One-compartment open model of drug disposition in the body

To understand how the design of a dosage regimen can influence the time course of a drug in the body, as measured by its plasma concentration–time profile, it is important to consider the complex pharmacokinetic processes of: drug input (i.e. administration); output (i.e. elimination/metabolism) and distribution within the body. This can be described using the one-compartment open model of drug disposition, shown in Figure 22.1.

Pharmacokinetic models are hypothetical constructs, which describe the fate of a drug in a biological system following its administration. The purpose of modeling is to characterize the ADME profile for a drug to indicate how the drug is handled by the patient and to characterize basic parameters. These basic parameters describe the fate of the drug following administration and are used to optimize a dosage regimen. In a *one-compartment model*, the drug is considered to be distributed instantly throughout the whole body following its release and absorption from the dosage form. Thus, the body behaves as a single compartment in which absorbed drug is distributed so rapidly that a concentration equilibrium exists at any given time between the plasma, other body fluids and the tissues into which the drug has become distributed.

Rate of drug input versus rate of drug output

In a one-compartment open model, the overall kinetic processes of drug input and drug output are described by first-order kinetics. Following administration of an oral dosage form, the process of drug input into the body compartment involves drug release from the dosage form and passage of drug (absorption) across the cellular membranes, in this case the gastrointestinal barrier. The rate of drug input (absorption) at any given time is proportional to the concentration of drug, which is assumed to be in an absorbable form, in solution in the gastrointestinal fluids at the site(s) of absorption, i.e. the effective concentration, C_e, of drug at time, t. Hence:

$$\text{rate of drug input at time } t \;\alpha\; C_e \tag{22.1}$$

and

$$\text{rate of drug input at time } t = -k_a C_e \tag{22.2}$$

where k_a is the apparent absorption rate constant.

The negative sign in Equation 22.2 indicates that the effective concentration of drug at the absorption site(s) decreases with time. The apparent absorption rate constant gives the proportion (or fraction) of drug which enters the body compartment per unit time. Unlike the rate of drug input into the body compartment, the apparent absorption rate constant, k_a, is independent of the effective concentration of drug at the absorption site(s). The rate of drug input will decrease gradually with time as the effective drug concentration at the site of absorption decreases (assumes first-order absorption). Other processes, such as chemical degradation and movement of drug away from the absorption site(s), will also contribute to the gradual decrease in the drug concentration with time at the absorption site.

In the case of a one-compartment open model, the rate of drug output or elimination is a first-order process. Consequently, the magnitude of this parameter at any given time is dependent on the concentration of drug in the body compartment at that time. Immediately following administration of the first dose of an oral dosage form, the rate of drug output from the body, i.e. elimination, will be low since a limited amount of drug has been absorbed into the body compartment. However, as absorption proceeds, initially at a higher rate than the rate of drug output, the net concentration of drug in the body will increase with time. As the rate of drug output from the body compartment increases whilst the rate of drug input into the body compartment

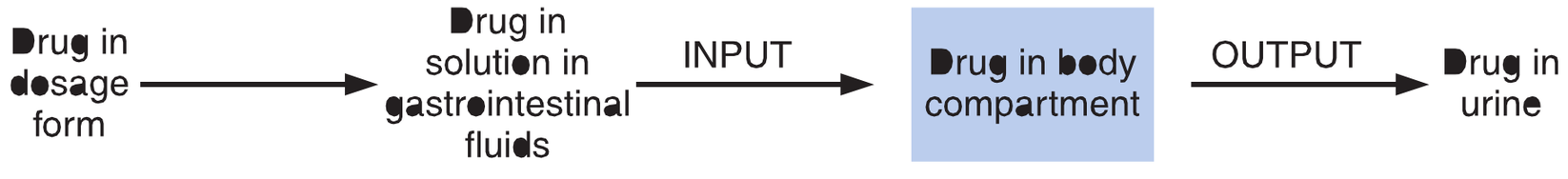

Fig. 22.1 • One-compartment open model of drug disposition for an orally administered drug.