- Loading doses are required for drugs that have a long half-life and where an immediate clinical effect is required at a target drug concentration. Loading doses are dependent on the drug's volume of distribution.

Dosage regimens: influence on the plasma concentration-time profile of a drug in the body

The design of a dosage regimen determines the therapeutic benefit for patients. The principles of clinical pharmacokinetics are applied to design a dosage regimen for a patient that ensures the appropriate formulation of drug is chosen for an appropriate route of administration. On the basis of the patient's drug handling parameters, which require an understanding of absorption, distribution, metabolism and excretion, the dosage regimen for the medicine in a particular patient, can be optimized. The pharmacist needs to ensure the appropriate regimen is prescribed to achieve optimal efficacy and minimal toxicity.

Clinical pharmacokinetics provides a basic understanding of the principles required to design a dosage regimen. Pharmacokinetics provides a mathematical basis to assess the time course of drugs and their concentrations in the body. It enables the following processes to be quantified:

- absorption
- distribution
- metabolism
- excretion.

It is these four pharmacokinetic processes, often referred to as ADME, that determine the drug concentration in the body following administration of a medicine (see also Chapter 18).

The influence that physiological factors, physicochemical properties of a drug and dosage form factors can have in determining whether a therapeutically effective concentration of a drug is achieved in the plasma following oral administration of a *single* dose of drug has been discussed previously in Chapters 19 and 20.

Whilst a single dose of certain drugs, e.g. single-dose hypnotics, analgesics and antiemetics, may be used in some clinical situations, most medicines are given as a *multiple dosage* regimen. For example, for the treatment of a respiratory tract infection, amoxicillin may be prescribed as one 250 mg capsule three times a day. The design of the regimen, i.e. formulation, route of administration, dose size and the dosage frequency are important factors which influence what plasma concentration is achieved and maintained in the body over the prescribed course of drug treatment. Other factors to consider are: patient choice and lifestyle, including the route of administration (the oral route is often preferred by patients), the dosing interval (once, twice or three times a day) needs to be suitable for a patient's work pattern and the dosage form must be appropriate, for instance a liquid may be preferable to a capsule for young and elderly patients.

Rates of ADME processes

To describe the processes of ADME, there is a need to consider the rates of the various processes. In *zero-order* reactions, the reaction proceeds at a constant rate and is independent of the concentration of a substance present in the body. An example is the elimination of alcohol. Drugs exhibiting this type of elimination will show accumulation of plasma levels of the drug, and hence non-linear pharmacokinetics. In *first-order* reactions, the reaction proceeds at a rate which is dependent on the concentration of a drug in the body. Most ADME processes follow first-order kinetics (Chapter 7).

The majority of drugs used clinically at therapeutic dosages will show first-order rate processes, e.g. the rate of elimination of most drugs will be first order. However, some drugs show non-linear rates of elimination, for instance phenytoin and high dose salicylates. First-order rate processes do not result in accumulation, i.e. as the amount of drug administered increases, the body is able to eliminate the drug accordingly. Hence, if the dose is doubled, the steady-state plasma concentration is doubled. Whether a drug shows first- or zero-order elimination is determined by its *Michaelis Constant* (K_m). This parameter is the plasma concentration at which the elimination of the drug proceeds at half the maximum *metabolic capacity* (V_m). If normal therapeutic plasma levels of the drug exceed the drug's Michaelis Constant, then the drug will show non-linear drug handling. For most drugs, the Michaelis Constant is much higher than the levels achieved through normal therapeutic use.