observed, the accurate prediction of human pharmacokinetics is complicated by interspecies differences in ADME mechanisms.

The pharmacokinetic profile of a compound can be influenced by a number of factors including the physicochemical properties of the drug (6–10), the nature of the drug delivery system (11), physiologic factors (12), environmental factors (13–16), and the presence of underlying disease (16–18). In this chapter, the pharmacokinetic mechanisms (ADME) involved in the disposition of small molecules, and the factors that influence these processes, are presented. For a discussion of ADME processes for large molecules (e.g., proteins), the reader is referred to Chapter 5.

2. PHARMACOKINETICS: GENERAL OVERVIEW

As stated above, pharmacokinetics involves the study of drug absorption, distribution, metabolism, and excretion. Typically, the pharmacokinetic profile of a compound is characterized by measuring the rate of change of drug concentrations in plasma over time following drug administration. Additional information is obtained by monitoring the excretion rate of drug in the urine.

The pharmacokinetic parameters that are commonly measured include the following:

- C_{max}: the maximum concentration of drug in the plasma,
- t_{max}: the time at which the maximal concentration is observed,
- AUC: area under the curve, area of the plasma concentration–time profile from time 0 (when dose is administered) to time ∞ (when dose is completely eliminated),
- V_D: volume of distribution, an indicator of the extent of distribution of a drug in tissue,
- Cl: clearance, an indicator of the rate at which a drug is removed from plasma,
- $t_{1/2}$: half-life, the time it takes for plasma concentrations to decline by 50%, and
- F: bioavailability, the fraction of administered dose reaching the systemic circulation.

The utility of these parameters is based on the concept of linear pharmacokinetics. The underlying assumption of linear pharmacokinetics is first order elimination; that is, the rate of drug elimination from the body is proportional to the plasma concentration. Accordingly, $t_{1/2}$ is constant (dose-independent), and plasma concentrations and AUC are proportional to dose (since V_D and Cl are also assumed to be constant). While linear pharmacokinetics can be applied in most situations, many drug disposition mechanisms (e.g., active transport, drug metabolism) are saturable.