concentration and total amount of duodenal contents refluxed back to the stomach were higher after lipid than after protein meals. The increased gastric concentration and accumulation of duodenal contents after lipid meals is due to slowed gastric clearing and increased reflux of duodenal contents. Under fasting conditions, the reflux rate was lower and the gastric concentration of duodenal contents was higher than after either type of meal[39].

The distribution of the fat within the stomach can be changed with disease. Patients with non-ulcer dyspepsia demonstrate an abnormal intragastric distribution of dietary fat. In control subjects, approximately three-quarters of the fatty test meal was located in the proximal stomach during the lag period and during emptying. In the group of patients with non-ulcer dyspepsia, significantly less of the fatty test meal was found in the proximal stomach during emptying, and the time taken for half the meal to empty was significantly delayed[40].

It is often believed that a high fat meal produces nausea in conjunction with motion. However, the nausea produced does not appear to be related to the fat being present in the stomach, but rather the small intestine[41]. Nausea is at its greatest when motion of the body occurs when half of a fatty meal has emptied into the small intestine, but is interesting that gastric residence of the fat is not correlated with the symptoms.

There is a positive correlation between lipid intake and reflux in morbidly obese people[42]. This is likely to be due to a combination of an increase in gastric residence of the meal due to the high calorific density of the fat, and a decrease in lower oesophageal sphincter pressure produced by fatty meals. Interestingly, intravenous lipid emulsions do not affect lower oesophageal sphincter pressure or increase pathological reflux episodes[43].

Physiological factors which influence gastric emptying

Gastric emptying follows a circadian rhythm, with slower emptying occurring in the afternoon compared to the morning (Figure 5.15)[44]. This effect can be very marked; in the study illustrated there was over a 50% decrease in emptying rate in the solid phase of the meal when it was eaten in the evening compared to the morning.

In women, pregnancy and the menstrual cycle can drastically alter the transit of materials in various regions of the gastrointestinal tract. Often pregnant women suffer from heartburn and constipation which is attributed to decreased oesophageal pressure and impaired colonic motility. During the normal menstrual cycle mouth to caecum transit is significantly longer in the luteal phase than in the follicular phase[45].

There are conflicting reports as to the effect of obesity on gastrointestinal transit. Some studies show no effect, whilst others report delayed emptying of solids particularly in men, a phenomenon which is not reversed after significant weight loss[46 47]. Other studies show an inverse association between body mass index and mean gastric emptying time of test meals such as radiolabelled cellulose fibre. Body mass index had no influence on other transit variables[48].

Heavy exercise was found to increase the gastric emptying rate of digestible solids in healthy men[49].

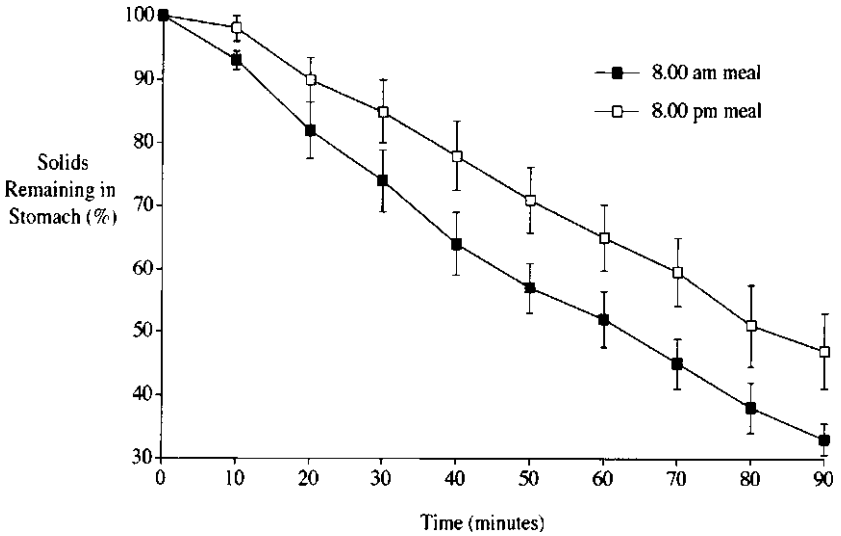

Figure 5.15 The effect of time of day on the rate of gastric emptying

Effect of disease on gastric emptying

Diseases which affect gastric motility and emptying are predominantly diseases of the gastrointestinal tract itself, disorders involving smooth muscle and extraintestinal diseases. Some diseases only affect one of the phases of gastric emptying. Generally duodenal ulcer produces accelerated emptying, while gastric ulcer reduces antral motility, producing normal emptying of liquids but delayed emptying of solids[50]. Emptying of a solid meal is slowed in patients with pernicious anaemia[51] and atrophic gastritis[52], but in achlorhydric patients liquids empty rapidly[53].

Gastro-oesophageal reflux is a common disease affecting between 10 and 20% of the general population[54], although the true magnitude of the condition is not known since a large proportion of sufferers self-medicate[55]. It is therefore likely that within a given patient group a significant proportion will be suffering from this disease to some extent. The effect of this disease on gastric emptying is unclear since some studies report no effect on the emptying of liquids[56] or mixed meals[57], whilst others demonstrate a delay[58–60]. It is possible that the emptying of solids in a mixed meal is selectively delayed[61] suggesting impaired antral motility. This would lead to a greater difference in emptying between liquids, pellets and tablets than in normal subjects.

Migraine is frequently associated with nausea (95%) and vomiting (20%) and there is some evidence that gastric emptying is delayed during migraine attacks.

The eating disorders bulimia nervosa and anorexia nervosa are believed to affect between 5 and 10% of adolescent females and young women in the western world. Bulimia does not affect gastric emptying, but anorexia produces both delayed solid and liquid emptying[62].

DISPERSION OF DOSAGE FORMS IN THE STOMACH

The most commonly used type of dosage form is the conventional compressed tablet. Despite the use of scintigraphy to evaluate more sophisticated dose forms[63], there has been surprisingly little study of the behaviour of ordinary tablets. Most workers assume that tablets will disintegrate rapidly *in vivo* due to the use of superdisintegrants and the evidence

of *in vitro* dissolution tests; however this is often not the case. Endoscopy has demonstrated that when multiple tablets are administered, all lie in the same place in the stomach, at the base of the greater curvature. This is a particular problem with formulations which cause gastric irritation or damage, for example non-steroidal anti-inflammatory drugs which can produce focal erosions due to repeated insult to a small area of the mucosa. Iatrogenically-produced ulcers can often be differentiated from those of natural origin, since drug-induced erosions usually occur at the base of the greater curvature, whereas peptic ulcers form on the lesser curvature. Multiple unit dose forms can also cause mucosal damage; for example microencapsulated potassium chloride showed similar gastric mucosal irritation to single units. This was attributed to poor dispersion of the potassium chloride, with clumps of the drug held together with gastric mucus[64].

Hard gelatin capsules

Hard gelatin capsules have found a variety of applications in drug formulation. The capsule can be used as a container for powdered drug, multiparticulate systems, a liquid-fill matrix or oily vehicle. The nature of the interior of the fill of the capsule is known to affect the rate of disintegration within the stomach. A hydrophobic interior reduces the rate of disintegration of the capsule compared to that of a water soluble material, and in addition it reduces the dispersion of the released material. When capsules contain components which are insoluble in gastric juice, then their disintegration time is of the order of 30 minutes in fasted volunteers and 100 minutes in fed volunteers[65]. Changing the fill to a water soluble material decreases the break-up time to 6 minutes.

The dispersion of the capsule fill is limited in fasted subjects, and the material empties from the stomach as a bolus[66–68]. Dispersion is increased if the capsule is taken with a meal, particularly if the meal has a high liquid content. This is of importance since patients are often instructed to take medications with a meal, but it is unclear whether this means before, during or after food. If capsules are given with 100 ml of water, they will initially float above the gastric folds. Rapidly the ends of the capsule become sticky and can become attached to the gastric wall, which may be another explanation for the poor dispersion of the capsule contents[64].

The dispersion of milled resin administered in a hard gelatin capsule in fasted volunteers was greatly reduced when it was milled from 25 μm to 9 μm[66 68]. It was proposed that this was due to changes in the hydrophobicity of the surfaces, arising from chemical and physical variations in the resin through the bulk of the particle. It is equally likely that milling changes the wettability of the material due to variations in particle surface roughness.

Soft gelatin capsules

There have been relatively fewer studies of the behaviour of soft gelatin capsules in man. Pilot studies indicate that the time of disintegration of soft gelatin capsule formulations is highly variable, particularly if the formulations are given without food. The capsules were predominantly broken up as they entered the pylorus immediately prior to leaving the stomach (unpublished data). Armstrong and co-workers[69] have compared the dispersion of oils from soft gelatin capsules in man and rabbits using x-ray techniques and gamma scintigraphy. Soft gelatin capsules were filled with iodinated cotton seed oil (Lipiodol) for x-ray studies, or iodine-123 labelled ethyl oleate for gamma camera studies in humans. In x-ray studies of rabbits, disintegration of the capsule began after 2 to 3 minutes, swelling into a more isometric shape. This behaviour was observable *in vitro* and was associated with the breakdown of the capsule at the sealing line. Subsequently it was difficult to assess whether the shell had dissolved with the oil as one discrete globule, or whether the oil had

emerged from the shell before it had completely dissolved. When a surfactant (1% polysorbate 80) was added to the formulation, the mean disintegration time of the soft gelatin capsule decreased markedly.

GASTRIC EMPTYING OF DOSAGE FORMS

For the majority of cases, oral drug delivery is the cheapest and most convenient method of dosing. Unfortunately it is difficult to achieve a precise control of the plasma concentration-time profile, which shows marked intra- and inter-subject variation even under the rigidly controlled conditions of the clinical trial. In the unrestricted patient this is exaggerated by poor compliance and anything more complicated than a b.d. schedule is impractical. Daily patterns such as food intake, activity and posture are large contributors to inter- and intrasubject variation. The nature of food intake is not only specific to race and geographic location but unique for each person, and varies on a day-to-day basis. This factor probably produces the largest physiological variation in the behaviour of oral dose forms. The rate of gastric emptying, the presence of food or other drugs, the particular formulation of the drug (size, shape and rate of disintegration), and the vehicle carrying it all influence the absorption of the drug.

Once the dosage form has reached the stomach, it meets an highly variable environment in terms of food content and pH. The gastric emptying of tablets, pellets and liquids is highly dependent on the presence and amount of food in the stomach. Large tablets can either disintegrate in the stomach and empty with the digestible phase of the meal, or if they are designed to remain intact will be treated as indigestible material since they do not possess a significant calorific value. Large non-disintegrating capsules will empty with phase III of the MMC, and since ingestion is not synchronised to any particular part of the cycle, the emptying will appear erratic, occurring any time between a few minutes and 3 hours after administration.

When a large unit is given after a light meal (1500 kJ) the emptying becomes more predictable at around 2 to 3 hours. The meal serves to put the motility cycle into phase by initiating the fed pattern until the small calorific load has been passed to the duodenum. The next MMC then removes the tablet approximately 2 hours after the stomach has been cleared of the digestible components of the meal. Dosage forms are often administered to fasting subjects during pharmacokinetic studies in an attempt to reduce variability, but the effect of erratic emptying can affect the time of appearance of the drug in the plasma. However if the formulation is given with food to synchronise motility, the absorption of the drug can be influenced by the food. A possible solution is to give the drug with apple juice, which is a clear liquid, but has sufficient calories to synchronise gastric motility.

If a large single unit is given with a heavy meal (3600 kJ) and the subject is fed at regular intervals, the unit can remain in the stomach for longer than 8 hours due to prolonged suppression of the MMC. The only time at which the stomach can revert to the fasted pattern of motility is during the night when there is a sufficient interval between dinner and breakfast[70]. The length of the retention is proportional to the meal size. Thus when given with a meal of 650kJ, the mean residence time of a controlled release ibuprofen formulation was 2.0±0.9 h; when the size of the meal was increased to 3330 kJ, the mean residence time was in excess of 9±3 h. In the fasted state, the mean residence time was 1.0 ±0.4 h[70].

The effect of administering a large non-disintegrating tablet (11×6 mm, density 1.4 g ml^{-1}) with several different feeding regimens is shown in Figure 5.16[71]. It can clearly be seen that the continual intake of small meals throughout the day, such as is common in the Western world, can delay the emptying of the tablets for more than 10 hours. Increasing the calorific value of a liquid meal by nearly 4-fold did not produce a proportionate increase in gastric residence time, but a mixed meal with similar calorific value to the liquid meal

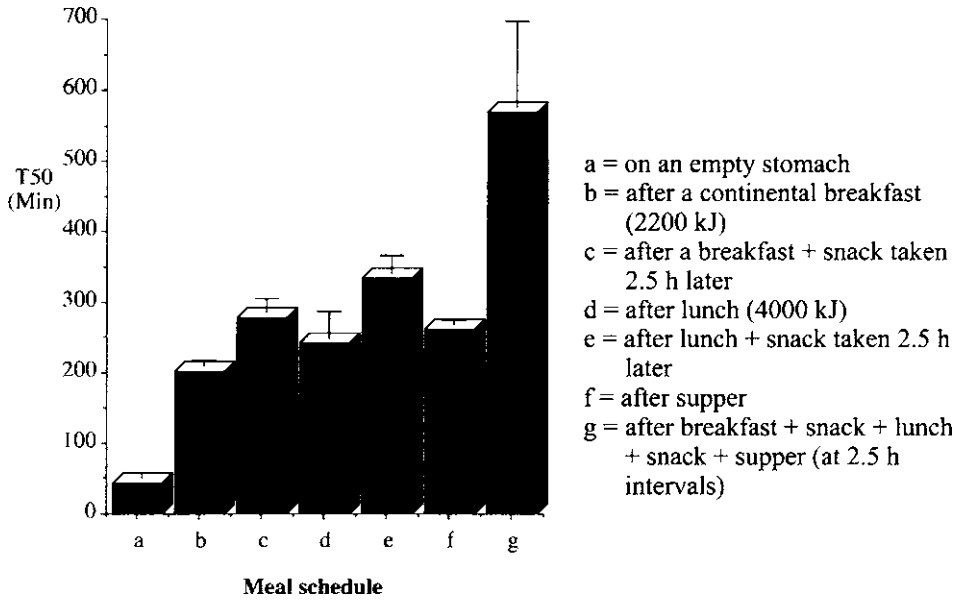

Figure 5.16 Gastric residence time of a large non-disintegrating unit (11×6 mm, density 1.4 g ml^{-1}) with different feeding regimens.

nearly doubled the residence time of the tablet. The ingestion of snacks increased the gastric residence time of the tablet by about 1.5 hours, but as the original meal size increased the difference became less significant due to the greater variation in emptying.

The effect of meal size on the gastric emptying times of single units is extremely important, especially for enteric coated preparations since this is the main factor influencing the onset of drug release from enteric coated tablets[72]. The definition of a "large" tablet is still not known for humans. Tablets of between 3 and 7 mm empty similarly from the stomach after light, medium and heavy meals, and it is the calorific value of the meal and not the size which influences the emptying significantly[73].

The gastric emptying rates of multiparticulate dosage forms are not as severely affected by the presence or absence of food as are large single units. The gastric emptying of encapsulated pellets from the fasted stomach depends upon the nature of the capsule, the speed at which it disintegrates and the degree of dispersion of the pellets in the low volume of gastric contents available[74]. It has been proposed that dispersion of the capsule contents occurs into the mucus, followed by clearance at the normal mucus turnover rate, so that the emptying of pellets from the fasted stomach was a random event with the pellets emptying as a series of boluses. When pellets are administered with a meal, they tend to empty in a similar fashion to the digestible component of the meal (Figure 5.17).

The discrimination of the emptying of dosage forms produced by the presence of food can clearly be seen in a study in which a large non-disintegrating single unit (an osmotic pump device) and a pellet formulation were administered together (Figure 5.18). When administered with the light breakfast, in the majority of subjects, the single unit had emptied by 2 hours amidst the pellets; however the heavy breakfast greatly delayed the gastric emptying of the single unit to more than 9 hours. The emptying of the pellets was also prolonged by the heavier meal, but not to the same extent as the single unit[75].

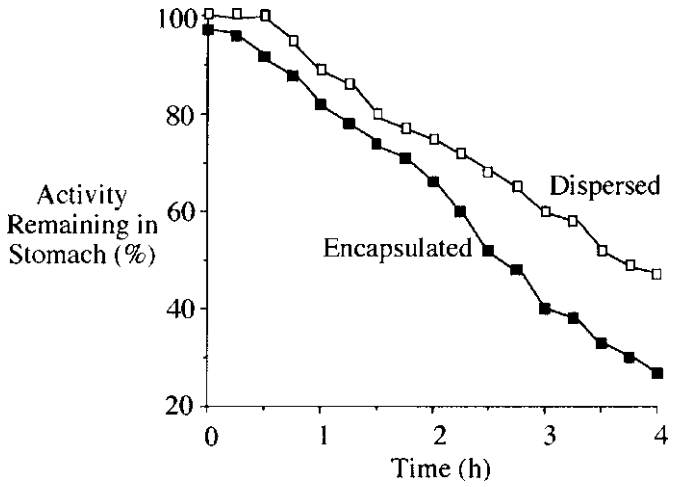

Figure 5.17 The gastric emptying of multiparticulates in a hard gelatin capsule taken either "with a meal or dispersed within a meal

Time of dosing relative to a meal

Often patients are instructed to take their medication "with a meal", but instructions are never precise and this can be interpreted by the patient as taking the medication immediately before, midway through or just after the food. After dosing with a capsule containing pellets during or 10 minutes after a meal, pellets tend to remain in the upper half of the stomach. In these cases, the gastric emptying pattern is approximately linear with time. If the capsule is taken 10 minutes prior to a meal, the pellets empty faster following an exponential pattern (Figure 5.19)[76].

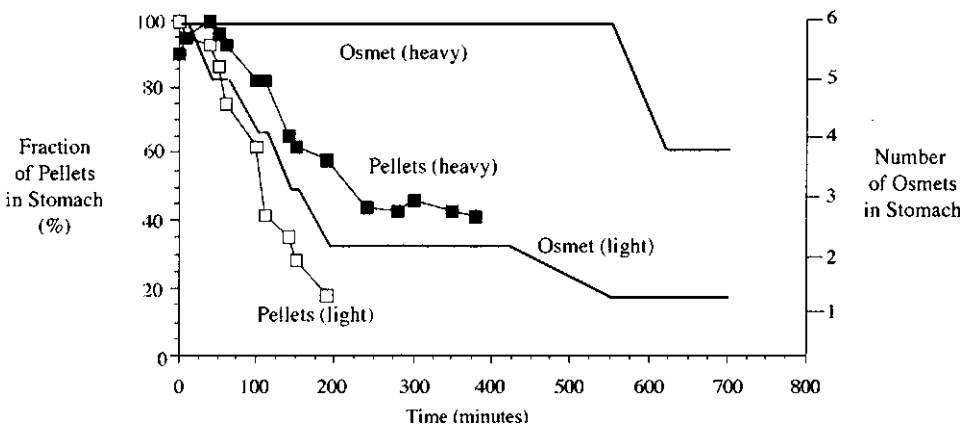

Figure 5.18 The effect of meal size on the emptying of single units (Osmets®) and multip articulates. Note that at 12 h four of the large units were still in the stomach, however, the released drug had emptied from the stomach

Anti-reflux agents provide an example of how certain medications, particularly those which float on the gastric contents, are affected by time of dosing relative to a meal. Ingestion of an anti-reflux agent prior to meal causes it to empty before the food, and in addition it does not form the floating raft which is required for its action[77]. However, the anti-reflux agent does float when administered 30 minutes after a meal and hence its emptying is delayed with respect to the food. The gastric residence of floating formulations can be prolonged by frequent intake of meals[27] since ingestion of subsequent meals will delay the emptying of both the original meal and the formulation[78].

Retention of formulations in the stomach

There are several advantages in the use of formulations which remain in the stomach. For example, improvement in local delivery of drug to treat infections such as *Helicobacter pylori,* or prolonging the exposure of the upper small intestine to high concentrations of drug. This also may be advantageous for drugs which are acid soluble. Gastroretentive dosage forms will significantly extend the period of time over which drugs may be released, and thus prolong dosing intervals and increase patient compliance.

Many systems have been reported in the literature and the majority rely on floatation mechanisms to produce gastric retention. The prolonged gastric emptying of these formulations relies entirely on the presence of food in the stomach and they are generally emptied either at the end of the digestive phase, or with the MMC if they are large.

A hydrodynamically balanced system (HBS) was the first low-density formulation to be described. It is simply a capsule containing a mixture of drug, gel-forming hydrophilic polymer and excipients such as hydrophobic fatty materials. Upon contact with gastric fluid the capsule shell dissolves and the drug-hydrocolloid mixture absorbs water and swells to form a soft-gelatinous barrier. As the outer layer is eroded, a new layer is continually formed and the drug is released by diffusion through the hydrated layer[79]. To improve buoyancy and drug release the formulation was modified by the addition of a second layer of HPMC. Flotation of the HBS was visualised in volunteers using endoscopy[80].

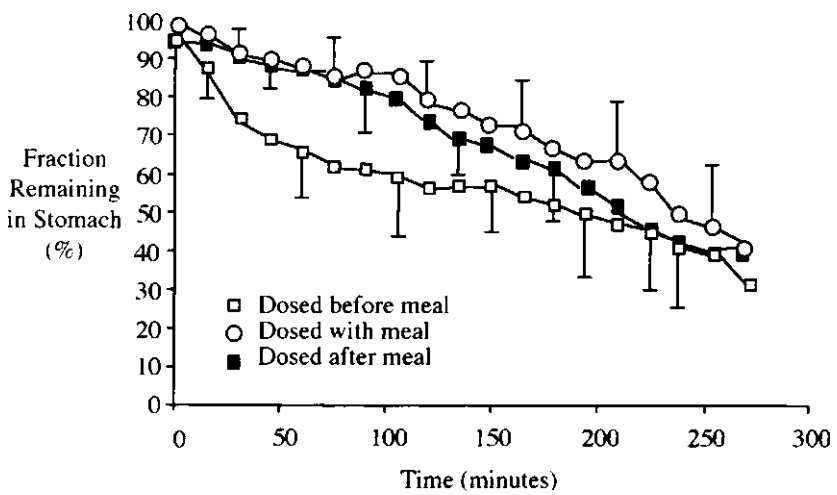

Figure 5.19 The effect on emptying of dosing time of a multiparticulate with respect to a meal

In order to improve buoyancy, an important strategy has been to incorporate gas producing agents such as sodium bicarbonate within the formulation. The systems may be composed of single or multiple layers and the gas-generation agent can be incorporated into any of the layers. Alternatively, ion-exchange resin can be loaded with bicarbonate and coated with a semipermeable membrane. Another approach has been to start with a buoyant core e.g. an empty hard gelatin capsule, polystyrene foam or concave tablet shell[81].

In vivo studies have shown that gastrically retained dose forms can produce up to 25% increase in bioavailability for agents such as riboflavin[82], but others report no effect for drugs such as acetaminophen in fasted or fed states[83]. Floating formulations can be a disadvantage for some drugs such as amoxycillin trihydrate, which show a reduction in bioavailability compared to conventional systems[84].

In contrast to floating systems, high density systems also have been investigated as a method for retaining dose forms in the stomach. The rationale behind this approach is that a dense object will fall through food and sit at the bottom of the greater curvature away from antral mixing. These devices have been used to great effect in animals, particularly ruminants, and early work in humans appeared promising at first. The studies reported that increasing the density of a multi-particulate dose form from 1 to 1.6 gcm^{-3} significantly increased the transit time in ileostomy subjects[85]. Unfortunately the results were later found not to be reproducible[86]. No differences in transit were found for pellets of 0.94 and 1.96 $g\ cm^3$ [87] or for single units with densities of 1.03 and 1.61 $g\ cm^3$ [88]. A number of subsequent studies have also failed to find an effect of formulation density until very high densities are reached e.g. 2.8 $g\ cm^{-3}$ [89]. In this case gastric emptying can be significantly prolonged in both fasted and fed subjects, but small intestinal transit time is unaffected.

Studies conducted in dogs have demonstrated that spheres empty from the fed stomach as a function of their diameter, their density and the viscosity of the gastric contents[90]. The smaller the diameter (between 1 and 5 mm), the faster the spheres emptied; however spheres smaller than 1 mm did not empty any faster than 1 mm spheres. Spheres which were more or less dense than water emptied more slowly than the same size spheres with unit density. The explanation given for this is that the lighter spheres floated and the heavier spheres sank and so moved out of the central aqueous stream. Increasing the viscosity of the gastric contents caused even large dense spheres to empty more quickly, possibly because it retarded the layering of the spheres to the base of the stomach. This phenomenon has been observed in human subjects dosed with different density pellets. Pellets which floated on or sank to the base of the stomach emptied more slowly then pellets of a similar density to food. When the light and heavy pellets were administered with a small meal, their emptying was similar to that seen with pellets of a similar density to food when administered with a large meal (Figure 5.20). This suggests that the light and heavy pellets are not caught up in the antral flow.

The gastric retention of solid dosage forms may also be achieved by mucoadhesion, in which case the dosage form will adhere to the mucosal surface of the stomach wall. Once attached, it will remain there until mucus turnover sloughs it off. The mucoadhesives which have been tried are polycarbophil and Carbopol®. Studies in animals and humans have produced rather disappointing results and the main problem appears to be that these polymers are such good adhesives that they stick to anything they come into contact with. Hence they will stick to the gelatin released from the capsules in which they were dosed, or to water-soluble proteins present in the stomach, and also sloughed mucus. This non-specific adhesion severely reduces the amount of bioadhesive available to stick to the epithelial mucus.

Earlier studies conducted in dogs used slurries of polycarbophil particulates (1–3 mm in diameter) at doses of 30 and 90 g[13]. The meal containing the 90 g polycarbophil slurry demonstrated a decreased rate of gastric emptying. At autopsy, the particles were shown not

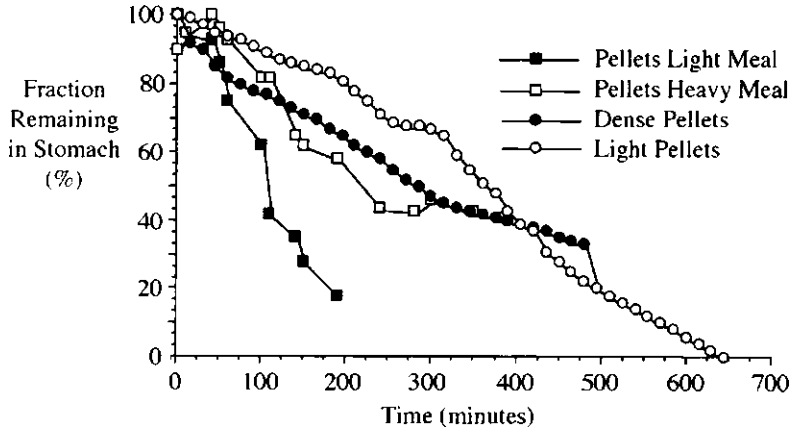

Figure 5.20 The effect of pellet density and size of a meal on the gastric emptying of multiparticulates

to have adhered to the mucosa, but to have formed large intragastric boluses. Apparently that the slow rate of emptying of the polycarbophil was due to the action of the stomach squeezing the particles together, causing a loss of surface-bound water and forming a large bolus; occasional retropulsion mixed the bolus with the gastric secretions causing some re-dispersion of particles. The gastric distension produced by the large indigestible mass elicited the fed pattern of activity and the fasting peristaltic waves were suppressed.

Another gastroretentive system is the magnetic dose form. This usually contains a magnet, or a mass of magnetic material such as a ferrite, in its centre and an externally placed magnet serves to anchor the dose form within the body. Drugs which have been delivered by this method include cinnarizine, acetominophen and riboflavin, all of which showed improved bioavailability. The major drawback with this method is that placing the external magnet to hold the tablet in the stomach is technically quite difficult. To make magnetic tablets commercially viable a better method for applying the magnetic field needs to be produced than that currently available.

Dose forms that unfurl or expand in the stomach, becoming too large to exit through the pylorus, have also been proposed to achieve prolonged gastric residence. Geometric shapes which have been studied include a continuous solid stick, a ring and a planar membrane. In fasted beagle dogs retention times of over 24 h were reported[91], but in humans the time was reduced to 6.5 h in the fed state and 3 h in the fasted state. The main problems with this type of system is that they have to exit the stomach eventually, and hence have to be biodegradable as well as having expanding properties. This can pose severe design restrictions. In addition, like all sustained release devices, the systems would have to have a high reliability since they would be designed to administer a large dose of drug over an extended period. Adhesion of dosage form to the oesophagus is common, and the possibility of a device sticking and expanding in the oesophagus is unpleasant to say the least. Swellable systems would also have to be able to withstand the 80 to 100 mmHg pressures generated in the human pylorus[22 92]. These combined difficulties have outweighed any potential advantaged for manufacturers to date.

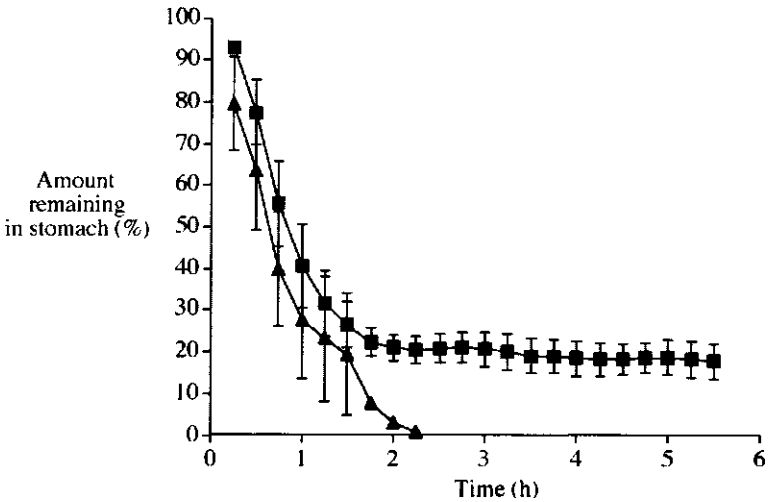

Figure 5.21—Gastric retention of a suspension of 20–40 μm ion exchange resin (■) compared to 99mTc-DTPA (▲) which is a water soluble marker

One promising method of achieving gastric retention is by the use of micronised ion exchange resins[93]. Ionic resins are already in use as drug delivery vehicles[94], in which release from the resin occurs through the replacement of the drug by another ion of the same charge. Recent studies[95] have shown that if micronized resins are administered in a small volume of water, they coat the stomach uniformly, and approximately 20% of the resin is retained for 5–6 hours and is not dislodged by subsequent meals (Figure 5.21). Anionic resins such as cholestyramine have been shown to display better mucoadhesive properties *in vitro* than cationic polymers[96]. This was thought to be due to ionic interactions between the highly charged surface of the polymers and the mucus.

Posture effects

Moving from the upright to the supine position markedly effects the emptying of formulations and hence the rate and extent of drug absorption. Bland, unbuffered liquids and pellet formulations empty more slowly from the stomach when the subject is lying down compared to when upright or sitting erect[67 97]. For floating formulations, such as raft-forming alginates, the buoyant raft empties faster than food in subjects lying on their left side or their backs, and slower in subjects lying on their right side with the raft positioned in the greater curvature[98]. When the subjects lay on their left side the raft was presented to the pylorus ahead of the meal and so emptied first. Oily materials float and hence also empty more slowly than the aqueous phase of the meal when subjects are in the sitting position[28]. Posture also affects the emptying of large non-disintegrating capsules from the fasted stomach. Capsules are only passed into the duodenum during phase III of the first MMC initiated when the subjects are lying in the right lateral position[99]. The gastric residence of floating and non-floating capsules is similar in supine subjects[100].

Posture can also affect drug absorption. The time to maximum plasma concentration of coadministered soluble paracetamol, nifedipine, and its metabolite produced at first pass, was significantly decreased when subjects are standing or lying on their right side compared to when they lay on their left side[101]. These postures also resulted in a significantly higher

peak plasma concentration and area under the plasma concentration-time curve of the nifedipine, but not its metabolite. The increased absorption of these drugs also produced a significantly higher heart rate. Lying down decreased the rate of gastric emptying when compared to sitting, and a combination of sitting and standing produced the most rapid gastric emptying[102].

Drug-induced effects on gastric emptying

Drugs contained within the formulations may also alter gastric motility. For example adrenergic agonists, particularly $ß_2$-agonists such as salbutamol, delay gastric emptying. In asthmatic subjects an variable quantity of the inhaled drug may be swallowed, and hence even though the drug is not taken by the oral route, it may still have an effect on the gastric emptying of other drugs. Tricyclic antidepressants and some anti-Parkinsonian drugs depress gastrointestinal motility. Dopaminergic antagonists e.g. domperidone, and cholinergic agonists e.g. bethanechol, enhance gastric motor activity.

GASTRIC pH AND ENTERIC COATINGS

In the past, the pH chosen by most formularies to represent the conditions in the stomach is 1.0 (100 mM HCl). However, there is some evidence that the basal gastric pH can be surprisingly high. It has been reported that 35% of humans have a resting gastric pH of 6 or above[103]. Less than 2% of the human subjects had a resting pH below 1.5. Basal gastric pH in normal healthy students is around 1.8, but occasional cases of achlorhydria are seen. Meals markedly alter the pH, which can increase to 3–5 after eating, particularly if the meal contains large amounts of easily digested protein.

These variations in pH will be especially important when developing products designed to be gastro-resistant, e.g. enteric coatings for acid-labile or potentially irritant drugs. In these cases gamma scintigraphy may be combined with *in vivo* pH measurement to investigate the efficiency and operation of the enteric coating. In a study which administered both radiolabelled pH radiotelemetry capsules and radiolabelled enteric coated naproxen tablets to fed subjects[72], it was found that the pH remained below 2 within the stomach, except for a transient rise after food. Five tablets disintegrated in the small intestine approximately 1.2 h after gastric emptying, 1 disintegrated in the stomach at pH 1.1 and 1 tablet remained intact in the stomach for 9 h.

DRUG/FORMULATION INDUCED ULCERATION

Acute and/or chronic lesions on the gastric mucosa may result from the ingestion of alcohol, and some drugs such as anti-inflammatory drugs, reserpine, histamine and caffeine. Salicylates are often reported to produce dyspepsia and gastric ulcers due to their widespread use. A single dose of 2 aspirin tablets produced haemorrhaging in the stomach of normal volunteers within 1 hour of ingestion, continued intake (2 tablets every 6 hours) resulted in gastric erosions in all subjects and duodenal erosions in 50% of the subjects[104]. Patients who require aspirin on a regular basis should take enteric coated or adequately buffered preparations.

ANIMAL MODELS FOR GASTRIC EMPTYING

Dogs are widely used to assess the absorption of drugs. However, the drug absorption profiles differ quite considerably from those in humans, and this is a particular problem when attempting to obtain useful data for either sparingly water-soluble drugs or sustained release preparations.

The anatomy and dimensions of the upper gastrointestinal tract of dogs and humans are essentially similar. The volume of the stomach is 1–1.6 L in man and about 1 L in dogs. The length of the duodenum is 25 cm in both species and the jejunum is 185–250 cm in dogs and 300 cm in man. The diameter of the small intestine is 2–2.5 cm in dogs and 3–4 cm in man. The ileum and colon are substantially shorter in dogs than man.

During fasting, intragastric pH in man varies between 1.3–1.8, but the corresponding pH in the dog is between 0.8 and 8. Kuna[103] reported that 77% of 403 dogs had a fasting pH of 6 or above. Sometimes the resting gastric pH is indistinguishable from the duodenal pH. The rate of acid secretion is much lower in dogs, being 0.1 $mEqh^{-1}$ compared to 2–5 $mEqh^{-1}$ in man.

It is also thought that dogs have a faster total gastrointestinal transit time than man, and hence bioavailability is generally underestimated. However, in dogs, a normal meal can induce a fed pattern for approximately 12 to 14 hours, but in humans this usually only lasts for between 3 to 4 hours. Rigidity is an important factor in the retention of dosage forms. In dogs, rigid rings with a diameter of 3.6 cm are well retained in the stomach for 24 hours, whilst pellets and strings demonstrated rapid emptying[105]. In dogs pellets tend to empty from the stomach entrapped in plugs of mucus[106]. Dogs have a delayed onset of MMC compared to man[107 108].

Pigs are also not a good model for the gastrointestinal transit of large non-disintegrating capsules. One study demonstrated a gastric residence time of 5 days for an enteric coated non-disintegrating magnesium hydroxide caplet (1.5 g ml density, 19.6×9.5 mm, 1.2 g weight)[109]. As a result of these differences, studies of oral dose forms in animals must be interpreted with caution, particularly if the operation of the formulation depends on its detailed behaviour in the gastrointestinal tract.

REFERENCES

1. McLaughlan G, Fullarton GM, Crean GP, McColl KEL. Comparison of gastric body and antral pH: a 24 hour ambulatory study in healthy volunteers. *Gut* 1989; 30:573–578.
2. McArthur K, Hogan D, Isenberg JI. Relative stimulatory effects of commonly ingested beverages on acid secretion in humans. *Gastroenterol.* 1982; 83:199–204.
3. Bumm R, Blum AL. Lessons from prolonged gastric pH monitoring. *Aliment. Pharmacol. Therap.* 1987; 1:518S–526S.
4. Richardson CT, Walsh JH, Hicks MI, Fordtran JS. Studies on the mechanisms of food-stimulated gastric acid secretion in normal human subjects. *J. Clin. Invest.* 1976; 58:623–681.
5. Moore JG. Circadian dynamics of gastric acid secretion and pharmacodynamics of H_2 receptor blockade. *Ann. New York Acad. Sci.* 1991; 618:150–158.
6. Lanzon-Miller S, Pounder RE, McIsaac RI, Wood JR. Does the timing of the evening meal affect the pattern of 24 hour intragastric acidity. *Gut* 1988; 29:A1472.
7. Bauerfriend P, Cilluffo T, Fimmel CJ, Gasser T, Kohler W, Merki H, et al. Die intragastrale Langzeit-pH-Metrie (Continuous intragastric pH-metry). *Scweitz. Med. Wochenschr.* 1985; 115:1630–1641.
8. Feldman M, Barnett C. Fasting gastric pH and its relationship to true hypochlorhydria in humans. *Dig. Dis. Sci.* 1991; 36:866–869.
9. Goldschmiedt M, Barnett CC, Schwarz BE. Effect of age on gastric acid secretion and serum gastric concentrations in healthy men and women. *Gastroenterol.* 1991; 101:977–990.
10. Dantas RO, Dodds WJ. Measurement of gastrointestinal pH and regional transit times in normal children. *J. Ped. Gastroenterol. Nutr.* 1990; 11:211–214.
11. Ke MY, Li RQ, Pan GZ. Gastrointestinal pH and transit times in healthy subjects with ileostomy. *Aliment. Pharmacol. Therapeut.* 1990; 4:247–253.

12. Kaufmann D, Wilder-Smith CH, Kempf M. Cigarette smoking, gastric acidity and peptic ulceration. What are the relationships? *Dig. Dis. Sci.* 1990; 35:1482–1487.
13. Russell J, Bass P. Canine gastric emptying of fiber meals: Influence of meal viscosity and antroduodenal motility. *Am. J. of Physiol.—Gastrointest. Liver Physiol.* 1985; 12:G662–G667.
14. King PM, Adam RD, Pryde A, McDicken WN, Heading RC. Relationships of human antroduodenal motility and transpyloric fluid movement: non-invasive observations with real-time ultrasound. *Gut* 1984; 25:1384–1391.
15. Kumar D, Ritman EL, Malagelada JR. Three-dimensional imaging of the stomach: Role of pylorus in the emptying of liquids. *Am. J. of Physiol.—Gastrointest. Liver Physiol.* 1987; 253:G79– G85.
16. Meyer JH, Thomson JB, Cohen MB, Shadcher A, Madola SA. Sieving of solid food by the canine stomach and sieving after gastric surgery. *Gastroenterol.* 1979; 76:804–813.
17. Hausken T, Ødegaard S, Berstad A. Antroduodenal motility studied by real time ultrasonography. *Gastroenterol.* 1991; 100:59–63.
18. Washington N, Steele RJC, Jackson SJ, Washington C, Bush D. Patterns of food and acid reflux in patients with low grade oesophagitis: the role of an anti-reflux agent. *Alim. Pharmacol. Therap.* 1998; 12:53–58.
19. Feldman M, Smith HJ, Simon TR. Gastric emptying of solid radiopaque markers: Studies in healthy subjects and diabetic patients. *Gastroenterol.* 1984; 87:895–902.
20. Stephens JR, Woolson RF, Cooke AR. Effects of essential and non-essential amino acids on gastric emptying in the dog. *Gastroenterol.* 1975; 69:920–927.
21. Hunt JN, Knox MT. A relation between the chain length of fatty acids and the slowing of gastricemptying . *J. Physiol.* 1968; 194:327–336.
22. Houghton LA, Read NW, Heddle R, Maddern GJ, Downton J, Toouli J, Motor activity of the gastric antrum, pylorus and duodenum under fasted conditions and after a liquid meal. *Gastroenterol.* 1988; 94:1276–1284.
23. Houghton LA, Mangnall YF, Read NW. Effect of incorporating fat into a liquid test meal on the relation between intragastric distribution and gastric emptying in human volunteers. *Gut* 1990; 31:1226–1229.
24. Hunt JN, Knox MT. Regulation of gastric emptying. In: Code CF, Heidel W, editors. *Handbook of Physiol.*. Washington D.C. Am. Physiol. Soc., 1968:1917–1935.
25. Sanford PA. The stomach. *Dig. System Physiol.*,. London: Edward Arnold, 1982:36, Chapter 3.
26. Meyer JH, Mayer EA, Jehn D, Gu Y, Fink AS, Fried M. Gastric processing and emptying of fat. *Gastroenterol.* 1986; 90:1176–1187.
27. Moss HA, Washington N, Greaves JL, Wilson CG. Anti-reflux agents: Stratification of floatation? *Europ. J. Gastroenterol. Hepatol.* 1990; 2:45–51.
28. Horowitz M, Jones K, Edelbroek MAL, Smout AJPM, Read NW. The effect of posture on gastric emptying and intragastric distribution of oil and aqueous meal components and appetite. *Gastroenterol.* 1993; 105:382–390.
29. Carney BI, Jones KL, Horowitz M, Sun WM, Penagini R, Meyer JH. Gastric-emptying of oil and aqueous meal components in pancreatic insufficiency—Effects of posture and on appetite. *Am. J. of Physiol.-Gastrointest. Liver Physiol.* 1995; 31:G 925–G 932.
30. Heddle R, Collins PJ, Dent J, Horowitz M, Read NW, Chatterton B, Houghton LA. Motor mechanisms associated with slowing of the gastric emptying of a solid meal by an intraduodenal lipid infusion. *J. Gastroenterol. Hepatol.* 1989; 4:437–447.
31. Benini L, Brighenti F, Castellani G, Brentegani MT, Casiraghi MC, Ruzzenente O, et al. Gastric-emptying of solids is markedly delayed when meals are fried. *Dig. Dis. Sci.* 1994; 39:2288–2294.
32. Sepple CP, Read NW. Effect of prefeeding lipid on food intake and satiety in man. *Gut* 1990; 31:158–161.
33. Konturek JW, Thor P, Domschke W, Konturek SJ. Role of CCK in the control of gastric emptying and gastric secretory response to fatty meal in humans. *Biomed. Res.* 1995; 16(Suppl. 2):141–146.
34. Edelbroek M, Horowitz M, Maddox A, Bellen J. Gastric-emptying and intragastric distribution of oil iln the presence of a liquid or a solid meal. *J. Nucl. Med.* 1992;

33:1283–1290.
35. Cunningham KM, Read NW. The effect of incorporating fat into different components of a meal on gastric emptying and postprandial blood glucose and insulin responses. *Br. J. Nutr.* 1989; 61:285–290.
36. Cortot A, Phillips SF, Malagelada JR. Gastric emptying of lipids after ingestion of a solid-liquid meal in humans. *Gastroenterol.* 1981; 80:922–927.
37. Cortot A, Phillips SF, Malagelada JR. Parallel gastric emptying of nonhydrolyzable fat and water after a solid-liquid meal in humans. *Gastroenterol.* 1982; 82:877–881.
38. Collier G, McLean A, Odea K. Effect of co-ingestion of fat on the metabolic responses to slowly and rapidly absorbed carbohydrates. *Diabetologia* 1984; 26:50–54.
39. Sonnenberg A, MuellerLissner SA, Weiser HF, Effect of liquid meals on duodenogastric reflux in humans. *Am. J. Physiol.—Gastrointest. Liver Physiol.* 1982; 6:G42–G47.
40. Mangnall YF, Houghton LA, Johnson AG, Read NW. Abnormal distribution of a fatty liquid testmeal within the stomach of patients with non-ulcer dyspepsia . *Europ. J. Gastroenterol. and Hepatol.* 1994; 6:323–327.
41. Feinle C, Grundy D, Read NW. Fat increases vection-induced nausea independent of changes in gastric emptying. *Physiol. Behav.* 1995; 58:1159–1165.
42. Rigaud D, Merrouche M, Le Moel G, Vatier J, Paycha F, Cadiot G, Facteurs de reflux gastrooesophagien acide dans l'obesite severe (Gastro-oesophageal reflux in morbid obesity). *Gastroenterol. Cliniq. Biologiq.* 1995; 19:818–825.
43. Casaubon PR, Dahlstrom KA, Vargas J, Hawkins R, Mogard M, Ament ME. Intravenous fat emulsion (intralipid) delays gastric emptying, but does not cause gastroesophageal reflux in healthy volunteers. *J. Parenter. Enter. Nutr.* 1989; 13:246–248.
44. Goo RH, Moore JG, Greenberg E, Alazaki NP. Circadian variation in gastric emptying of meals in man. *Gastroenterol.* 1987; 93:515–518.
45. Wald A, Van Thiel DH, Hoechstetter L, Gavaler JS, Egler KM, Verm R, et al. Gastrointestinal transit: the effect iof the menstrual cycle. *Gastroenterol.* 1980; 80:1497–1500.
46. Wright RA, Krinsky S, Fleeman C, Trujillo J, Teague E. Gastric emptying and obesity. *Gastroenterol.* 1983; 84:747–751.
47. Hutson WR, Wald A. Obesity and weight-reduction do not influence gastric-emptying and antral motility. *Am. J. Gastroenterol.* 1993; 88:1405–1409.
48. Madsen JL. Effects of gender, age, and body mass index on gastrointestinal transit times. *Dig. Dis. Sci.* 1992; 37:1548–1553.
49. Moore JG, Datz FL, Christian E. Exercise increases solid meal gastric-emptying rates in men. *Dig. Dis. Sci.* 1990; 35:428–432.
50. Miller LJ, Malagelada JR, Longstreth GF, Go VLW. Dysfunctions of the stomach with gastric ulceration. *Dig. Dis. Sci.* 1980; 25:857–846.
51. Bromster D. Gastric emptying rate in gastric and duodenal ulceration. *Scand. J. Gastroenterol.* 1969; 4:193–201.
52. Davies WT, Kirkpatrick JR, Owen GM, Shields R. Gastric emptying in atrophic gastritis and carcinoma of the stomach. *Scand. J. Gastroenterol.* 1971; 6:297–301.
53. Halvorsen L, Dotevall G, Walan A. Gastric emptying in patients with achlorhydria or hyposecretion of hydrochloric acid. *Scand. J. Gastroenterol.* 1973; 8:395–399.
54. Castell DO, Holtz A. Gastroesophageal reflux. Don't forget to ask about heartburn. *Postgrad. Med.* 1989; 86:141–144.
55. Graham DY, Smith JL, Patterson DJ. Why do apparently healthy people use antacid tablets? *Am. J. Gastroenterol.* 1983; 78:257–260.
56. Behar J, Ramsey G. Gastric emptying and antral motility in reflux esophagitis. *Gastroenterol.* 1978; 74:253–256.
57. Coleman SC, Rees WDW, Malagelada J-R. Normal gastric function in esophageal reflux (abstract). *Gastroenterol.* 1979; 76:1115.
58. Baldi F, Corinaldesi R, Ferrarini F, Stanghellini V, Miglioli M, Barbara L. Gastric secretion and emptying of liquids in reflux esophagitis. *Dig. Dis. Sci.* 1981; 26:886–889.

59. Hillemeier AC, Grill BB, McCallum R, Gryboski J. Esophageal and gastric motor abnormalities in gastroesophageal reflux during pregnancy. *Gastroenterol.* 1983; 84:741–746.
60. Donovan IA, Harding LK, Keighley MRB, Griffin DW, Collis JL. Abnormalities of gastric emptying and pyloric reflux in uncomplicated hiatus hernia. *Br. J. Surg.* 1977; 64:847–848.
61. McCallum RW, Berkowitz DM, Lerner E. Gastric emptying in patients with gastrooesophageal reflux. *Gastroenterol.* 1981; 80:285–291.
62. Hutson WR, Wald A. Gastric-emptying in patients with bulimia nervosa and anorexia-nervosa. *Am. J. Gastroenterol.* 1990; 85:41–46.
63. Wilson CG, Washington N. Assessment of disintegration and dissolution of dosage forms *in vivo* using gamma scintigraphy. *Drug Dev. Ind. Pharm.* 1988; 14:211–281.
64. Graham DY, Smith JL, Bouvet AA. What happens to tablets and capsules in the stomach– endoscopic comparison of disintegration and dispersion characteristics of two microencapsulated potassium formulations. *J. Pharmaceut. Sci.* 1990; 79:420–424.
65. Casey DL, Beihn RM, Digenis GA, Shambhu MB. Method for monitoring hard gelatin disintegration times in humans using external scintigraphy. *J. Pharmaceut. Sci.* 1976; 65:1412–1413.
66. Hunter E, Fell JT, Calvert RT, Sharma H. *In vivo* investigation of hard gelatin capsules in fasting and non-fasting subjects. *Int. J. Pharmaceut.* 1980; 4:175–183.
67. Hunter E, Fell JT, Sharma H. The gastric emptying of pellets contained in hard gelatin capsules. *Drug Dev. Ind. Pharm.* 1982; 8:751–757.
68. Hunter E, Fell JT, Sharma H. The gastric emptying of hard gelatin capsules. *Int. J. Pharmaceut.* 1983; 17:59–64.
69. Armstrong NA, James KC. Drug release from lipid-based dosage forms *Int. J. Pharmaceut.* 1980; 6:185–193.
70. Wilson CG, Washington N, Greaves JL, Kamali F, Rees JA, Sempik AK, Bimodal release of ibuprofen in a sustained-release formulation: a scintigraphic and pharmacokinetic open study in healthy volunteers under different conditions of food intake. *Int. J. Pharmaceut.* 1989; 50:155–161.
71. Ewe K, Press AG, Bollen S, Scuhn I. Gastric emptying of indigestible tablets in relation to composition and time of ingestion of meals studied by metal detector. *Dig. Dis. Sci.* 1991; 36:146–152.
72. Hardy JG, Evans DF, Zaki I, Clark AG, Tønnesen HH, Gamst ON. Evaluation of an enteric coated naproxen tablet using gamma scintigraphy and pH monitoring. *Int. J. Pharmaceut.* 1987; 37:245–250.
73. Khosla R, Feely LC, Davis SS. Gastrointestinal transit of non-disintegrating tablets in fed subjects. *Int. J. Pharmaceut.* 1989; 53:107–117.
74. Hunter E, Fell JT, Sharma H, McNeilly AM. The *in vivo* behaviour of hard gelatin capsules filled with thixotropic liquids. Part 2: Quantitative aspects. *Pharmazeutische Industrie* 1983; 45:433–434.
75. Davis SS, Hardy JG, Taylor MJ, Whalley DR, Wilson CG. The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). *Int. J. Pharmaceut.* 1984; 21:331–340.
76. O'Reilly S, Hardy JG, Wilson CG. The influence of food on the gastric emptying of multiparticulate dosage forms. *Int. J. Pharmaceut.* 1987; 34:213–216.
77. Washington N, Greaves JL, Wilson CG. Effect of time of dosing relative to a meal on the raft formation of an anti-reflux agent. *J. Pharm. Pharmacol.* 1990; 42:50–53.
78. Horowitz M, Maddox A, Bochner M, Wishart J, Bratasiuk R, Collins P, Relationships between gastric-emptying of solid and caloric liquid meals and alcohol absorption. *Am. J. Physiol.* 1989; 257:G291–G298.
79. Sheth PR, Tossounian J. The hydrodynamically balanced system (HBS™): A novel drug delivery system for oral use. *Drug Dev. Ind. Pharm.* 1984; 10:313–339.
80. Khattar D, Ahuja A, Khar RK. Hydrodynamically balanced systems as sustained release dosage forms for propranolol hydrochloride. *Pharmazie* 1990; 45:356–358.
81. Watanabe S, Kayano M, Ishino Y, Miyao K. Solid therapeutic preparations remaining in the stomach. *US Patent* 1976; 3, 976, 764.

82. Ingani HM, Timmermans J, Moes AJ. Conception and *in vivo* investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. *Int. J. Pharmaceut.* 1987; 35:157–164.
83. Phuapradit W, Bolton S. The influence of tablet density on the human oral absorption of sustained release acetominophen matrix tablets. *Drug Dev. Ind. Pharm.* 1991; 17:1097–1107.
84. Hilton AK, Deasy PB. *In vitro* and *in vivo* evaluation of an oral sustained-release floating dosage form of amoxicillin trihydate. *Int. J. Pharmaceut.* 1992; 86:79–88.
85. Bechgaard H, Ladefoged K. Distribution of pellets in the gastrointestinal tract. The influence on transit time exerted by density or diameter of pellets. *J. Pharm. Pharmacol.* 1978; 30:690–692.
86. Bogentoft C, Appelgren C, Jonnson WE, Sjögren J, Alpsten M. Intestinal transit time of 51 Crlabelled pellets of different densities. In *Radionuclide imaging in drug research*. Wilson, C.G., Hardy, J.G., Frier, M. and Davies, S.S. (eds) 1982; Croome Helm, London: 294–296.
87. Bechgaard H, Christensen FN, Davis SS, Hardy JG, Wilson CG, Taylor MJ, Whalley DR, Gastrointestinal transit of pellet systems in ileostomy subjects and the effect of density. *J. Pharm. Pharmacol.* 1985; 37:718–721.
88. Kaus LC, Fell JT, Sharma H, Taylor DC. The intestinal transit of of a single non-disintegrating unit. *Int. J. Pharmaceut.* 1984; 20:315–323.
89. Devereux JE, Newton JM, Short MB. The influence of density on the gastrointestinal transit of pellets. *J. Pharm. Pharmacol.* 1990; 42:500–501.
90. Meyer JH, Dressman J, Fink AS, Amidon G. Effect of size and density on gastric emptying of indigestible solids (abstract). *Gastroenterol.* 1985; 88:1502.
91. Curatoto WJ, Lo J. Gastric retention systems for controlled drug release. *U.S. Patent* 1995; 5, 443, 843.
92. Houghton LA, Read NW, Heddle R, Horowitz M, Collins PJ, Chatterton B, Dent J. Relationship of the motor activity antrum, pylorus and duodenum to gastric emptying of a solid-liquid mixed meal. *Gastroenterol.* 1988; 94:1285–1291.
93. Burton S, Washington N, Steele RJC, Musson R, Feely L. Intragastric distribution of ion-exchange resins: A drug delivery system for the topical treatment of the gastric mucosa. *J. Pharm. Pharmacol.* 1995; 47:901–906.
94. Borodkin S. Ion-exchange resin delivery systems. In: *Polymers for Controlled Drug Delivery.* Tarcha P, (ed.) Florida: CRC Press, Boca Raton, 1991:215–230.
95. Thairs S, Ruck S, Jackson SJ, Steele RJC, Feely L, Washington C, Washington N. Effect of dose size, food and surface coating on the gastric residence and distribution on an ion exchange resin. *Int. J. Pharmaceut.* 1998; 176:47–53.
96. Park H, Robinson JR. Physico-chemical properties of water insoluble polymers important to mucin/epithelial adhesion. *J. Cont. Rel.* 1985; 2:47–57.
97. Hunt JN, Knox MT, O'Ginskey A. The effect of gravity on gastric emptying of various meal. *J. Physiol. (London)* 1965; 178:92–97.
98. Bennett CE, Hardy JG, Wilson CG. The influence of posture on gastric emptying of antacids. *Int. J. Pharmaceut.* 1984; 21:341–347.
99. Mojaverian P, Chan K, Desai A, John V. Gastrointestinal transit of a solid indigestible capsule as measured by radiotelemetry and dual gamma scintigraphy. *Pharmaceut. Res.* 1989; 6:719–724.
100. Sangekar S, Vadino WA, Chaudry I, Parr A, Beihn R, Digenis G. Evaluation of the effec of food and specific gravity of tablets on gastric retention time. *Int. J. Pharmaceut.* 1987; 35:187–191.
101. Renwick AG, Ahsan CH, Challenor VF, Daniels R, Macklin BS, Waller DG, et al. The influence of posture on the pharmacokinetics of orally-administered nifedipine. *Br. J. Clin. Pharmacol.* 1992; 34:332–336.
102. Moore JG, Datz FL, Christian PE, Greenberg E, Alazraki N. Effect of body posture on radionuclide measurements of gastric-emptying. *Dig. Dis. Sci.* 1988; 33:1592–1595.
103. Kuna S. The pH of gastric juice in the normal resting stomach. *Arch Int Pharmacodyn.* 1964; 151:79–97.

104. O'Laughlin JC, Hoftiezer JW, Ivey KJ. Effect of aspirin on the human stomach in normals: endoscopic comparison of damage produced one hour, 24 hours and 2 weeks after administration. *Scand. J. Gastroenterol.* 1981; 16 Suppl. 67:211–214.
105. Cargill R, Caldwell LJ, Engle K, Fix JA, Porter PA, Gardner CR. Controlled gastric emptying. 1. Effects of physical properties on gastric residence times of nondisintegrating geometric shapes in beagle dogs. *Pharmaceut. Res.* 1988; 5:533–536.
106. Gruber P, Rubinstein A, Hon Kin Li V, Bass P, Robinson JR. Gastric emptying of nondigestible solids in the fasted dog. *J. Pharmaceut. Sci.*. 1987; 76:117–122.
107. Kaniwa N, Aoyagi N, Ogata H, Ejima A. Gastric emptying rates of drug preparations. I Effects of size of dosage forms, food and species on gastric emptying rates. *J. Pharmacobiol. Dyn.* 1988; 11:563–570.
108. Kaniwa N, Aoyagi N, Ogata H, Ejima A, Motoyama H, Yasumi H. Gastric emptying rates of drug preparations. II. Effects of size and density of enteric-coated drug preparations and food on gastric emptying rates in humans. *J. Pharmacobiol. Dyn.* 1988; 11:571–575.
109. Hossain M, Abramowitz W, Watrous BJ, Szpunar GJ, Ayres JW. Gastrointestinal transit of nondisintegrating, nonerodible oral dosage forms in pigs. *Pharmaceut. Res.* 1990; 7:1163–1166.