ESSENTIALS OF PHARMACOLOGY FOR NURSING PRACTICE

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ROUTES OF DRUG ADMINISTRATION AND DRUG ABSORPTION

2

LEARNING OUTCOMES

By the end of this chapter, you should be able to:

1 Describe the anatomical structures and physiological processes relevant to the routes of drug administration
2 Explore the different routes of drug administration
3 Critically appraise the factors which affect the rate and extent of drug absorption

INTRODUCTION

Chapter 2 will explore the various routes of drug administration, the normal physiology relevant to the mode of drug administration and examine the advantages, disadvantages and considerations for each route as applied to safe and therapeutic medicine management.

The first stage of the pharmacokinetic process is *drug absorption*, defined as the movement of the drug from the site of administration into the systemic circulation. This is important so that the drug is transferred to its intended site of action and can exert its clinical effect.

It is important to note, however, that there are several groups of drugs which do not require absorption because their mode of action occurs within the cavity they have been directly administered into. Examples include the instillation of medication to the eye to treat infection and **laxatives** or anti-diarrhoea medications.

The factors which affect the rate and extent of drug absorption can be categorised in two ways. Firstly, factors which relate to the *physio-chemical properties of the drug* and secondly the different *anatomical and physiological characteristics of the human body*.

The routes of drug administration are summarised as:

1 **Enteral**
   i Oral
   ii Rectal
2 **Buccal**
3 **Sublingual**
4 **Topical**
5 **Transdermal**
6 **Parenteral**
   i **Subcutaneous**
   ii **Intramuscular**
   iii **Intravenous**
   iv Intra-arterial
   v Intraosseous
7 Inhalation

THE ENTERAL ROUTE OF DRUG ADMINISTRATION

The enteral route refers to the administration of drug into the gastrointestinal system.

The most common enteral route of drug administration is the oral route with over 80% of medications administered in this way, primarily because it is convenient, with oral dosage forms deemed relatively simple and cost effective to manufacture compared to other routes of administration.

The gastrointestinal tract anatomically comprises many sections, and therefore multiple physiological factors influence the rate and extent of the absorption of drugs.

The gastrointestinal tract is a muscular tube, measuring approximately 9 metres from the mouth to the anus in the adult, and has varying diameters along its length. The gastrointestinal tract is a complicated system, with each organ containing multiple distinct tissues dedicated to digesting food efficiently while preventing non-food molecules from entering pre-systemic circulation (see Figure 2.1).

It extends from the mouth to the anus and is divided into four distinct anatomical regions:

1 The oesophageal sphincter
2 The stomach (cardia, fundus, corpus, antrum, pylorus)
3 The small intestine (duodenum, jejunum, ileum)
4 The large intestine (colorectum)

The tube's inner luminal surface is extremely uneven, which increases the surface area available for absorption. The wall of the gastrointestinal tract is essentially identical along its length, consisting of four major layers (see Figure 2.2).

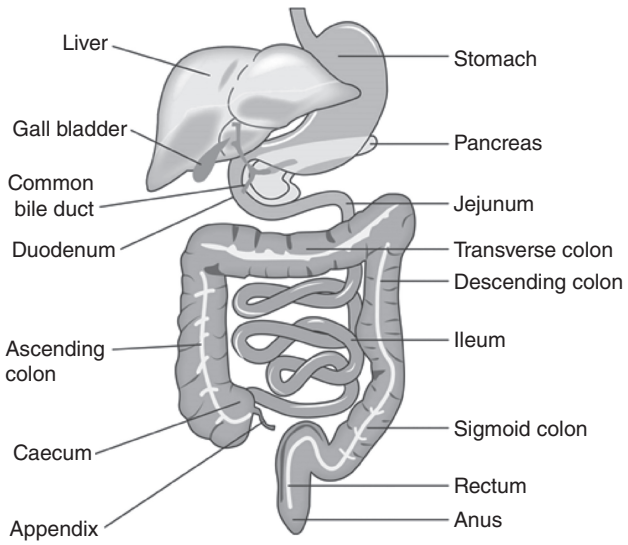

Figure 2.1 The gastrointestinal tract

1 The serosa – the outer layer of epithelium
2 The muscularis externa comprised of three layers of smooth muscle, two inner layers with circular fibres and a thin outer layer that runs longitudinally. These muscles contract to provide contractions to move the gastrointestinal contents and physically break it down
3 The submucosa – a connective tissue layer rich in blood and lymphatic vessels that contains some secretory tissue and nerves
4 The mucosa

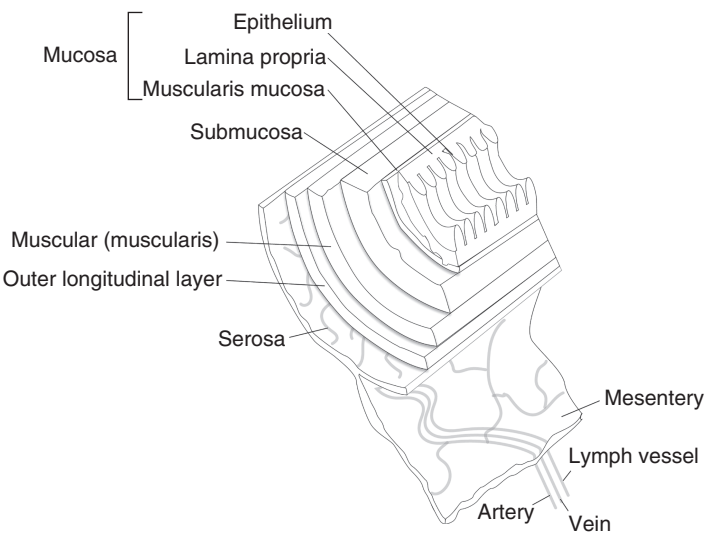

Figure 2.2 The major layers of the gastrointestinal tract

Most of the gastrointestinal epithelium is mucous coated (mucous: adjective and mucus: noun). This is a sticky, clear mucin-water complex that is secreted as a protective layer and mechanical barrier in the gastrointestinal tract. Mucus is mainly a water-based mixture of many secretions and exfoliated epithelial cells, but its exact makeup changes all the time. Its other components contribute to its physical and functional properties, such as mucins, which are large glycoproteins. Along the length of the gastrointestinal tract, the mucous layer varies in thickness. This mucous layer is continuous in organs such as the stomach and duodenum whereas further down the gastrointestinal tract there may be areas where there is no mucus. Mucus is constantly debrided from the surface of the gastrointestinal tract by abrasion, acids and enzymes, and resupplied from below over a few hours. The mucus is thicker in the stomach because it needs to have a sufficiently robust barrier against gastric acids. As an adverse effect, drugs such as non-steroidal anti-inflammatory drugs (**NSAID**s) and steroids can prevent the production of mucus of the appropriate constitution and consistency, which collectively compromise this protective barrier, resulting in damage to the gastric lining.

The gastrointestinal tract has several barriers that ensure that only the essential building blocks of life, such as glucose, amino acids and vitamins, are absorbed. This is a defence mechanism designed to mitigate the risk of **toxicity**. Of course, drugs are absorbed, so this is not a perfectly evolved system, but in summary, the barriers are as follows:

- pH and enzymes – many toxins are ionised at alkaline pH which corresponds to the pH of the small intestine, the site of maximum drug absorption
- Gastrointestinal mucosa
- Metabolic state prior to the onset of systemic disease

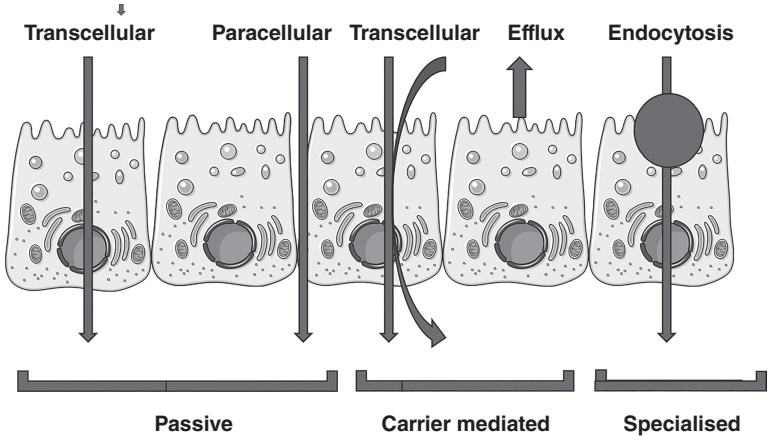

Figure 2.3 Mechanisms of drug absorption

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The five mechanisms (described in Chapter 1; see Figure 2.3) by which drugs are absorbed through the gastrointestinal membrane are:

1 Transcellular
2 Paracellular
3 Active transport
4 Endocytosis
5 Passive or facilitated diffusion

To offer some examples, insulin and the cardiac glycoside group of drugs are transported by paracellular transport, vitamin B12 complex by active transport with **lipophilic** drugs (e.g. those which are required to enter the central nervous system and cross the blood–brain barrier by passive diffusion).

Oesophagus

The mouth is the primary route of administration for most drugs. Contact with the oral mucosa is usually very short because patients tend to swallow quickly. The oesophagus connects the oral cavity to the stomach via the gastro-oesophageal junction. The oesophagus is made up of a thick muscular layer that measures approximately 250 millimetres in length and 20 millimetres in diameter.

Apart from the lower 20 mm, which resembles the gastric mucosa, the oesophagus is lined with a well differentiated squamous epithelium of non-proliferating cells. The oesophagus has glands that secrete mucus into the lumen to lubricate food and protect the lower part of the oesophagus from stomach acid. The oesophageal lumen typically has a pH of between 5 and 6. The act of swallowing transports materials down the oesophagus. Following ingestion, a single peristaltic contraction wave travels down the length of the oesophagus, increasing in speed. After the initial swallow, secondary contractions occur spontaneously to push any remaining sticky lumps of material or refluxed material into or back to the stomach. Gravity helps materials through the oesophagus when in the upright position. The oesophageal transit time for dosage forms is extremely short, typically between 10 and 14 seconds. Whilst the oesophagus does not play a role in drug absorption it can be affected by drugs. For example, the instruction to individuals prescribed doxycycline capsules, an antibacterial drug to take with a full glass of water, preferably in a standing or sitting position, is because doxycycline is caustic to the oesophagus. Because the mucus here is not as protective as that found in the stomach, there is a risk of ulceration if the drug becomes lodged.

Stomach

The stomach is the next section of the gastrointestinal tract that food and pharmaceuticals will encounter. The stomach serves three primary functions.

1 A reservoir for ingested food to slowly deliver it to the duodenum to make sure the duodenum does not receive volumes too great for it to function optimally
2 Acid and enzyme digestion to make chyme which is a uniform creamy paste that helps absorption further down the gastrointestinal tract. It does this because the paste ensures greater contact between the ingested foods and the mucus membrane of the intestines than would blocks of food
3 Protection of the intestine by preventing toxins from reaching it. Drugs and toxins can be destroyed by the enzymes and acids in the stomach

The pyloric sphincter controls its connection to the duodenum. The stomach is anatomically divided into five regions (see Figure 2.4).

1 The cardia
2 The fundus
3 The corpus (body)
4 The antrum
5 The pylorus

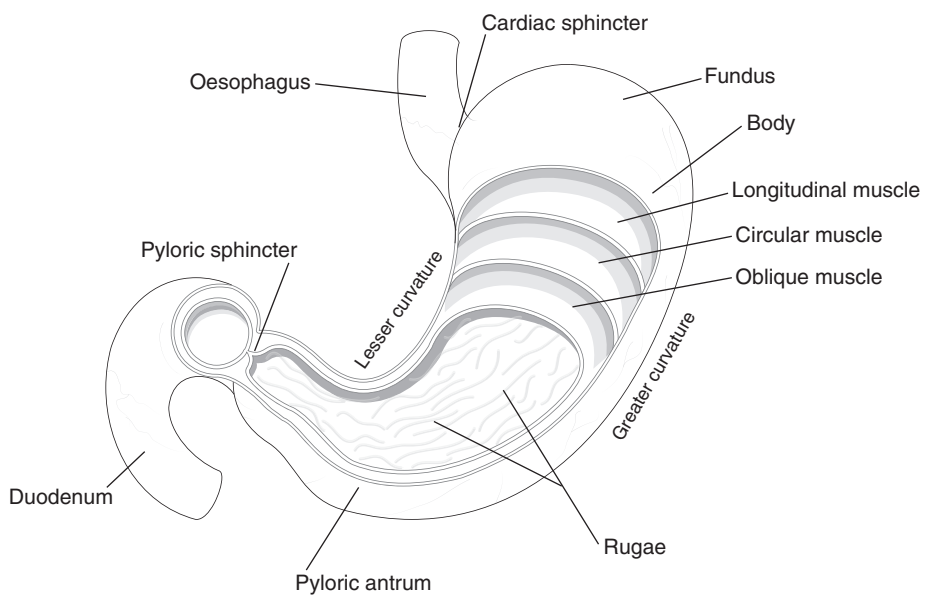

Figure 2.4 The stomach

Although the stomach usually contains small amounts of fluid, often less than 50mL, it can hold about 1.5L if necessary.

The secretions of the stomach are:

- HCl secreted by parietal cells, maintaining the stomach's pH at 1–3.5 during fasting
- The hormone gastrin, that stimulates the gastric acid and pepsinogen production from the stomach's G cells. Gastrin is released in response to peptides, amino

acids and gastric distension, which results in increased gastric motility. Pepsins are peptidases that degrade proteins to peptides when the pH is low. Pepsin is denatured above pH 5

- Mucus, secreted by the mucous-neck cells that line the gastric mucosa. Mucus protects the gastric mucosa digesting itself with its own pepsin-acid combination. Without an effective mucous layer gastritis and ulceration can result

Surprisingly, the stomach absorbs very little medication because of its tiny surface area in comparison to the small intestine. In relation to medication, a factor for consideration is that the rate of gastric emptying determines how quickly drug absorption from the small intestine can start to happen. This is significant because the small intestine is where most drug absorption occurs.

The pH of the stomach is typically between 1 and 4. As a result, acidic drugs are largely non-ionised and can be absorbed through the stomach (e.g. aspirin). However, because the small intestine has a much larger absorptive surface area (even for acidic drugs), most absorption occurs there and not in the stomach.

Even when there is no specific interaction, the adaptive phase of gastric emptying, when a meal has just been consumed, causes hormones like cholecystokinin to be secreted and this retains food and drugs (if they happen to be there at the same time) for longer in the stomach. The foods that do this the most are fatty foods as they cause the most secretion of cholecystokinin. Whilst the total amount of drug absorption will not be affected, the time to a peak in the systemic circulation will be delayed and that could delay therapeutic effect.

It is important to remember that some drugs need to be taken with food. This can be to enhance their effect, or to prevent an adverse effect. An example is ascorbic acid (vitamin C) which increases the absorption of iron. As another example, a fatty meal increases the **bioavailability** and pharmacokinetic variability of the absorption of the antiretroviral saquinavir. It is uncertain why this is, but it could be because the drug becomes enveloped by lipid and absorbed within the lymphatic system, thereby avoiding first-pass metabolism.

PAUSE AND REFLECT 2.1

Reflect on the impact of lifestyle factors on drug therapy. Think about a medication that requires dietary restrictions or lifestyle modifications. How do these factors influence the drug's effectiveness and safety?

Intestine

The small intestine, the ileum, is the gastrointestinal tract's longest most complicated segment. It begins at the stomach's pyloric sphincter to the ileo-caecal junction and at that point meets up with the colon. It has a diameter of approximately 25 to 30 mm.

Its primary functions are:

- *Digestion*: The small intestine completes the process of enzymatic digestion that began in the stomach.
- *Absorption*: The small intestine is the site of greatest absorption from the gastrointestinal tract.

There are three parts to the small intestine: the duodenum, the jejunum and the ileum (see Figure 2.5).

The small intestinal wall is densely packed with blood and lymph vessels. This is the area of gastrointestinal tract with the best blood supply, which is crucial for absorption as this creates concentration gradients. In fact, the blood supply accounts for about 30% of total cardiac output via the superior mesenteric artery. The small intestinal circulation flows into the hepatic portal vein, which transports it to the systemic circulation via the liver. The liver metabolises drugs prior to them reaching the systemic circulation; this process is referred to as first-pass metabolism.

The small intestine wall also contains lacteals, which contain lymph and are therefore a component of the lymphatic system. The lymphatic system plays a critical role in fat absorption from the gastrointestinal tract; some drugs can be absorbed in this way and bypass **first-pass metabolism** after fatty meals.

The small intestinal surface area is significant and has adaptations that increase the surface area more than 500 times what it would be if it was a smooth cylinder. These adaptations are:

- Submucosal folds that wrap around the intestine in a circular fashion and are particularly developed in the duodenum and jejunum. They have a depth of several millimetres
- Villi, which are finger-like projections into the lumen (approximately 0.5–1.5 mm in length and 0.1 mm in diameter). They have an abundance of blood vessels. Each villus contains an arteriole, a venule and a lymphatic vessel that never ends (lacteal)
- Microvilli – 600–1000 of these brush-like structures with a length of 1 um and a width of 0.1 um cover each villus, providing the greatest surface area increase

The small intestinal luminal pH increases to between 6 and 7.5. The secretions that produce these pH values in the small intestine come from the following sources:

- Brunner's glands, located in the duodenum, produce bicarbonate, which neutralises the acid excreted from the stomach.
- Intestinal flora are found throughout the small intestine and are responsible for the production of mucus and enzymes. The digestive process is continued by enzymes, hydrolases and proteases.

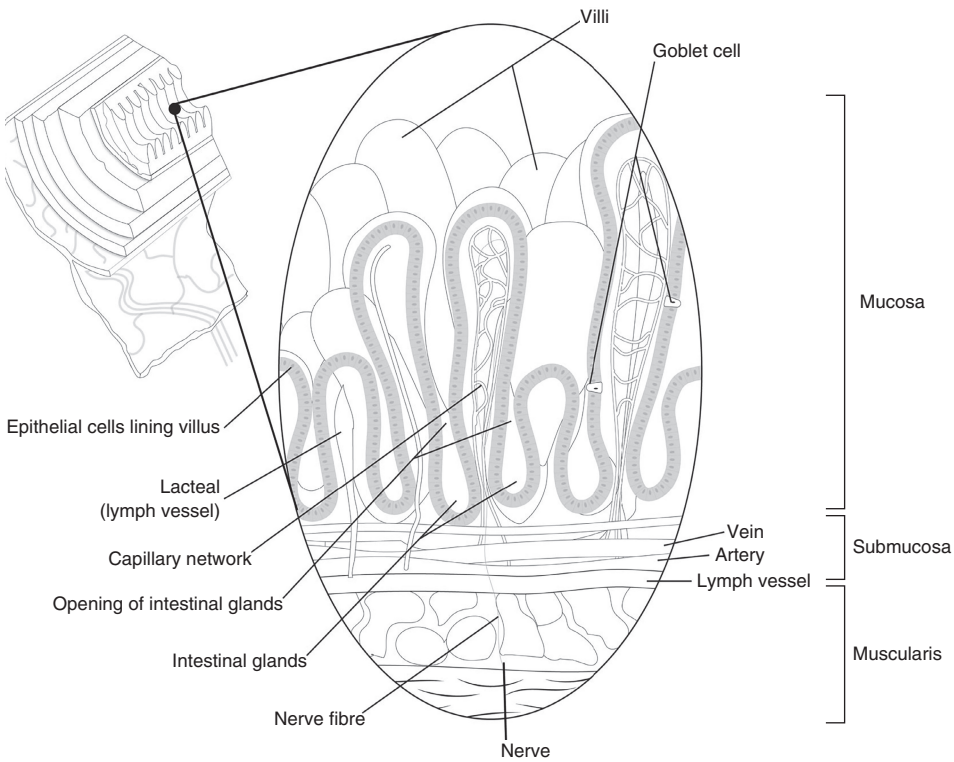

Figure 2.5 The small intestine

- The pancreas secretes pancreatic fluid into the small intestine every day. Pancreatic juice is composed of sodium bicarbonate and proteases, lipase and amylase.
- Bile, a complicated mixture of organic and inorganic substances, is produced by the liver and stored in the gall bladder. It is made up of bile acids, phospholipids (especially lecithin, cholesterol, and bilirubin) as well as other organic and inorganic substances (such as the plasma electrolytes sodium and potassium). Bile pigments, the most common of which is bilirubin, are removed from the body in the faeces. Bile acids, on the other hand, are reabsorbed in the terminal ileum through a process that is very active as the body can reuse them. Because of their high clearance rate in the liver, they return to the liver through the portal vein and are then released into the bile again. The term 'enterohepatic recirculation' is used to describe this phenomenon and it can happen to some drugs as well. The main function of bile is to help the body absorb fats from food, like fatty acids and cholesterol, by emulsifying and dissolving them into micelles and emulsions. It also helps the body get rid of waste products that have been broken down.

Unless drugs are administered intravenously, they must pass through the phospholipid membranes before they reach the systemic circulation. Fat-soluble drugs (lipophilic) are more likely to be absorbed in the intestines because of the prevalence of villi and microvilli. Water-soluble (hydrophilic) drugs can be absorbed through special transport mechanisms or facilitated diffusion. Even if all the drug is absorbed by the intestinal epithelium, it can be transported back into the intestinal lumen or metabolised by the liver, so not all doses may get to the systemic circulation. This is referred to a pre-systemic or first-pass metabolism. The principle of first-pass metabolism will be explained more fully in Chapter 4.

The rate and extent of drug absorption depends on the physiochemical properties of the drug along with the physiological conditions of the gastrointestinal system. In practice, oral drug absorption typically only varies person to person with a clinically significant effect in a subset of patients with certain characteristics or with a limited number of drugs.

PHYSIOLOGICAL FACTORS THAT INFLUENCE THE RATE AND EXTENT OF ABSORPTION

There are a number of physiological factors that influence the rate and extent of absorption, outlined in the next section of this chapter.

Gut Motility and Transit Time

Gut transit time is defined as the time it takes for food to move through the gastrointestinal tract from the mouth to the anus, and will vary with age, sex, dietary habits or disease (see Figure 2.6 on gut motility). For example, if drugs move through the small intestine quickly (i.e. diarrhoea) then the contact time is reduced and hence the extent of absorption. This may be particularly problematic for modified-release drugs when absorption should take place over several hours. Alternatively, if drugs are held in the stomach for a long time before exiting, then absorption may be delayed. An example is metoclopramide, which increases the rate of gastric emptying and is therefore prescribed for nausea and vomiting.

The Polarity of the Drug

Drugs defined as '**polar**' are highly water soluble. Polar drugs move poorly, or not at all, across cell membranes, which are mainly composed of lipids. Some drugs are so highly water soluble that they do not cross the cell membranes of the gut and cannot enter the systemic circulation. A good example of this is gentamicin which is so water soluble that it can only be delivered systemically by injection. This is a general rule, but it should be remembered that some polar molecules can cross cell membranes through specific transport mechanisms or channels. For example, glucose, a polar molecule, is absorbed

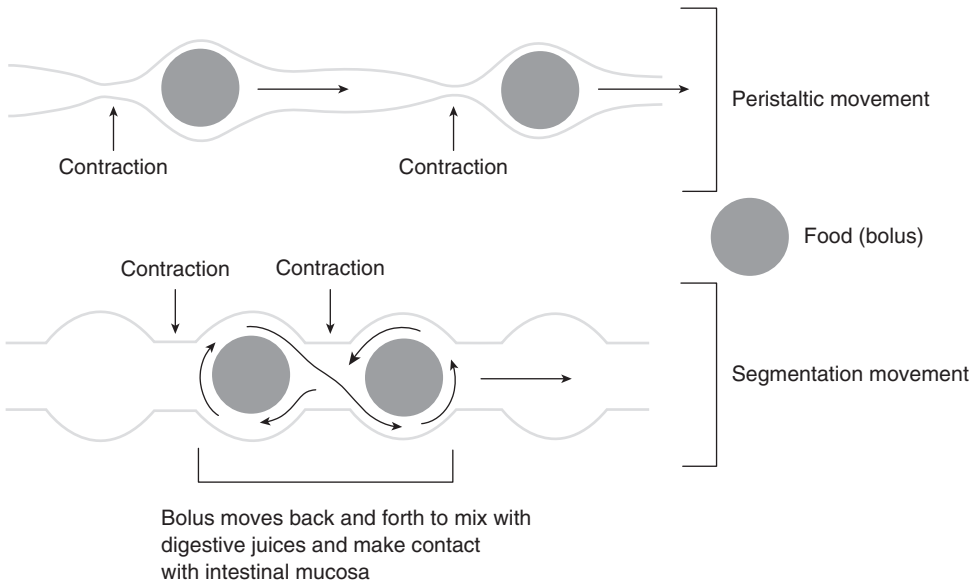

Figure 2.6 Gut motility

in the small intestine primarily through a process called facilitated diffusion which is supported by specialised glucose transporter proteins embedded in the cell membranes of epithelial cells lining the small intestine.

Changes to pH Within the Gastrointestinal Tract

The extent to which a drug is absorbed depends on the pH within the gastrointestinal tract. For example, aspirin is an acidic drug so is non-ionised (uncharged) in the stomach environment, which is itself acidic. Therefore the drug can cross cell membranes more easily. However, even though aspirin becomes ionised in the small intestine, the large surface area and good blood supply still means that most of the absorption of aspirin occurs here. Surface area and diffusion gradients surpass all other factors. Some drugs (e.g. **antacids**) and proton pump inhibitors will alter the pH of the stomach and may alter the extent of dissolution of the drug and subsequent extent of absorption. For example, whilst antacids (e.g. aluminium hydroxide) will increase the absorption of beta-blockers (e.g. propranolol), anti-fungal agents (e.g. ketoconazole) require this acidic environment for dissolution and therefore any drugs which increase the gastric pH will result in reduced absorption.

The presence of physiological enzymes can result in the destruction of some drugs which means they cannot be taken orally for a systemic effect. For example, peptide hormones such as insulin are denatured by gastric acid and digested by the gastrointestinal tract in the same way that proteins from our diet would be.

Drug–Drug Interactions

The concomitant administration of drugs may result in variations in treatment failure or drug toxicity by affecting the extent and rate of drug absorption. This may be because there is a delay in the dissolution of the drug in the stomach, or gastric emptying and gut transit time are affected. Prokinetic agents prescribed to increase the rate of gastric emptying (e.g. metoclopramide for nausea and vomiting) risk increasing the rate of absorption of other drugs but in the case of digoxin, an increase in gut motility has the opposite effect. By reducing the contact time with the absorptive surface of the gastrointestinal tract, a reduction in the rate of absorption is seen. This is particularly noticeable with drugs administered as controlled-release or modified-release formulations. Alternatively, metoclopramide may increase the absorption of alcohol or paracetamol. Iron can reduce the absorption of the Parkinsonian drug, levodopa.

PAUSE AND REFLECT 2.2

Reflect on the concept of drug–drug interactions. Choose two or three commonly prescribed medications and investigate whether they have any known interactions. How do these interactions affect the efficacy or safety of the drugs involved?

Drug–Food Interactions

The influence of food on drug absorption is highly complex and somewhat unpredictable (see Table 2.1). The presence or absence of food in the stomach may inhibit, enhance or delay drug absorption and hence affect the extent of drug availability. It is important to note that the specific effect can vary greatly depending on the drug. Some drugs are better absorbed with food, while others are absorbed more effectively on an empty stomach.

Some drugs are termed ‘acid labile’, which means they are susceptible to alteration in acidic environments. An example of this is flucloxacillin. Patients given the oral form of this drug are advised to take it an hour before food or a couple of hours after. This is because when we start eating, or are about to, our body lowers gastrointestinal pH ready for the meal to be eaten. This then would reduce the amount of flucloxacillin that could be absorbed and will result in treatment failure or **antimicrobial** resistance. Alternatively, if gastric pH is increased, for example if drugs such as proton pump inhibitors like omeprazole are taken (these treat gastro-oesophageal reflux disease, or stomach ulcers) then drugs like the anti-fungal itraconazole or the antiretroviral atazanavir are not absorbed to the same extent.

Tetracycline should not be administered with milk as it contains metal ions (e.g. calcium and magnesium) or drugs like antacids which contain aluminium salts.

The molecular complex which is formed (the process is commonly known as 'chelation') is too large to be absorbed and tetracycline will not have any therapeutic effect.

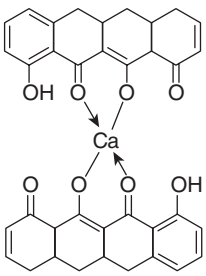

Figure 2.7 An example of calcium chelation

Some foods affect absorption. In Figure 2.7 calcium from milk or antacids has bonded to two tetracycline molecules and now the structure is too large to be absorbed.

Table 2.1 Levels of absorption in common drugs and food

Drug	Food	Interaction
Iron	Vitamin C	Increases absorption
Iron	Phytates – e.g. found in wholegrains, seeds and nuts	Decreases absorption
	Tannin in tea	Decreases absorption
Tetracycline	Milk	Decreases absorption
Iron or tetracyclines	Calcium salts	Increases absorption
Levodopa	Protein-containing food	Decreases absorption
Albendazole (antiprotozoal agent)	Lipid-containing food	Increases absorption

Pathology Affecting the Jejunum and Ileum

The extensive surface area of the ileum allows for maximum drug absorption. However, several factors may affect both the rate and extent of absorption.

The functional integrity of the gastrointestinal tract will adversely influence absorption. For example, disease (e.g. Crohn's Disease), malabsorption syndrome or surgical resection will result in variability of the rate and extent of drug absorption. Malabsorption syndrome will reduce the absorption of drugs. Similarly intestinal obstruction will reduce peristalsis, drug movement through the gastrointestinal tract and drug absorption.

Coeliac disease risks reducing the surface area of the ileum, altering intestinal transit time and permeability of the gut wall which independently and collectively affect drug absorption.

Age-Related Changes

In the older adult, a reduction in gastric hydrochloric acid production and pepsin, with a resultant decrease in gastric pH, may affect the solubility of drugs and hence the extent of absorption. Whilst these changes are not pharmacologically significant, the absorption of calcium drugs may be affected and there is a risk of early dissolution of enteric-coated drugs (e.g. aspirin, erythromycin) which may result in adverse gastric effects. A reduction in the active transport mechanisms may also affect the absorption of iron and vitamin B12, so if given as a treatment they may need to be given by a different route.

Similarly, a reduction in the blood flow to the intestinal wall and a loss in the number of absorbing cells collectively risk affecting absorption. Age-related reduction in gut motility will prolong the movement of the drug from the stomach to the small intestine. For drugs which are primarily absorbed in the upper small intestine (e.g. paracetamol), absorption will be delayed as will its pharmacological action.

Reduction in Gut Motility in People Who Are Critically Ill

The rate and extent of oral absorption becomes unpredictable for many reasons in acute and critical illness. During physiological stress, the sympathetic nervous system is activated, which results in a decrease in the blood supply to the jejunum and ileum and a resultant increase in cardiac, renal and hepatic supply. This will have an adverse effect on the extent of drug absorption and is likely to cause enteral feed intolerance.

The use of supplementary feeding regimes via nasogastric tubes, percutaneous endoscopic gastrostomy or jejunal devices can result in absorption problems due to drug interaction with enteral feeds. For example, the bioavailability of phenytoin can be reduced as can the antimicrobial ciprofloxacin.

Presence of Drug-Metabolising Enzymes in the Gut

The small intestine is a potential site for drug metabolism. The concept of drug metabolism is more fully explored in Chapter 4 but suffice to say that the presence of enzymes in the intestinal epithelial cells results in extrahepatic metabolism of several drugs (e.g. ciclosporin, nifedipine and verapamil). Grapefruit juice has been shown to inhibit the action of the CYP3A cytochrome 450 isoenzyme, a drug-metabolising enzyme found in the liver and intestine, and will therefore increase the availability of felodipine, for example.

Dissolution of Drugs by Digestive Enzymes or Activity of the Gut Flora

Chloramphenicol, an antimicrobial agent, is degraded by gut microbes, reducing its bioavailability, whilst for several drugs (e.g. digoxin and steroid hormones) bioavailability is enhanced.

Physical and Chemical Properties of the Drug

The extent and rate of drug absorption can be purposefully influenced by the formulation of the drug. Before absorption can take place, a tablet or capsule must be dissolved or disintegrated, whereas liquids will be absorbed faster. Tablets can be coated or uncoated. It may simply be that a sugar coating is more palatable, or the drug preparation is designed not to release in the stomach but in the small intestine (e.g. bisacodyl can irritate the stomach and induce nausea and enteric-coated erythromycin improves bioavailability as it is destroyed by gastric acids). However, it is important to note that enteric-coated aspirin and prednisolone cannot prevent the systemic effects of these drugs on the stomach, which may far outweigh the local irritation.

Some enteric coatings are developed to deliver the drug to a specific site within the gastrointestinal tract, for example sulfasalazine in the treatment of Crohn's disease needs to be further down in the gastrointestinal tract rather than in the acidic stomach or the alkaline small intestine.

This highlights the reason to avoid crushing enteric-coated tablets since this might result in medicines being released prematurely, to be destroyed by stomach acid, or to irritate the stomach lining.

Extended-release products are designed to release drugs over a longer period, typically 12 to 24 hours. This may be advantageous to avoid frequent dosing of the drug or to avoid the short-term side effects seen with high plasma concentrations. Whilst extended-release formulations are designed to create a constant plasma drug concentration, it is still worth remembering that there will still be minor fluctuations during drug release. Extended-release formulations usually have abbreviations on the drug packs such as CR (controlled release), ER (extended release), MR (modified release) to SR (sustained release), but other abbreviations exist. The way that the extended release is achieved varies significantly from coating the tablets in a slowly dissolving polymer, to embedding them in a matrix like MST Continus, or even to just making the particle size of the drug larger or the form more insoluble as in Tegretol Retard and Adalat Retard. In cases where the gut transit time is increased (e.g. diarrhoea) there will be a reduction in drug absorption.

It is extremely important not to change the formulation of the drug by crushing an extended-release formulation as this will alter the extent of absorption. It is likely to result in an unintentional and hazardous bolus dose that could cause an overdose.

In summary, the factors which affect the dissolution and absorption of a drug from the form administered, the drug's solubility and the ability of the drug to effectively traverse the small intestine to enter the mesenteric vessels and ultimately the systemic circulation as a therapeutic dose are summarised in the list below:

- The formulation of the drug
- Drug-drug interactions
- Drug-food interactions

- Gastric pH
- Integrity of the gastrointestinal tract
- Gastric motility
- Gastric emptying time
- Intestinal transit time and motility
- Length and vascularity of the gastrointestinal tract
- Expression of intestinal metabolising enzymes
- Intestinal pH
- Enterohepatic recycling

Colon

The colon is the gastrointestinal tract's final organ. It goes from the ileo-caecal junction to the anus and makes up about 25% of the length of the gastrointestinal tract. It comprises the ascending, descending and sigmoid colon, and the rectum (see Figure 2.8).

Whilst the ileum has specialised villi, the colon does not. However, there are crypts in the colon, and there are irregularly folded mucosae. All these things make the colon's surface area ten times bigger than a simple cylinder, but this is still 30 times less surface area in comparison to the ileum. Therefore, the colon is not a major area of drug absorption.

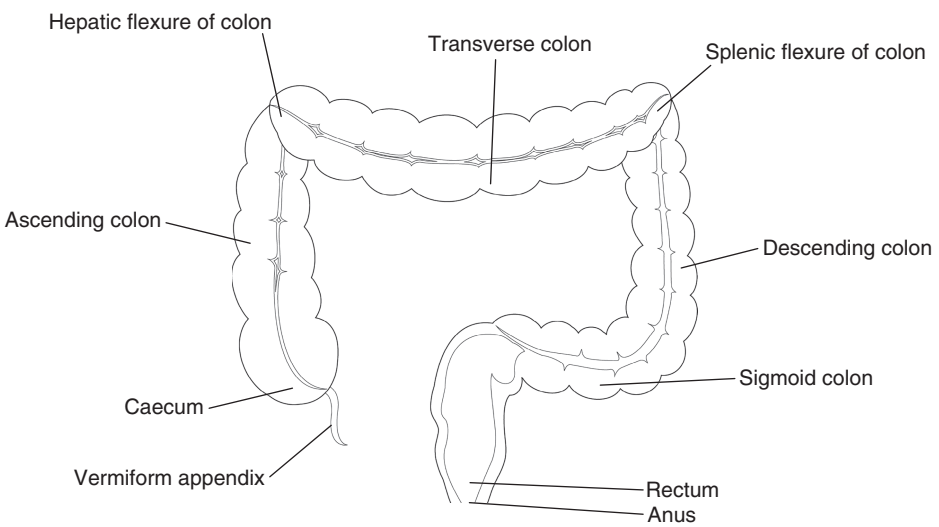

Figure 2.8 Anatomy of the colon

The colon's primary functions are:

- Absorption of water and electrolytes
- Storage and compaction of faeces
- Maintenance of gut microbiota

The colon is permanently colonised by a diverse array of bacteria. This massive bacterial population is capable of a variety of metabolic reactions, including the breakdown of fats and polysaccharides. The bacteria rely on undigested polysaccharides and carbohydrates from secretions such as mucus for their energy. The caecum's pH ranges between 6 and 6.5 rising to 7 to 7.5 in the distal colon. Affecting the bacterial flora can have several effects relating to drug absorption. For example, some metabolised drugs can be excreted in bile. The bacteria in the gastrointestinal tract then metabolise these conjugated drugs back to their active form and they can be reabsorbed. Antibiotics that change the bacterial composition of the gut might then affect this system and reduce the amount of drug that is absorbed back into the systemic circulation within the colon. For example, oral antibiotics are thought to reduce the effectiveness of certain oral contraceptives. The antibiotics may destroy the bacteria in the gut that deconjugate the contraceptive and prevent it being reabsorbed. This puts women who take these oral contraceptives at the same time as antibiotics at risk of contraceptive failure.

Rectum

The extent of drug absorption from the rectum is variable and this, along with patient preference, limits it adoption. However, the rectum is used to administer drugs either for a local effect (e.g. laxatives, steroids) or when the oral route is not suitable (such as benzodiazepines during seizure activity). One of the complicating factors is that drugs absorbed from the upper part of the rectum will be transported to the liver and undergo first-pass metabolism, whilst drugs absorbed from the lower part of the rectum will enter systemic circulation directly. The conventional thinking is that, in general, 50% of the drug that is absorbed from the rectum will avoid the first-pass effect.

The challenge is determining where the upper part of the rectum ends and the lower part begins during conventional administration of suppositories or other rectal medicines. Similarly, there are differences in the anatomy of individuals' venous drainage from the rectum that will also affect absorption, poor venous drainage leading to decreased absorption. Conditions that can affect the integrity of the rectal barrier such as anal fissures and ruptured haemorrhoids can lead to increased drug absorption.

ENTERAL DRUG ADMINISTRATION

The following section introduces you to several pharmacological concepts which relate to the enteral route of drug administration.

First-Pass Metabolism (Pre-Systemic Metabolism)

When an orally administered drug is absorbed from the lumen of the small intestine of the gastrointestinal tract (GIT), it enters the mesenteric vessels which in turn join to

form the large hepatic portal vein. This blood is rich in absorbed nutrients as well as drug molecules. The hepatic portal vein takes this nutrient-rich blood to the liver. However, one of the main roles of the liver is detoxification, which includes drug metabolism, and so, to a greater or lesser extent, some of the drug dosage which has been absorbed may be destroyed before it leaves the liver and enters the systemic circulation by the hepatic vein. This reduces the concentration of the active drug before it reaches its site of action. The presence of gut-metabolising enzymes can also result in a reduction in active drug availability. This process is called first-pass metabolism. When a drug is developed, the drug's 'bioavailability' or 'oral availability' is published as part of the drug's pharmacokinetic profile. This represents the percentage of the originally administered drug which leaves the liver. Several drugs undergo significant first-pass metabolism that means they cannot be administered orally but other routes must be employed (e.g. intravenous administration) where drugs have 100% bioavailability as they bypass first-pass metabolism (see Figure 2.9).

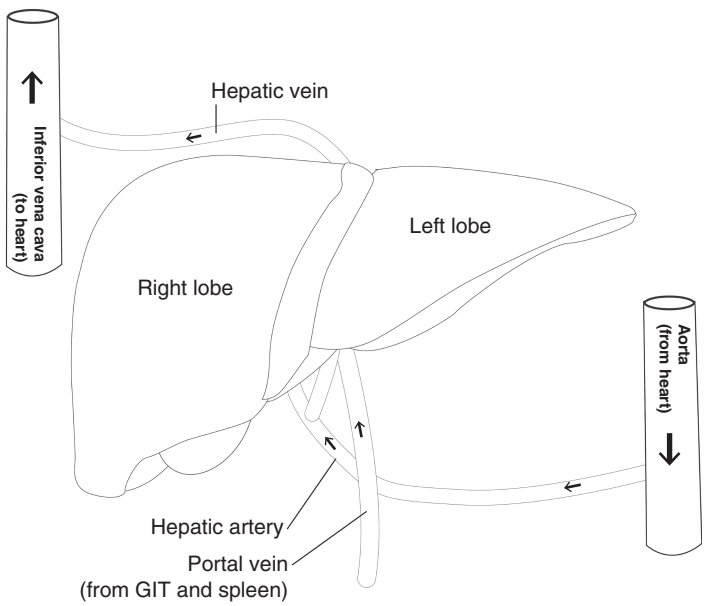

Figure 2.9 First-pass metabolism

Some drugs are significantly metabolised during first-pass metabolism. Morphine sulphate has 23% bioavailability and propranolol approximately 15%, which explains the significant differences in oral and IV doses for both these drugs.

Bioavailability

The term 'bioavailability' describes the extent to which a substance is absorbed into the systemic circulation. It does not consider the rate of drug absorption but simply

the extent. Bioavailability is expressed as a percentage of the systemic dose for intravenous administration of the drug which is 100%. A bioavailability of 0% indicates that no drug enters the systemic circulation, whereas 100% bioavailability indicates that the entire dose is absorbed into the systemic circulation. In hepatic failure, drugs may not be metabolised correctly and so may accumulate if dosing continues, as there is no way for the body to inactivate them. Prodrugs (e.g. ramipril for hypertension), are inactive forms of a drug made into pharmacologically active compounds once they have undergone first-pass metabolism in the liver. They can be developed for several reasons. Primarily their development is to improve the bioavailability of the active drug, getting more of it into the systemic circulation.

There are many differences in drug bioavailability and whilst it might be assumed that the same drug will have the same bioavailability, different pharmaceutical formulations, age, presence or absence of gastrointestinal disease and other medications all influence the percentage bioavailability (see Table 2.2). These factors undoubtedly influence the therapeutic dose achieved and may risk therapeutic failure or toxicity.

Some drugs are so extensively metabolised following first-pass metabolism that they cannot be administered orally (e.g. glyceryl trinitrate, streptomycin and gentamicin). Glyceryl trinitrate is metabolised to the extent that if swallowed rather than used sublingually very little or no glyceryl trinitrate will enter systemic circulation and the drug will have no effect. This resulted in the production of other drugs such as isosorbide mononitrate which could be taken orally as it was less subject to first-pass metabolism.

Table 2.2 Drugs and bioavailability

Drug – oral administration	% Bioavailability (oral availability)
atenolol	56
diazepam	100
digoxin	70
fluoxetine	60
lithium	100
nifedipine	50

Different pharmaceutical formulations of the same drug can also affect the bioavailability such that there is potential for drug doses and effects to vary between formulations. The rate at which the drug is absorbed is also important (along with the extent of absorption), and this affects how long it takes to reach the peak plasma concentration. Slow-release drugs are sometimes used to make it easier to take the drug once a day or to avoid the short-term side effects that come with high plasma concentrations. People who want to use one of these preparations instead of the other may need to stay

on the same brand unless the alternative brands are what is called 'bioequivalent'. This isn't the case for all modified release preparations but can be significant, especially in cases where small variations can have a big effect. As examples, drugs that are modified release and have a narrow **therapeutic window**, such as theophylline preparations, would be prescribed by brand to avoid inadvertent small variations in blood plasma levels that would result in toxic or sub-therapeutic drug levels.

PAUSE AND REFLECT 2.3

Identify the advantages, disadvantages and considerations when administering drugs via the enteral route.

Buccal and Sublingual Routes (Oral Transmucosal)

These routes involve administering drugs using the oral cavity (mouth). Sublingual administration of a drug is the placing a drug under the tongue whilst buccal administration refers to placing the drug between the gums and cheek. They come in the form of tablets, films or sprays (see Figure 2.10).

Like topical medication, buccal and sublingual medication are transported via paracellular and transcellular routes (see next section). However, unlike topical medication drugs administered via the buccal and sublingual routes are designed to act systemically.

The buccal and sublingual mucosa comprise a layer of stratified squamous epithelium on the surface which is linked to underlying connective tissue (lamina propria and submucosa) by a basal lamina. Within this connective tissue, there is a network of blood capillaries where drugs that have permeated through the epithelium can enter the systemic circulation.

Just like the other routes mentioned above (i.e. transdermal, subcutaneous, intravenous), they can be good alternatives to the oral route for drug delivery, particularly for drugs that may be extensively metabolised due to the first-pass effect or that are susceptible to degradation within the gastrointestinal tract. For example, as discussed above, glyceryl trinitrate (or nitroglycerin) (GTN), a drug used in the treatment of angina, when administered orally is extensively metabolised due to the first-pass effect, and therefore is given by the sublingual route. Here it is well absorbed and rapidly taken up into the circulation. Buccal administration has a similar effect, and this route is used for more prolonged action over a few hours. This is because the sublingual mucosa has a thinner epithelium than the buccal mucosa.

These routes have further advantages. The mouth has a large area for drug application and is more easily accessible than other mucosa such as that found in the nose, rectum and vagina. The oral mucosa is more permeable and has higher **perfusion** than the skin, leading to the drugs being absorbed more readily. This is particularly

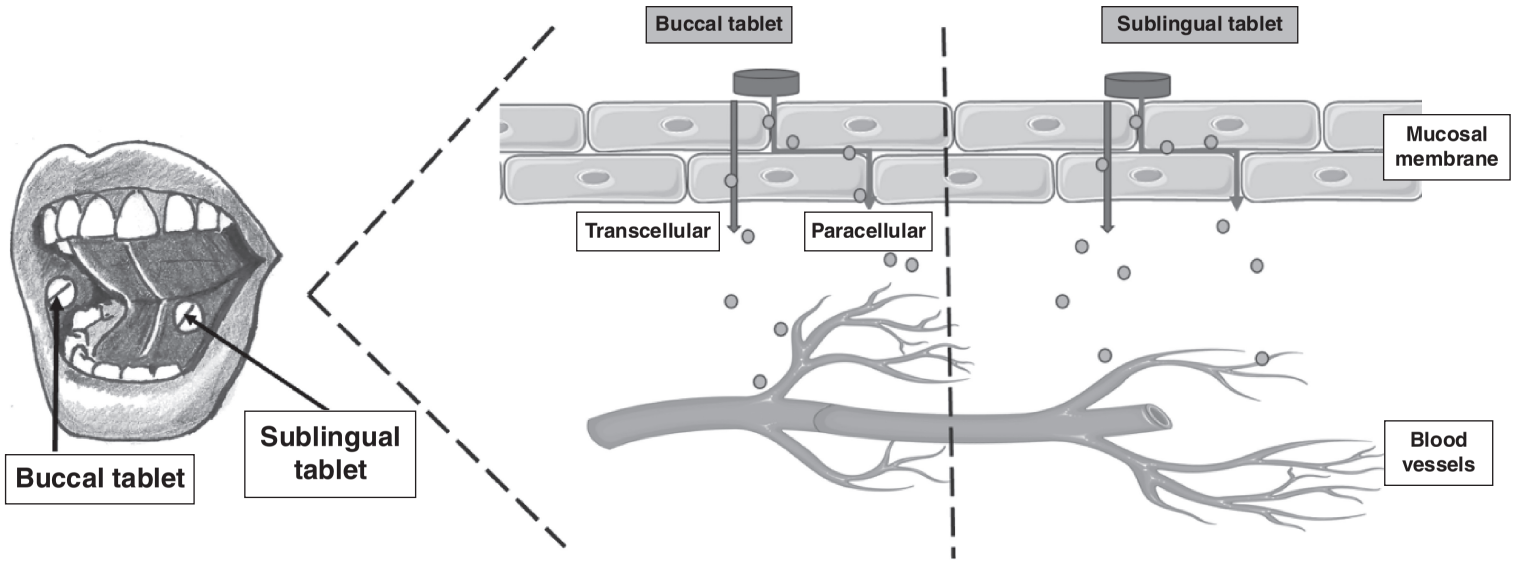

Figure 2.10 The buccal and sublingual mucosa

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important for drugs that need to be absorbed quickly such as GTN. When an individual is experiencing angina, GTN needs to be absorbed in a fast acting, easy and accessible way. The drug can quickly enter the systemic circulation, act upon vascular smooth muscle, causing it to relax and dilate, increasing blood flow to the heart and thus reducing the risk of myocardial infarction. Midazolam is another drug that requires a fast-acting approach. It is a benzodiazepine, used in reducing the length of seizures and in preventing early seizure recurrence. It can be administered via the buccal/sublingual route providing a more effective and socially acceptable alternative to the rectal route.

TOPICAL AND TRANSDERMAL ADMINISTRATION

Topical and transdermal drugs are both applied to the skin. To understand the absorption of drugs via these methods it is important to have knowledge of the structures and functions of the skin.

The Skin

The skin is the most accessible organ of the body. It is also the largest organ, covering a surface area of 1.7m² of the body, and the heaviest, weighing between 3.5 and 10 kgs, almost 16% of the total body mass of an individual. The skin is part of the integumentary system along with accessory structures such as hair, nails, oil glands and sweat glands and

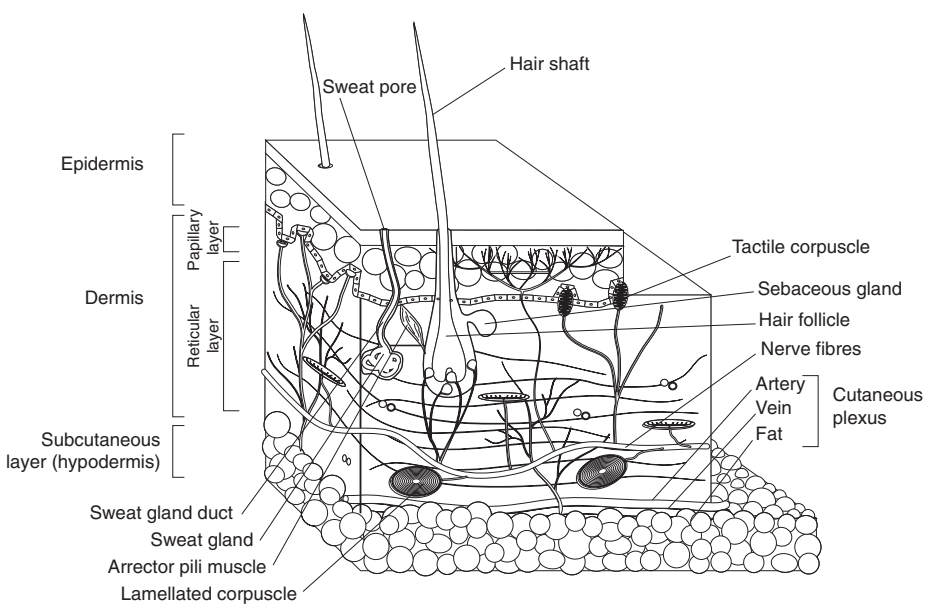

Figure 2.11 Layers of the skin

their ducts. It has several functions, mainly to act as a protective barrier between the body and the external environment. This includes protection from the sun, micro-organisms, allergens, chemicals and loss of water. It comprises three layers: epidermis (the outermost layer), the dermis (the middle layer) and the hypodermis (the innermost layer also known as the subcutaneous layer). Let's explore these layers in more detail (see Figure 2.11).

Epidermis

The epidermis comprises five separate layers, from the stratum germinativum (the innermost layer or basal layer which is attached to the dermis) to the outermost layer, the stratum corneum. It varies in thickness ranging from 0.5 mm on your eyelids to 4.0 mm on the heels of your feet. It consists mainly of keratinocytes but also contains melanocytes (which produce melanin and protect the skin from UV radiation), Langerhans cells (integral to providing an appropriate immune response to the environment they encounter) and Merkel cells (mechanoreceptors that are involved in the sensation of touch). The basal layer contains cuboidal, highly active epithelial cells which are constantly dividing. As new cells form, they are pushed up through the layers away from the nutrient and blood source located in the dermis. Their structure and shape change as they make this journey. Once they reach the outer layer the cells are dead, flat and thin in shape and mainly contain the fibrous protein keratin. They are known as corneocytes.

Dermis

This layer is tough but elastic. It consists of collagen, connective tissues and elastic fibres. Blood vessels are located in the dermis, providing nutrients for both the dermis and the epidermis. It also contains sweat glands (and ducts), sebaceous glands and nerve endings. These nerve endings are specialised to detect touch, temperature, pressure and pain. The presence of these nerve endings means that the skin is one of the most important sensory organs in the body.

Hypodermis

This is the deepest, innermost layer of the skin and is often called the subcutaneous layer. This acts as a contact layer between the skin and the underlying bones, muscle and tissue. The hypodermis mainly consists of fat cells, fibroblasts and macrophages and its main function is storage of energy and protecting the body from heat loss and harm. This will be explored in more depth later in administration by subcutaneous injection.

Topical Delivery

A topical medication is one that is applied to a location on the body with the intention that it treats the condition or ailment locally or at the site of application. Topical

medications are applied to mucous membranes (including those found in ears, eyes and the nose) but most often they are applied to the skin.

A transdermal medication is one whose use is intended to penetrate the skin and have a therapeutic effect on the tissues below and vessels below, often to have a systemic effect (see Figure 2.12).

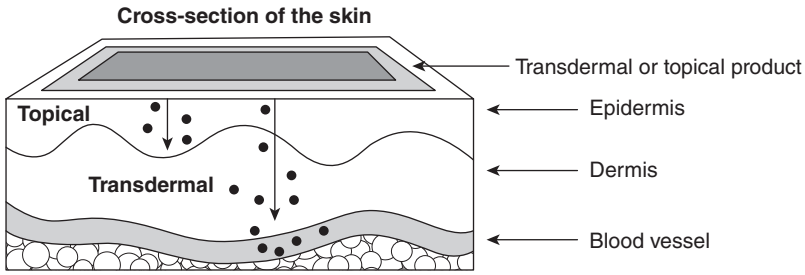

Figure 2.12 A transdermal medication

Topical drug delivery can avoid the need for systemic administration of drugs, most commonly through the oral route. As it is acting directly at the site of delivery it can reduce the total drug dose needed and therefore the risk of adverse side effects.

Topical medications will contain materials both active (the drug) and inactive (the vehicle). The choice of vehicle will depend on where the drug is to be applied, how easy it is to apply, how long it remains on the skin and how it looks. The vehicle determines the consistency of the product which could be thick and greasy such as ointments, creams or gels or could be more watery such as lotions, foams or sprays. Ointments are generally better at delivering the active ingredient than creams because they are often more evenly applied and spread across the skin. However, creams are more easily absorbed, able to cover larger areas of skin and are also more readily accepted by individuals as ointments can be messy, greasy and difficult to wash off.

Topical delivery of drugs is predominantly used in the treatment of dry itchy skin, skin inflammation, allergic reactions and microbial and fungal infections.

One of the most common topical preparations used in the management of dry and itchy skin is emollient. **Emollients** moisturise the skin by increasing the amount of water stored in the stratum corneum. As the skin becomes dry by losing moisture, the corneocytes become smaller and gaps begin to open between the cells, which may reduce the barrier function of the epidermis. When applied to the skin, the emollient traps the water and rehydrates the corneocytes and mimics the natural lipid complex. The 'greasier' the substance the better the sealing and trapping of the water, such as those which have high concentrations of petroleum jelly. Some emollients also draw water from the dermis to the epidermis as they may contain substances known as humectants (e.g. urea and glycerine). Emollients are often used to manage skin conditions such as eczema. It is recommended that emollients are used as adjuncts to other therapies, such as topical/oral **corticosteroids** in the control of such chronic skin conditions. Some research suggests that emollients should be applied first, before topical

corticosteroids, as this allows for the stratum corneum to be well hydrated and thus makes it easier for the corticosteroid to be absorbed, and that time should be left between applications, so the emollient does not to dilute the effects of the corticosteroid. National Institute for Health and Care Excellence (NICE, 2024) guidelines support this and recommend a 30-minute interval if practically possible.

For microbial and fungal infections of the skin, topical antibiotics and topical antifungals may be applied (e.g. erythromycin which is frequently used for the treatment of acne). Acne can be a chronic condition, starting in puberty and extending into adulthood. It is caused by the enlargement of the sebaceous glands and an increase in sebum production that is stimulated by the beginning of puberty. Also, an accumulation of keratin within the intrafollicular duct leads to a build-up of this sebum. These actions lead to the plugging of the hair follicles trapping *Cutibacterium acnes* (*C. acnes*) which ordinarily is a common and harmless bacterium, but thrives on the extra sebum, overgrows and produces an inflammatory response leading to skin lesions. Topical antibiotics such as erythromycin inhibit the enzyme and protein synthesis involved in bacterial growth. Due to the concern about the rise of antibiotic resistance over recent decades, topical antibiotics for acne are usually prescribed with another topical agent to reduce the length of time the antibiotics are required. The most common of these is benzoyl peroxide. This can help with the breakdown of keratin, therefore unblocking the drainage of sebum and 'unclogging pores', and also inhibiting the growth of *C. acnes*.

Transdermal

Drugs administered transdermally are designed to penetrate the epidermis and dermis without accumulation in the dermal layer, to reach the deeper tissues and blood vessels beneath, thus having a systemic effect. This mode of absorption has several advantages over other routes. It avoids the first-pass effect and so increases the bioavailability of the drug. It can be an alternative to parenteral administration which can be painful and have a higher risk of infection. Transdermal routes benefit patients who are nil by mouth or who cannot swallow. It can also help with patient concordance, due to a reduction in dosage frequency. Furthermore, it has been found to administer the drug constantly and reliably, maintaining therapeutic blood levels and thus minimising side effects.

In order for the drug to reach the systemic circulation it must be able to permeate the dermis and the epidermis. The main barrier to this is the stratum corneum (this is also the case for topical medication).

The stratum corneum can be likened to a wall, with the corneocytes as the bricks and the intercellular lipid matrix being the cement or mortar. This construction is critical to its barrier function. If a drug formulation is applied to the skin surface it can cross the epidermis in three ways, through the (a) transappendegeal route, (b) the intracellular (transcellular) route or (c) the intercellular (paracellular) route. The route will depend on the chemical properties of the permeating drug molecule. Lipophilic or non-polar solutes will be mainly transported through the intercellular route (through the matrix layers) whilst hydrophilic or polar solutes will permeate via the intracellular route

(through the corneocytes). The transappendegeal route allows drug molecules to move through the sweat glands and across hair follicles.

At present, most transdermal drugs have been delivered by adhesive patches. The patch increases drug absorption due to the longer application time. The drug is contained in high doses in a liquid or gel-based reservoir, which along with the occlusive nature of the patch drives the drug via passive diffusion through the skin. However, the drug must possess the right properties to passively permeate the skin (i.e. being lipophilic and of low molecular weight) and this often limits the variety of drugs that can be delivered transdermally. Chemical enhancers are often added to the medication to improve permeability by modifying the chemical barrier properties of the stratum corneum. The enhancers work in a variety of ways, including disruption of intercellular lipids, increase in the fluidity of the stratum corneum lipid bilayers and increase in thermodynamic activity. Some examples of chemical enhancers are alcohols, sulphoxides essential oils, fatty acids and urea. However, they can often cause skin irritation. There are many drugs that can be delivered transdermally (e.g. fentanyl, which is a strong **opioid** used to relieve chronic pain). Another common drug that uses patches for transdermal delivery is hyoscine. This is administered to prevent motion sickness and is placed on the postauricular area (the hairless area behind the ear) because the stratum corneum is at its thinnest in this location and therefore the drug is more readily absorbed.

Today, there are more 'active' transdermal delivery systems available that use non- and minimally invasive technologies, such as iontophoresis, microneedles, electroporation and sonophoresis, to enhance drug delivery across the skin and thus broaden the number of drugs that can be delivered transdermally. Iontophoresis and electroporation are both techniques that use electrical impulses to help deliver medication across the skin, whilst sonophoresis uses ultrasound to reduce the skins resistance. More recently, there has been intensive research into the use of microneedles. Patches support multiple microscopic projections or needles that are of a shape and length to avoid nerve endings in the dermis. One of the most favoured uses of this technique is for vaccinations, as they offer a pain-free method that could possibly be self-administered.

Transdermal patches are increasingly being used with children and young people and some have been particularly designed for use in children such as the methylphenidate patch for the treatment of attention deficit hyperactivity disorder. However, despite the advantages of this non-invasive and acceptable route of drug delivery for children and young people there are still issues with formulation for neonates who have an immature skin barrier. However, it is important to note that the extrauterine environment triggers rapid maturation, so that by two or three weeks of age the skin has similar barrier properties to that of a term infant.

In fact, age must be considered when administering topical/transdermal medication as the skin changes throughout the life stages of an individual. Young children have a thinner stratum corneum and larger skin-surface to body-mass ratio. Any topical drug is therefore likely to be absorbed much more readily than in an older child or adult due to the increased permeability of the skin.

As an individual grows older there are significant changes to the skin in both function and structure. However, evidence has shown that in practice there are no significant differences in absorption of drugs from transdermal delivery systems (Kaestli et al., 2008). The need for dose adaptation in elderly individuals is often not due to the absorption of the drug through the skin but to what happens when the drug reaches the systemic system and concerns with age-related cardiovascular, cerebral, hepatic and/or renal compromise that cause pharmacokinetic and pharmacodynamic changes.

PARENTERAL ROUTES OF DRUG ADMINISTRATION

'Parenteral' means any non-oral means of administration, but usually refers to injecting directly into the body and bypassing the skin and mucous membranes, 'par' meaning 'beyond' and 'enteral' relating to the intestines. Parenteral routes are almost perfect ways of administering drugs due to the high bioavailability and quick onset of action. In intravenous (IV) drug administration, all the dose reaches the systemic circulation and has an immediate physiological response. In contrast, subcutaneous (SC) and intramuscular (IM) administrations involve an absorption process from the injection site leading to a more delayed and slower response. This is due to the drug molecules having to diffuse across the interstitial space to reach the capillaries. However, absorption is still a lot quicker than via the enteral route.

Common means of parenteral administration of drugs include subcutaneous, intravenous and intramuscular methods, which will now be explored.

Subcutaneous Injection

As previously stated, the subcutaneous layer (hypodermis) is the deepest layer of the skin. It is mainly made up of fatty molecules and drugs can be administered directly and deposited into this layer via subcutaneous injection.

Subcutaneous administration is often required when drugs are not compatible with oral delivery as they may be highly metabolised by the first-pass effect or are partially or fully destroyed by the gastric juices such as insulin.

Insulin is a naturally occurring hormone that is secreted by the pancreas and is involved in the control of blood glucose levels. In type 1 diabetes, **endogenous** insulin is either minimal or non-existent and therefore SC insulin is administered to replace this deficiency. Insulin cannot be administered orally due to its chemical properties. It is a very large molecule and highly polar. It has difficulty crossing the gastrointestinal epithelium therefore as it is too polar to diffuse through the cell membrane and too big to move between the cells. Also, insulin is a protein, and proteins are extensively metabolised by enzymes present in the stomach. Therefore, delivering insulin via an SC injection ensures that it reaches its target cells.

Complications associated with subcutaneous injections include infection, abscess formation and lipohypertrophy. Lipohypertrophy, the accumulation of fatty scar tissue,

can be caused by repeated injections in the same area of the skin and will display unpredictable drug absorption. The rotation of injection sites is recommended for this reason.

There are four recommended sites to inject into the SC tissue even though subcutaneous tissue is quite easy to reach from all injection sites on the body surface. These four sites are chosen because of the depth of SC tissue (see Figure 2.13).

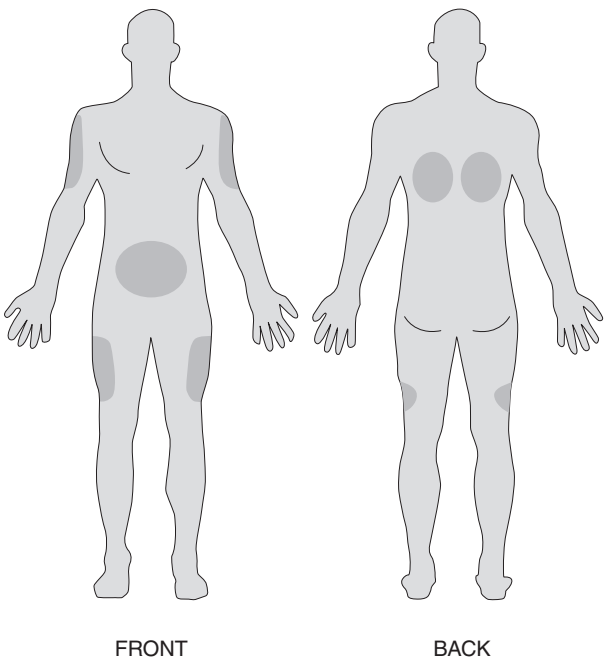

Figure 2.13 Four recommended sites for injection

Source: British Columbia Institute of Technology. http://open.bccampus.ca

Another example of a drug that is poorly absorbed in the gastrointestinal tract is heparin. This is due to its molecular size and ionic repulsion from negatively charged epithelial tissue in the gut and therefore has poor oral bioavailability. Heparin belongs to a family of **anticoagulant** drugs that activate the natural anticlotting protein antithrombin, which interrupts the factors involved in the clotting process of the blood. There are two forms of heparin in use which include original heparin and the more recent low-molecular-weight heparins such as tinzaparin, dalteparin and enoxaparin. These drugs are commonly given post-surgery where immobility may encourage clotting in the deeper veins of the legs.

Drugs administered subcutaneously are often small in volume, usually up to between 1.5 and 2 mls as larger volumes are associated with pain and adverse effects at the site. Subcutaneous administration is often used when drugs are required to be released more slowly (such as the examples above), because just as subcutaneous tissue can store fat, it can also provide a good depository for drugs that need to be absorbed gradually due to its limited blood flow.

There are several factors that may affect drug absorption via the SC route. including exercise and changes in environmental temperature. It is thought that the absorption of SC medications may increase during exercise because of increased blood flow to the area and the massaging effect of the exercising muscle. Conversely, drugs may not be absorbed so readily in patients with conditions where there is impaired blood flow, such as circulatory shock.

Intramuscular Administration

Lying underneath the epidermis, dermis and subcutaneous tissue is skeletal muscle (see Figure 2.14). Skeletal (striated) muscle has an abundant blood supply and therefore the injected drug reaches the systemic circulation more quickly. Skeletal muscle can also absorb larger volumes of fluid due to the rapid uptake of the drug into the bloodstream via the muscle fibres. Due to this increase in drainage away from the muscle fibres, complications like abscess and granuloma formation are less common after intramuscular injections than after subcutaneous injections.

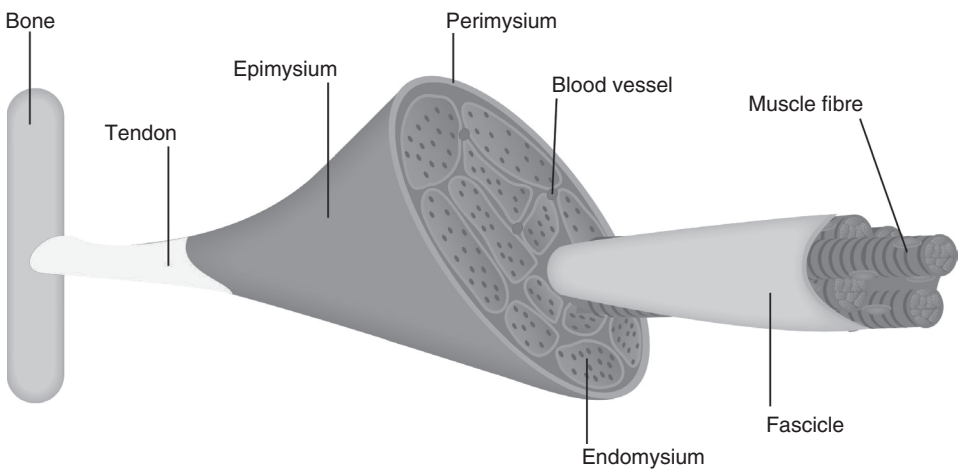

Figure 2.14 Skeletal muscle

Also, the skeletal muscle contains fewer pain receptors than SC tissue and so IM injections can be less painful and can be utilised to deliver concentrated and irritant drugs that would otherwise damage the SC tissue.

There are a variety of recommended sites for IM injection which are often chosen because of patient preference and the volume of the drug that needs to be administered (see Figure 2.15). For smaller volumes (approximately up to 2 mls) the deltoid site can be used, whereas for larger volumes the ventrogluteal site is preferred in adults and the vasterus lateralis/rectus femoris in young infants. The ventrogluteal site is the site of choice as it is free of nerves and has a thick layer of muscle and a thin layer of fat, as opposed to the dorsogluteal site. Evidence suggests that using the dorsogluteal site comes with a high risk of administering the drug into subcutaneous tissue rather than the muscle and a high risk of damaging the sciatic nerve (Jung Kim and Hyun Park, 2014).

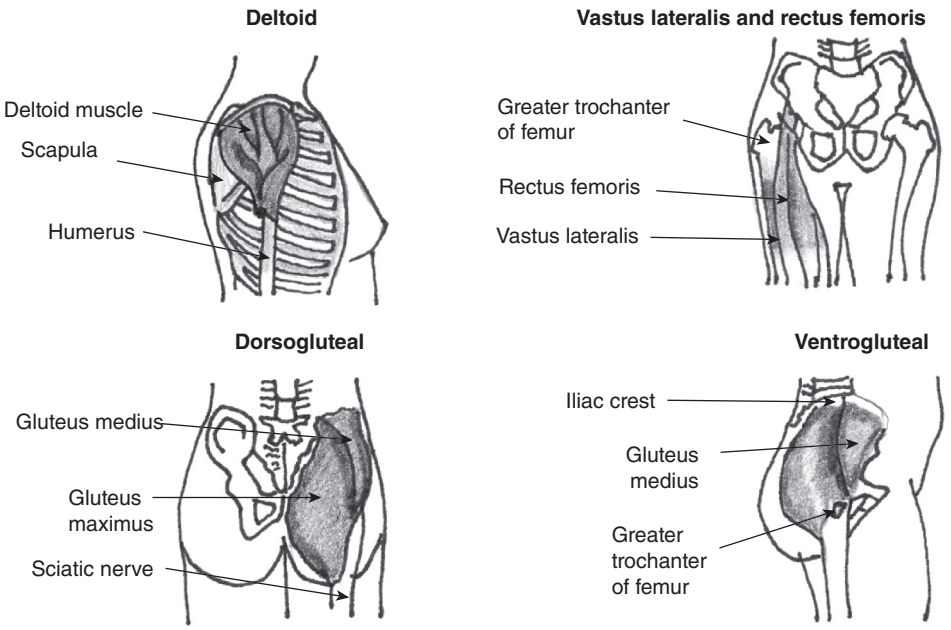

Figure 2.15 Recommended sites for IM injection

IM injections are one of the most common procedures to be performed, although they are often avoided in children due to fear, pain and anxiety. However, there are also physiological and pharmacological reasons for not using the IM route in children. Young infants have less muscle mass and therefore absorption of the drug can be unreliable.

Ageing also brings about changes in body composition and older people have less muscle mass. This, along with reduced blood flow, leads to lower or unpredictable absorption of the drug.

Even though we try to avoid administering drugs to children via the IM route, some are routinely delivered this way, such as vaccinations. Most vaccinations are delivered via the IM route but there are some exceptions such as the BCG vaccine (for tuberculosis), which is delivered intradermally (just under the epidermis of the skin) and flu vaccine for children is delivered via nasal drops.

The IM route is chosen for a variety of reasons. Muscle contains many immune cells called dendritic cells that can recognise antigens and carry them to the lymph nodes. Lymph nodes act as reservoirs for white blood cells, which are a fundamental part of our immune response. The dendritic cell will present the antigen to the white blood cells causing them to multiply and start producing antibodies to defend our body against specific pathogens. The most common place for vaccines is in the deltoid muscle. This is close to the armpit which contains many lymph nodes and an abundance of white cells.

PAUSE AND REFLECT 2.4

Consider the advantages, disadvantages and other considerations when administering drugs via an intramuscular injection.

Intravenous Route

Intravenous drug administration is the direct delivery of a drug into the venous, systemic circulation. The drug is administrated via devices (e.g. peripheral intravenous cannula, peripherally inserted central catheter (PICC), centrally inserted central catheter (CICC)) which are sited in the vein. As veins return deoxygenated blood via the inferior vena cava to the right side of the heart, the drug will be distributed around the body once it has passed through the cardiac chambers and into the aorta.

The administration of a drug directly into the venous, systemic circulation means that intravenous drugs are immediately available to the body for therapeutic action.

The advantages of intravenous drug administration include the following circumstances:

- Bioavailability is 100% as there are no barriers to absorption and the drug does not undergo first-pass metabolism
- There is minimal delay in drug response and it is therefore valuable in emergency situations (e.g. cardiac arrest)
- Drug titration – if a drug is administered via an intravenous infusion, then the dose can be manipulated to control the physiological response (e.g. blood glucose levels and insulin, noradrenaline infusion and blood pressure control, propofol (sedative) and sedation score)
- The infusion can be stopped if there are adverse effects. However, if the drug has a long **half-life**, then the drug effects will persist as they would with orally administered drugs (e.g. the drug amiodarone, prescribed for cardiac arrythmia, has a half-life of 50 days)
- Intravenously administered drugs with a relatively short duration of action (e.g. the sedative midazolam) are useful for invasive procedures where prolonged sedation is not required
- Administration of drugs which are poorly absorbed from the gastrointestinal tract, drug degradation by gastrointestinal enzymes or bioavailability is significantly compromised when administered orally and therefore they can only be administered intravenously (e.g. gentamicin)
- Several drugs administered via the intramuscular or subcutaneous route are painful because they risk staying in the muscle or adipose tissue respectively as a potential toxic concentration
- The intima of the vein is insensitive and therefore drugs which are irritating or non-isotonic can be administered
- Allows for the administration of large volumes of fluid

There are, however, several considerations and potential disadvantages to the intravenous administration of drugs, which include:

- Intravenous access devices are potential vehicles for microbial contamination, which risks the development of sepsis
- Risk of thrombophlebitis (e.g. diazepam), although improved drug formulations have reduced this risk
- Risk of necrosis caused by extravasation of the drug into the tissues. If the peripheral inserted cannula becomes displaced within the vein or the vein is ruptured during insertion of the access device, then the drug will enter the surrounding tissues and may lead to tissue death. This is seen particularly with **cytotoxic** drugs
- For drugs which are administered in intravenous fluids to dilute the drug prior to administration, there is a risk that the drug is incompatible with the **solvent**/dilution fluid. This incompatibility may result in precipitation of the drug out of solution and risk embolism. For example, drugs should not be administered to blood products: hypertonic mannitol results in the crenation (shrinkage and change in shape) of red blood cells; glucose results in the clumping of red blood cells
- Rapid drug delivery into the intravenous system may result in cardiac arrythmias or toxicity. For this reason, cardiac monitoring may be advised (e.g. phenytoin) or the drug is not licensed for IV administration (e.g. stemetil (anti-emetic))
- If the drug is administered too quickly, 'speed shock' is a systemic reaction resulting in flushing, headache and cardiac arrythmias
- Significant costs incurred due to consumables, personnel time and requirement for training and education

INTRA-ARTERIAL DRUG ADMINISTRATION

The intra-arterial route involves the administration of the drug via an artery. This route is usually reserved for the administration of contrast medium for diagnostic purposes (e.g. angiography), direct delivery of the drug to treat neoplasms or the administration of vasodilators in arterial embolism (e.g. alteplase in ischaemic stroke).

The intra-arterial administration of drugs is contraindicated as an alternative route to intravenous administration as the drug would be delivered as a bolus directly to tissues, which would result in compromised tissue perfusion.

Inhalation

The upper airway consists of the structures of the nose, nasal cavity, nasopharynx and oropharynx. The function of the upper airway is to provide initial protection to the internal environment of the body by warm filtering and humidifying the air entering

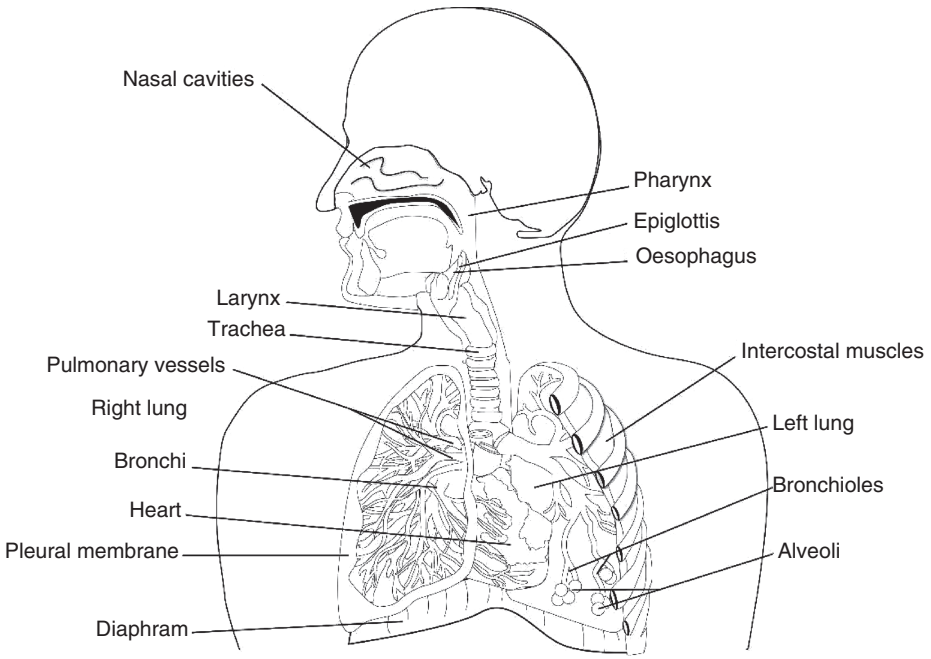

Figure 2.16 Inhalation

the body. The folds of the nasal cavity provide an increased surface area with which to humidify and warm air entering the body to limit drying out of the lower airway and minimise insensible thermal loss. Small hairs in the nose and the mucous coating in the nasal cavity help capture and prevent larger airborne particles from progressing into the lower airway.

The lower airway consists of the larynx, trachea, left and right main bronchus, bronchi and bronchioles culminating in the alveoli. The trachea, bronchus and bronchi are predominantly surrounded by hyaline cartilage rings which serve to support the airway and help maintain its patency. It again has a layer of mucous which coats the internal lumen and helps capture any microparticulate debris that has managed to pass into the lower airway (see Figure 2.16).

The alveoli are the terminal point of this bronchial tree, and it is the site where gaseous exchange takes place, allowing oxygen to diffuse into the bloodstream and carbon dioxide out. This process of two-way **diffusion** is referred to as external respiration.

There are three distinct layers to a large proportion of the tissues within the respiratory tract: the uppermost layer (epithelium); the supportive structure below (lamina propria) is referred to commonly as the mucosa; below this exists the submucosa which contains the smooth muscle that envelops the airway and for the larger airway structures also contains cartilage. The final outer layer of the airway is the adventitia consisting primarily of connective tissue that anchors the structures within the organ system.

The large surface area of the pulmonary system, particularly the bronchial tree and alveoli spaces, are advantageous to drug delivery. Small-particle drugs (e.g. anaesthetic

gases) are rapidly diffused across the alveolar membrane to induce effect, with bronchodilator therapies acting locally in the pulmonary structures. For drugs which are administered for local effect, the size of the drug particle is such that there is limited systemic absorption – for example, when administering salbutamol, a short-acting β_2 adrenergic receptor **agonist**, the systemic side effects of **tachycardia** and palpitations are reduced.

Drugs administered via the pulmonary system frequently adopt dry powder, aerosol pressurised metered-dose inhalers or nebuliser delivery systems. Developments in technology and design of devices have improved drug delivery; however, poor technique and user coordination will result in inconsistent drug deposition. Another factor to be considered is that pulmonary disease may be a barrier to successful drug delivery. The bronchoconstriction seen in asthma, airway obstruction by mucus plugging, hypersecretion or a foreign body will result in increased airway resistance. As the diameter of the airway reduces it becomes exponentially more difficult to pass the same volume of air through the respiratory tree, lowering the tidal volume, and therefore reducing the ability to transport any medication suspended within the air to the areas of the lung.

Reduced compliance is a reduction in the lung's elasticity and its ability to stretch. This can result from pneumonia, pulmonary oedema or potentially scarring from previous tissue damage, which when present can affect the lung's ability to expand, limiting the tidal volume and reducing the capability to deliver medications. Several structures act as natural immune defences and along with mucociliary clearance, drug deposition is likely to be further reduced.

PAUSE AND REFLECT 2.5

Consider the different routes of drug administration that you have seen. Reflect on the advantages and disadvantages of oral, intravenous and topical routes. Can you think why these drugs were administered by this specific route?

CHAPTER SUMMARY

Chapter 2 has focused on the first stage of pharmacokinetics – drug absorption. The different routes of drug administration employed in medicine management have been explained with respect to normal physiology. Whilst the aim of drug absorption is to ensure that the drug reaches the systemic circulation so it can be distributed around the body, there are many factors which impact the rate and extent of drug absorption. Whilst not exhaustive, these relate to the physiological barriers the drug needs to navigate, the formulation of the drug, the physical and chemical properties of the drug, the presence of disease and age-related changes.