Table 33-1 Drug–Plasma Protein Binding

Drug	% Bound to plasma proteins (1)
Dicumarol	99.9
Warfarin	99.5
Phenylbutazone	99.5
Digitoxin	97
Diazepam	96
Phenytoin	87
Carbamazepine	75
Gentamicin	50
Penicillin G	50
Digoxin	23
Caffeine	10

DRUG METABOLISM AND EXCRETION

Drugs are eliminated from the body either by metabolism or excretion. Drug metabolism primarily occurs in the liver through processes of hydrolysis, enzymatic reduction, or oxidation. The liver, unlike the brain, does not have "tight junctions" between endothelial cells that allow all dissolved substances in the plasma, even plasma proteins, to pass from plasma into liver cells. Drug metabolism also occurs, to a lesser extent, in other organs including the skin, lungs, kidneys, and gastrointestinal mucosal cells. Drug excretion occurs primarily through the kidneys. Excretion can also occur, to a much lesser extent, through the bile, lungs, sweat, saliva, and breast milk. In general lipid-soluble drugs are metabolized in the liver and water-soluble drugs are readily excreted through the kidneys. The reason many drugs cannot be administered orally is that they are completely metabolized and rendered inactive in the liver prior to reaching the systemic circulation.

Drug elimination determines the biological half-life of the drug, that is, the time required for reduction of one-half of the drug concentration in the bloodstream. Since most drugs are eliminated by first order kinetics, where the rate of elimination (k_e) is dependent on drug concentration and as drug concentration decreases, the rate of elimination decreases, the biological half-life of a drug undergoing first-order elimination rate kinetics is expressed as

$$t_{1/2} = 0.693/k_e$$

Biological half-lives for a few injectable drugs are given in Table 33-2, just to illustrate how wide-ranging biological half-lives are and how important it is to know these values. Biological half-lives are published in the package inserts of commercial drug products, typically under the clinical pharmacology section of the insert.

PHYSICOCHEMICAL FACTORS AFFECTING DRUGS ADMINISTERED BY INJECTION

The bioavailability of drugs administered by IM or SC injection (or any other injectable route except for intravenous or intra-arterial) depends on several physicochemical and physiological factors. Physicochemical factors include solubility, partition coefficient, particle size, viscosity, and solid-state morphology, all of which affect the ability of the drug to diffuse passively from the injection site to the blood circulation. The primary physiological factor is blood flow with blood flow depending on the capillary bed density at the injection site.

Solubility

Drugs administered into muscle or subcutaneous tissue primarily rely on passive diffusion to be absorbed into the blood stream. To diffuse through tissue and be available to the bloodstream, the drug must be in solution. The solubility of drugs in aqueous solution varies from being completely soluble to partially or sparingly soluble to being insoluble. Drug solubility is dictated by its chemical structure, the orientation of its structure in water, and the propensity of its functional groups to interact with water molecules. Besides chemical structure, factors that