1 BASIC CONCEPTS IN PHARMACOLOGY AND THERAPEUTICS

KEY POINTS

- Drugs and pharmacology are relevant to dentistry, not only in what is prescribed but also in how the patients' medicines impact on oral health, dental diagnosis and procedures.
- Fundamental concepts of pharmacology are important for understanding appropriate management of drugs in dentistry.
- Drug interactions are increasingly relevant in dentistry as they are an important yet often-ignored source of adverse drug events.

1.1 Introduction

Drugs are a part of everyday life and may be defined as 'any pharmacologically active substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease' (1). Whether a drug is a conventional medicine, a herbal remedy, or the caffeine in your coffee, drugs are an integral part of human existence and have been since ancient times. Drugs may be synthetic in origin or naturally derived from plants, animals, or biotechnology. A 'medicine' is a pharmaceutical product containing one or more pharmacologically active substances in a formulation administered for a therapeutic purpose.

1.2 Role of drugs in dentistry

In clinical practice, dentists interact with drugs and medicines in four main ways. These interactions are with the patient's own medicines, with the medicines used during a procedure, the medicines used in the practice for medical emergencies, and the medicines prescribed for patients for use after a consultation or procedure. Although dental practitioners do not prescribe medicines very often, with tertiary level education about drugs and broad prescribing privileges, dentists are expected to have a comprehensive understanding of the science of drugs and how their use can impact on dental conditions and procedures. As drugs may be administered by dentists during dental procedures or in the event of a medical emergency in the dental practice, dentists have a responsibility to understand how to use them safely and effectively, their side effects, drug interactions, place in therapy, and their impact on patient care.

1.2.1 What is pharmacology?

The term 'pharmacology' is derived from the Greek word *pharmakon* ('drug, poison' and -λογία, -logia 'study of', 'knowledge of') and refers to the study of drugs. In pharmacology, the chemical structures of pharmacologically active substances are elucidated, their mechanisms of action and target sites examined, and their route around the body mapped to eventually become the drug's pharmacodynamics and pharmacokinetics.

1.2.2 What is the study of therapeutics?

Therapeutics is the science of treatment and care of a patient for the purpose of preventing and combating disease or injury (1). Medical Britannica states that 'the term "therapeutics" comes from the Greek *therapeutikos*, which means "inclined to serve"' (1). In the area of pharmacology, therapeutics involves the application of drug knowledge to patient care through the judicious, safe, appropriate, economic, and effective use of medicines. This area is also referred to as 'pharmacotherapeutics'.

1.2.3 How is pharmacology different from therapeutics?

Pharmacology and therapeutics are similar disciplines in that both require an understanding of the properties and actions of pharmacologically active substances. However, pharmacology places more emphasis on the mechanisms of action, chemical structures, and movement of the drug around the body, while therapeutics focuses on the practical aspects of safe and effective medicines use in clinical practice.

1.2.4 How is pharmacy different from pharmacology?

Pharmacy is the study of medicines, from their design and development to their regulation and distribution in the community and finally to their safe use by prescribers and consumers. Pharmacy training covers all aspects of drug usage including pharmacology, manufacture, acquisition, storage, dispensing, administration, and disposal of medicines—as well as patient aspects such as management of adverse effects, drug interactions, prevention and management of medication error, medication review and deprescribing. Those who study pharmacy typically become pharmacists who prepare and dispense medication and collaborate with other healthcare providers to optimise medication use in patient care (4). Many pharmacists work in non-dispensing roles as well: in hospitals, community pharmacies, general medical practice, residential aged care, government, regulatory authorities, academia, the armed forces and the pharmaceutical industry. Those who study pharmacology, however, are qualified as scientists and generally work in research settings or incorporate their qualification into another health-based degrees. For example, clinical pharmacologists are medical practitioners who have specialised in pharmacology and usually work in hospitals.

1.2.5 What is toxicology?

Toxicology is the study of the harmful effects of chemicals, drugs and poisons on living organisms. Toxicologists are medical experts in poisons and poisoning and are consulted to analyse and advise on the treatment of ingestions, bites, and stings from acute

or chronic drug or toxin exposure (3). Poisons information centres are operated by toxicologists and pharmacists trained in toxicology.

1.2.6 The importance of patient-centred care

One of the key themes of pharmacotherapeutics in the 21st century is patient-centred care. This type of care moves away from the prescriber being the focus of treatment choices towards the patient being at the centre of decision-making. Treatments are tailored to individual patient characteristics with patients' treatment goals and health-related beliefs respected. Some of the move towards patient-centred care has been driven by medico-legal considerations in healthcare, but also a greater understanding that respect for patient rights and responsibilities, preferences and consent leads to better health outcomes. This is further encouraged with greater understanding that medications work differently in different people and are used more safely if prescribed in a way that is considerate of each patient's medical history, pharmacogenetic profile, co-morbidities, and concomitant medications.

1.3 The fundamentals of drug response

Many factors contribute to inter-individual differences in drug response. These are broadly divided into three principal areas:

1. Pharmacodynamics = the actions of drugs (what the drug does to the body).
2. Pharmacokinetics = the movement of drugs (what the body does to the drug).
3. Pharmacogenetics = the influence of genes and their protein products on drug dynamics and kinetics.

1.3.1 What is pharmacodynamics?

Marino, Jamal and Zito describe pharmacodynamics as 'the study of a drug's molecular, biochemical, and physiologic actions' (4). The term is derived from the Greek words *pharmakon* which means 'drug' and *dynamikos* meaning 'power.' (4) The pharmacodynamics of a drug are its pharmacological actions and effects, often described as 'what the drug does to the body'.

Drugs work by binding to a variety of targets including external receptors on target tissues, active sites on enzymes, cell surface signalling proteins, and molecules circulating in the blood stream. The pharmacological aim is that, subsequent to the drug-target interaction, downstream dynamic effects occur which can be measured by biochemical or clinical means such as decrease in pain, killing of infectious organisms, reduction of blood pressure or lowering of blood-glucose levels (4).

1.3.2 What is pharmacokinetics?

The pharmacokinetics of a drug are its movements around the body, which are described in terms of four steps: absorption, distribution, metabolism and excretion (5). It is also described as 'what the body does to the drug'. The term 'pharmacokinetics' is derived from the Greek words *pharmakon* meaning 'drug' and *kinisi* meaning 'movement' (4).

1.3.2.1 Key pharmacokinetic parameters

Key parameters of every drug's pharmacokinetics are its bioavailability, maximum serum concentration reached (Cmax), time to maximum concentration (Tmax), volume of distribution and half-life (see Section 1.3.2.3).

These parameters are used to describe how a drug's disposition changes over time, or in certain disease and physiological states. For example, drug use in renal and liver impairment is guided by the changes in a drug's pharmacokinetics depending on the degree of organ impairment.

The pharmacokinetics of paracetamol, for example, can be described as follows: Orally administered paracetamol is rapidly and almost completely absorbed, attaining peak blood levels (Tmax) at 1–3hrs, with negligible binding to plasma proteins. It is widely and almost uniformly distributed in the body (volume of distribution ~ 1L/kg); extensively metabolised in the liver and the metabolites are excreted renally.

Pharmacokinetics also guide drug use in pregnancy and breastfeeding as it helps to measure to what extent a drug distributes across the placenta or into breastmilk, and when drug concentrations peak in the breastmilk in order to plan the timing of breastfeeding.

1.3.2.2 Bioavailability

Bioavailability describes how much of the originally administered drug reaches the systemic circulation and is expressed as a fraction or percentage. It depends largely on the physicochemical properties of the substance such as its lipophilicity, route of administration and whether the drug is passively or actively transported across the gut wall. Other factors that affect bioavailability include drug formulation, the presence or absence of food, pharmacogenomic variations in metabolic enzymes and drug transporters, gastric motility, and mesenteric blood flow.

For example, drugs administered intravenously have 100% bioavailability as they are delivered directly into the blood stream, with all the administered drug entering the systemic circulation. Drugs administered orally must navigate the gastrointestinal (GI) tract, survive gastric acid and digestive enzymes, achieve drug transport across the gut wall and survive first pass metabolism in the gut and liver. As a result, only a small amount of orally administered drugs may reach the systemic circulation.

1.3.2.3 Cmax and Tmax

As shown in Figure 1.2, Cmax describes the maximum serum concentration reached after a single dose of the drug and Tmax describes the time taken to reach peak concentration (Cmax) after a single dose of the drug (6). Cmax will be reached more quickly for intravenously administered drugs than for those administered orally. So, drugs administered intravenously have a shorter Tmax than the oral drugs, but both could have the same Cmax (see Figure 1.1).

Figure 1.1 Graphical representation of Cmax, Tmax and AUC and half-life as they vary with time and drug concentration.

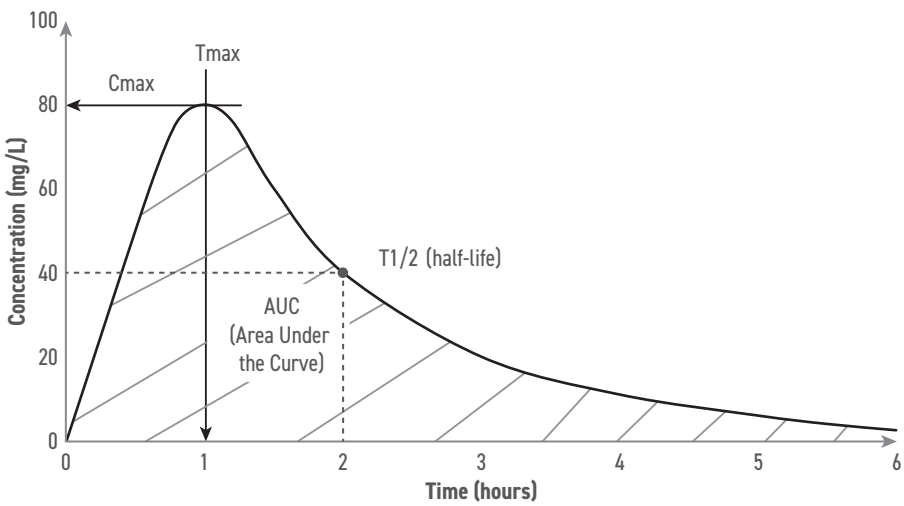
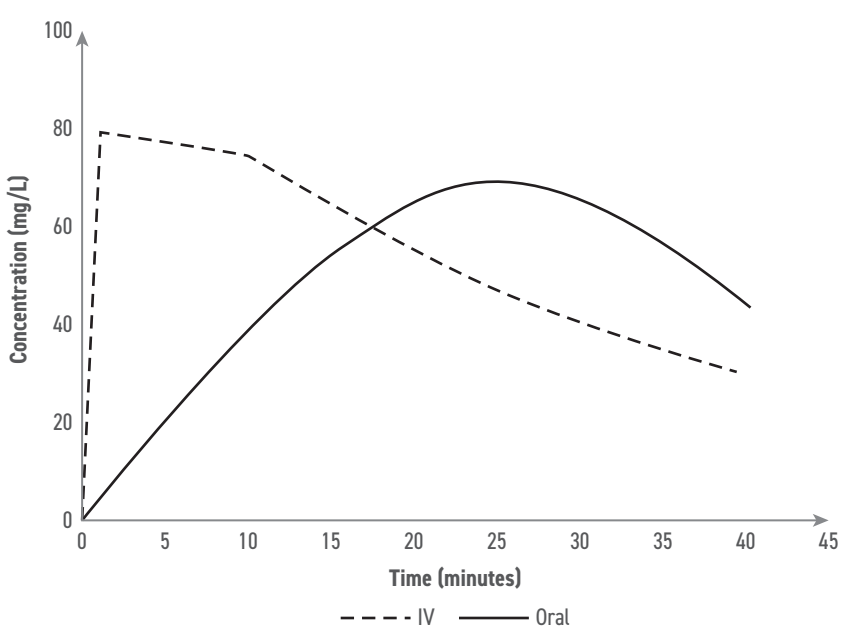


Figure 1.2 Graphical differences between Tmax and Cmax for the same drug administered via IV and oral routes.



1.3.2.4 Area under the Curve (AUC)

AUC represents the total amount of drug absorbed into the systemic circulation from a single dose. AUC is determined by mapping plasma concentrations of the drug over the entire dosage interval, then measuring the area under the plasma concentration time

curve (see Figure 1.1). AUC can be a useful tool for comparing different formulations of the same drug and dose; for example, a capsule versus a tablet. Plasma concentration time curves show how drug concentrations from each formulation vary over time, and how the AUCs from the two different products compare.

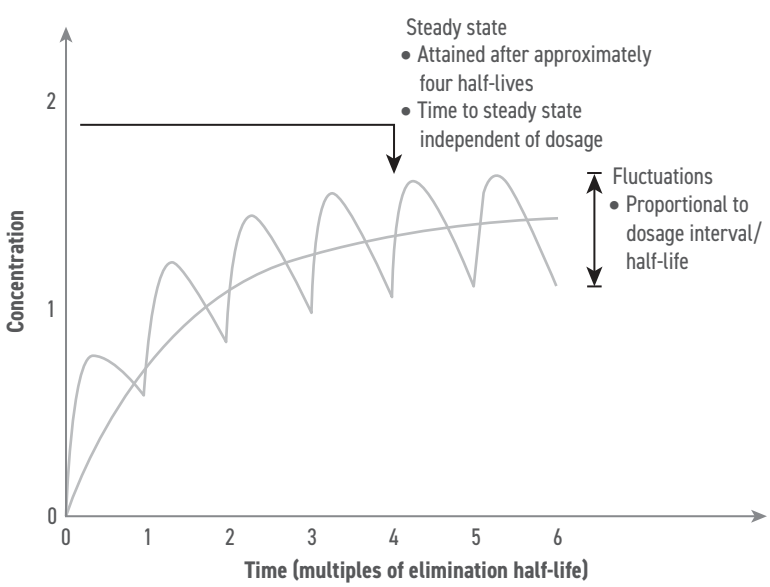
1.3.2.5 Half-life

The half-life (T1/2) of a drug is the time it takes for the drug's serum concentrations to decrease to half its Cmax. Although this is a mathematical parameter, it forms the basis for calculating how long each drug dose persists in the body, for determining drug dosing interval, and to calculate when a drug is completely eliminated. The convention for the latter is to multiply the half-life by 5, as this is when the drug is 98.5% eliminated (i.e. close enough to 100%). Drugs that linger in specific compartments in the body (e.g. bone or fat) will have a different half-life for each one of those compartments.

1.3.2.6 Steady state

When a drug is administered repeatedly, it eventually reaches a plateau, which is called 'steady state'. This is where an equilibrium is reached between the amount of drug entering the body and the amount excreted with each dose. Steady state is usually achieved after approximately five half-lives (see Figure 1.3). Knowing a drug's half-life and steady state allows clinicians to predict when a drug's effects will stabilise and, if the drug is ceased, when its effects wear off.

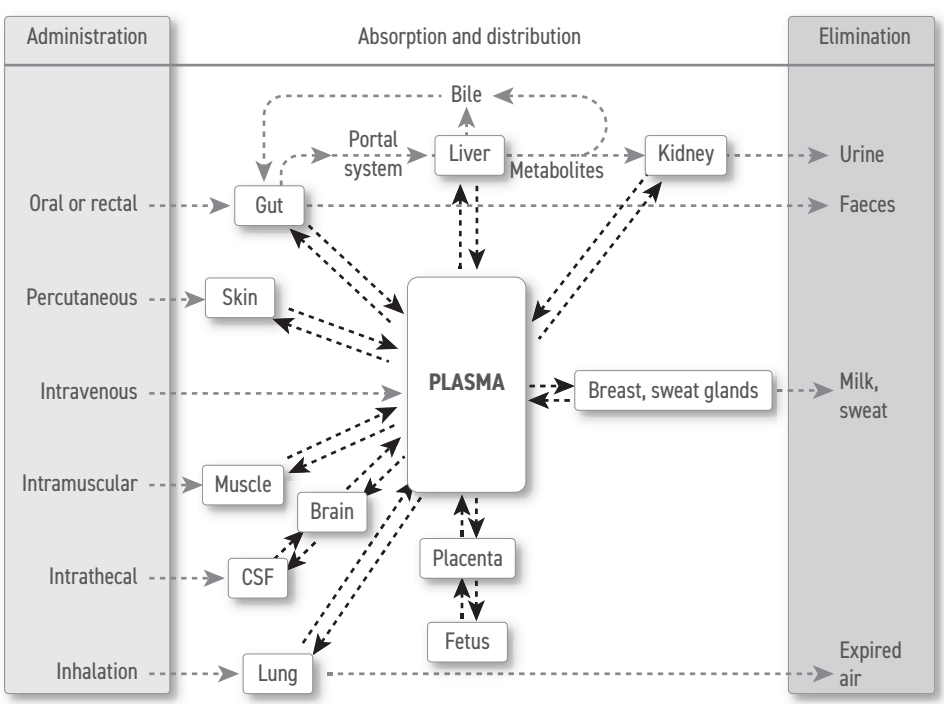
Figure 1.3 Drug concentrations with repeated administration. Adapted from (6).



1.4 Administration and absorption of drugs

Drugs can be administered by many different routes, after which they are absorbed into the blood for delivery to their site of action. Common routes of administration include oral (swallowed), sublingual (under the tongue), oromucosal/buccal (via the inside of the cheek), rectal, transdermal, parenteral (intravenous, intramuscular, subcutaneous, intrathecal), or via inhalation (see Figure 1.4).

Figure 1.4 Drug absorption, distribution and elimination sites (32).



1.4.1 Oral drug absorption

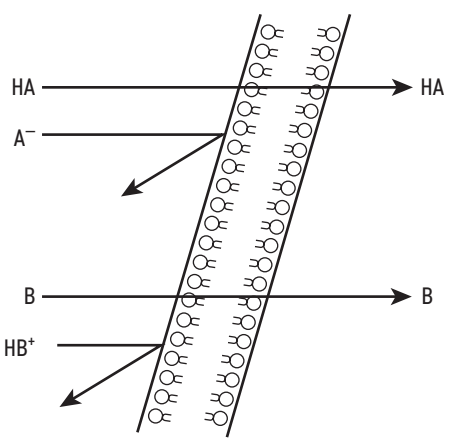
The term 'absorption' describes the transfer of a drug from its site of administration into the blood stream. For drugs administered directly into the blood stream, there is no absorption phase. Absorption of drugs administered via the skin or muscle will have an absorption phase dependent on the administration site. Most drugs used in dentistry are prescribed for oral administration, so their absorption will involve transit through the GI tract.

After swallowing, these formulations transit into the stomach where they might be absorbed or transit further down in the small intestine. Factors that affect oral drug absorption include the drug's degree of ionisation, availability of active and passive transporters in the intestinal wall, GI motility, the presence or absence of food, mesenteric blood flow, formulation, and physicochemical properties of the drug (6).

1.4.2 Absorption of weak acids and bases

Many drugs are weak acids or weak bases; for example, local anaesthetics are all weak bases. Weak acids and bases exist in both ionised and unionised forms and their absorption through barriers such as the gut wall, skin or nerve fibres, depends on their lipophilicity and degree of ionisation. Figure 1.5 shows how ionisation influences the absorption of weak acids and weak bases. The more lipophilic a drug and the less it is ionised, the greater its ability to penetrate through a lipid bilayer such as a nerve fibre (6).

Figure 1.5 Oral absorption of weak acids and bases (20).



The degree of ionisation is determined by the pK_a of weak acids and bases and the pH of the solution they are in. Each pK_a is the pH at which the drug exists in equal concentrations of both ionised and unionised forms, as expressed in the Henderson-Hasselbalch equation below:

$$\log \frac{[\text{ionised form}]}{[\text{unionised form}]} = pK_a - pH$$

The Henderson-Hasselbalch equation is used to calculate the pH of buffer solutions:

$$pH = pK_a + \log \frac{[\text{base}]}{[\text{acid}]}$$

Acidic drugs will have a pK_a <7, and basic drugs will have a pK_a >7.

For example, local anaesthetics, which are weak bases, are better absorbed in basic conditions as this pH promotes conversion to the unionised state. At their site of action, the presence of infection such as an abscess can change the local tissue pH to acidic conditions, which is thought to be one reason why a local anaesthetic injected into an abscess is less effective and less well absorbed (see Section 7.3).

1.4.3 Absorption via drug transporters

The movement of drugs and endogenous molecules across cell membranes in almost every part of the body is dependent on transporters. Transporters are membrane-bound proteins that play a key role in the absorption, distribution, and excretion of drugs. Some transporters pump drugs into a cell (uptake) and others pump them out (efflux).

Drug transporters not only play an important role in individual drug pharmacokinetics, but also in their vulnerability to drug–drug interactions. This is because certain drugs can inhibit and/or induce the action of drug transporters, interrupting the absorption of the victim drug (see Section 1.14).

1.4.4 Other factors influencing GI absorption

A range of other factors influence drug absorption in the gut, including GI motility, the presence or absence of food, mesenteric blood flow, drug formulation, physiochemical properties of the drug and competitive drug interactions (6).

Increased GI motility speeds up GI transit time, decreases drug-villus contact time and decreases drug absorption. Conversely, slowed GI motility prolongs gastric transit time, increases drug-villus contact time and increases overall drug absorption. Excessively rapid movement of the GI tract (e.g. diarrhoea) can reduce drug absorption completely.

Co-administration of many drugs with food slows down their oral absorption and reduces their Cmax. For example, when non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are administered in the presence of food, their Cmax is reduced by about 30% and their Tmax delayed by about one hour (7). Therefore, in acute pain, it is preferable to administer these drugs on an empty stomach, as this promotes a faster onset of action and higher Cmax which confers faster and more effective pain relief. There is also little evidence that administration with food improves safety.

Conversely, some drugs are absorbed better in the presence of food. For example, the antifungal itraconazole requires a low pH for maximal absorption so it is recommended to be orally administered immediately after a meal (8). For the antifungal griseofulvin, less than 50% of the oral dose is usually absorbed, but ingestion with a fatty meal increases the rate and extent of its absorption substantially (9).

Mesenteric or 'splanchnic' blood flow (i.e. the blood supply to abdominal organs including the stomach, liver, spleen, pancreas, small intestine, and large intestine) affects the passage, absorption and removal of drugs from the body. In some conditions where there is a reduction in blood flow to the gut (e.g. hypovolaemia), a reduction in drug absorption is seen. Splanchnic blood flow tends to increase after a meal, which may increase drug absorption (10).

Certain formulations can influence the rate of release and absorption of drugs such as transdermal patches or sustained release tablets. Prolonged release preparations usually present drugs via coated tablets, multi-layered preparations or embedded in a waxy matrix which release the drug slowly over a prolonged period. Drugs formulated with an 'enteric' coating are designed to stay intact while they traverse the acidic pH of the stomach (enteric) but dissolve once they pass into the more alkaline pH of the small intestine.

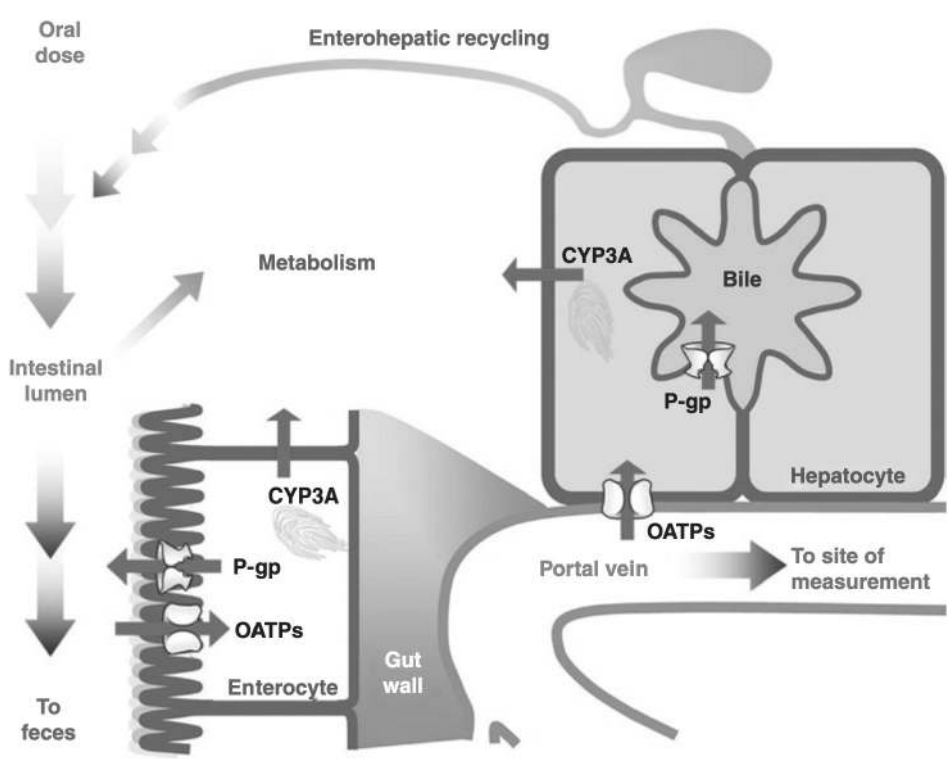
Drugs of a relatively smaller particle size and/or increased lipophilicity are more likely to cross the lipid bilayer of the intestine by diffusion. Prior disintegration of drug formulations is often required for drugs to be optimally absorbed, so liquid formulations that are already disintegrated can provide better drug absorption than tablets that require disintegration to take place with prior chewing or in the stomach.

Drug interactions can increase or decrease drug absorption in the gut. This can be used to an advantage; for example, the absorption of drugs taken in overdose onto activated charcoal to prevent the drug from being absorbed. Drug interactions occurring via competition, inhibition or induction of drug transporters can alter drug absorption. Pharmacogenomic variability in drug transporters and transport mechanisms can also affect the oral absorption of drugs.

1.5 First pass metabolism

'First pass metabolism' is a broad term given to the overall effect of drug destruction and elimination by transporters and metabolic enzymes in the gut wall and the liver that prevent a drug from reaching the systemic circulation (see Figure 1.6).

Figure 1.6 Overview of first pass transport and metabolism (11).



After a drug is administered orally it is taken up into enterocytes in the gut wall, either by passive diffusion or by drug transporters. Within the enterocyte, the drug may pass through unchanged but may also be metabolised to active or inactive metabolites. If it survives this process, the drug is transported out of the enterocyte into the portal circulation and carried via the portal artery to the liver, where it is transported into hepatocytes and can be further metabolised (11). If the drug survives all this, it can be transported out of the hepatocyte into the general circulation. The fraction that survives is considered 'bioavailable' and, when expressed as a percentage, describes the drug's oral bioavailability. Drug interactions can occur at any step in a drug's 'first pass' and are further described in Section 1.14.