quantitatively converted *in vivo* to the parent drug (Cho et al., 1986). Results from *in vitro* studies are therefore most useful in screening a series of prodrugs to determine the promising candidates for further study.

Anderson and Conradi (1987) point out that "while coupling of a drug and a solubilizing moiety in a bioreversible manner may indeed constitute the synthesis of a water-soluble prodrug, this is not prodrug design. Prodrug design entails the optimization of the physical and chemical properties of the prodrug so that its effectiveness as a delivery system for the parent drug is also optimized." If intended for parenteral use, the prodrug should be sufficiently stable *in vitro* to allow the development of a ready-to-inject solution. For example, a disadvantage to dicarboxylate hemiesters as a prodrug form is that their solubility is usually limited at the pH optimum for solution stability (Anderson et al., 1985).

Water-soluble prodrugs that are unstable in solution may be prepared as a lyophilized mixture to be reconstituted before use, although this adds significantly to the production cost, and proves to be an inconvenience to those responsible for administration. Ideally, a water-soluble prodrug product in aqueous solution should have a shelf life of 2 years or more at room temperature, in which case the half-life *in vitro* should be at least 13 years. If the only purpose of prodrug formation is to improve the solubility of the parent drug, then bioconversion *in vivo* should be extremely rapid. If it is assumed that more than 90% of the prodrug is converted to the parent drug within 30 min of the injection, the *in vivo* half-life should be 10 min or less. Ideal water-soluble prodrug design therefore requires an *in vivo*/*in vitro* lability ratio of nearly 10^6. This can be readily achieved only if the bioconversion is enzyme-catalyzed (Anderson and Conradi, 1987).

Three general principles that are valuable in the design of solution-stable prodrugs are that 1. pH-solubility behavior is an important determinant of solution stability, 2. pH-degradation rate profiles can be optimized by considering the effects of neighboring substituents on hydrolysis rates, and 3. building micelle-forming properties into a prodrug can be advantageous in improving stability and solubilizing otherwise insoluble degradation products (Anderson, 1985; Anderson and Conradi, 1987). Many prodrug design problems require the simultaneous application of all three principles to achieve the necessary degree of stability improvement.

With regard to the first principle, the formulation pH can be a major influence on the rate of acid- or base-catalyzed reactions, especially hydrolysis. The above-mentioned discussion of the pH effect on the solubility of prodrugs that were derived using promoieties possessing different ionizable groups serves as a simple illustration of how the selection of the pH and the ionizable functional group can be critical to solubilization. Nevertheless, solution stability of the prodrug must also be considered. Achieving high solubility in the region of optimum solution stability might require selection of an ionizable promoiety with a pK_a far removed from the pH-degradation rate minimum. For example, it has been recommended that the investigator select a sulfonate- or an amine-bearing promoiety, with pK_a values of approximately 1.5 and 9.0, respectively, for a prodrug with a pH-degradation minimum at 3.5–5 (Anderson, 1985).

In the investigations applying the second principle, it has been found that acid-catalyzed hydrolysis is relatively insensitive to polar substituent effects; it is primarily influenced by steric effects. Hydroxide-catalyzed reactions, on the other hand, are sensitive to both steric and electronic effects (Anderson, 1985). In the case of esters of methylprednisolone, by using a nonpolar spacer to increase the distance between the ionizable group of the disposable moiety and the ester function, it was possible to effectively reduce the hydroxide-ion-catalyzed hydrolysis rate. Sterically hindered promoieties were employed to reduce the hydrolysis rates of hemiesters of hydrocortisone, which therefore proved to be more stable than hydrocortisone hemisuccinate (Garrett and Royer, 1962). However, since enzymatic hydrolysis is clearly hindered by steric effects, and since rapid conversion is usually desirable if the prodrug goal is improved solubility alone, deliberate increases in steric bulk should not be pursued (Anderson, 1985).

Dicarboxylic acid hemiesters of methylprednisolone illustrate the third principle since they were shown to undergo micellization in aqueous solution (Anderson et al., 1983). This self-stabilizing