TABLE 10.1
Major Limitations to Drug's Usefulness That May Be Overcome by Prodrugs

Formulation and administration
Insufficient aqueous solubility
Insufficient shelf life for liquid and solid dosage forms
Irritation or pain after local administration
Unpleasant taste or odor
Absorption
Insufficient dissolution rate due to low aqueous solubility
Poor membrane permeability and low oral or topical bioavailability due to poor lipophilicity
Insufficient stability during first-pass metabolism or in acidic gastric juices
Insufficient availability due to efflux mechanisms
Distribution
Lack of site specificity (e.g., poor brain or tumor targeting)
Excessively strong protein binding in plasma or disposition in lipophilic compartments of body
Metabolism and excretion
Lack or need of site-specific bioactivation
Short duration of action
Toxicity
Lack of site specificity
Lack or need of site-specific bioactivation
Irritation or pain after local administration
Need to temporarily mask a reactive, inherently active, functional group
Life cycle management
Development of a prodrug with improved properties that may represent a life cycle management opportunity for an existing drug

management of an existing drug. The major barriers which limit drug's usefulness and may be overcome by prodrug modification, are listed in Table 10.1, and some of the issues are also briefly discussed in the following sections.

10.5.1 Improved Formulation and Administration

Inadequate water solubility of a drug is a prerequisite for the formulation of aqueous parenteral or injectable dosage forms. Prodrug approaches have become a worthy opinion, when conventional formulation techniques, such as salt formation, particle size reduction, solubilizing excipients, and complexation agents have proved unsuccessful and failed. The most common prodrug approach for increased water solubility has been the introduction of ionizable or polar neutral group, such as phosphate, amino acid, or sugar moiety, to the poorly soluble parent drug. Phosphate esters are widely used prodrug strategy for improving the aqueous solubility of orally and parenterally administered drugs which contain hydroxyl or amine functionalities. Their synthesis is quite straightforward and their chemical stability is usually good or at least adequate. Bioconversion of phosphate prodrugs back to their active parent drugs usually occurs rapidly in the intestinal brush border epithelium before or during the absorption, or during first-pass metabolism in the liver, and is catalyzed by phosphatases. However, the premature enzymatic cleavage of a very insoluble parent drug may result in its precipitation in intestinal lumen yielding to the reduced bioavailability.

One successful example of phosphate prodrugs is fosamprenavir, an orally administered phosphate ester of antiretroviral protease inhibitor amprenavir. Amprenavir is poorly soluble in water (approximately 0.04 mg/mL at 25°C), and its dosage regimen is as high as 1200 mg twice a day.