Therefore, in some cases, pharmacokinetics is nonlinear, making dose selection difficult.

Almost 10 years ago, Benet (19) identified the important pharmacokinetic and pharmacodynamic parameters that should be obtained during both preclinical and clinical development. These parameters were ranked (in order of importance) as follows: clearance, effective concentration range, extent of availability, fraction of the available dose excreted unchanged, blood/plasma concentration ratio, elimination half-life, toxic concentration, extent of protein binding, volume of distribution, rate of availability. Therefore, the most important determinant of drug disposition is clearance. Since clearance is the parameter used to establish a suitable dose for a patient, intersubject variability in clearance (due to genetic differences, disease, or drug interactions) can significantly impact pharmacotherapy.

3. MECHANISMS OF SMALL MOLECULE ABSORPTION

When a compound is administered intravenously, the dose is delivered directly into the systemic circulation. All other routes of administration are collectively termed extravascular routes (e.g., oral, nasal, rectal). Following extravascular administration, drug must be absorbed into the bloodstream across a membrane before it is available to distribute to its site of action. For this reason, the bioavailability of the drug is an important issue for drug development. Here, both the physicochemical properties of the drug and the performance of the delivery system influence drug absorption. The impact of formulation and route of administration on drug absorption is the focus of Chapter 7. Presented in this chapter are general mechanisms of drug absorption, with particular focus on oral drug delivery.

3.1. Passive Absorption

The traditional view of oral drug absorption is that it occurs primarily from the small intestine and proceeds via a passive transcellular process. The small intestine represents the primary site of absorption in the GI tract because of the functional specialization of the intestinal cells (creating a large surface area for absorption) combined with the prolonged intestinal transit time.

Passive absorption is usually described by Fick's Law, with the driving force being the concentration gradient across the membrane (20). Passive absorption is governed by several physicochemical properties including solubility, permeability, pK_a, lipophilicity, stability, and integrity, each of which can influence drug absorption and pharmacokinetics (10). Lipinski (6) formulated the "Rule of Five," based on an evaluation of more than 2000 compounds from the World Drug Index. According to this rule, the following properties are ideal for durg absorption, for an ideal drug-like