reported for the ALT elevations and it was not determined if any characteristic of the prodrug may have contributed to the adverse event.

12.4 Prodrugs to Address Solubility-limiting Absorption

Aqueous solubility is an important factor determining the bioavailability of an oral agent. Poorly soluble drugs are not able to present a high concentration of drug at the intestinal lumen and thus lack a concentration gradient driving force for absorption across the epithelial membrane. Charged prodrugs of poorly soluble drugs have been used successfully to improve aqueous solubility and consequently oral absorption (Figure 12.1B).[75] This is accomplished by taking advantage of membrane-associated enzymes that can convert the charged prodrug to the parent drug close to the brush border membrane. Such a strategy has been implemented with several prodrugs developed to treat viral diseases.

Amprenavir (APV, Agenerase) (**26**, Figure 12.14) is an HIV protease inhibitor with several positive attributes that include a favorable resistance profile, lack of food effect and potentially fewer metabolic effects.[76] Amprenavir showed high membrane permeability in a Caco-2 cell model and the clinical formulation demonstrated a relative bioavailability in the dog of 100%.[77,78] However, APV's poor aqueous solubility (0.04 mg mL^{-1}) required a high ratio of excipient to drug to afford gastrointestinal tract solubility and eventually absorption. The clinical formulation required a large number of excipients, some of which posed potential toxicity problems, especially for pediatric administration. Consequently, the resulting high pill burden (16 capsules) in humans had the potential to lead to reduced adherence to therapy. To address the solubility-limiting absorption, a phosphate ester prodrug, fosamprenavir (GW4339808) (**27**, Figure 12.14) with an aqueous solubility of 0.31 mg mL^{-1}

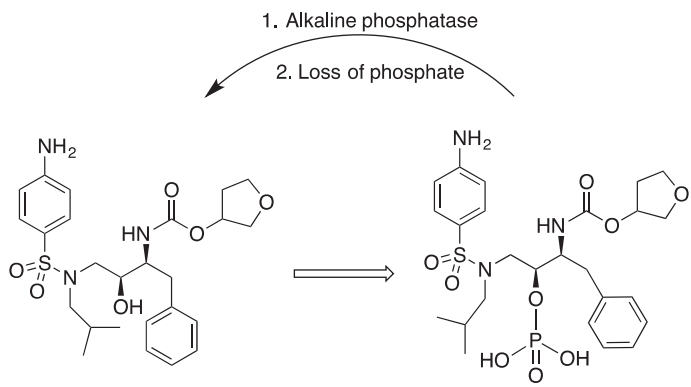

Figure 12.14 Fosamprenavir (**27**) is the phosphate prodrug of the HIV protease inhibitor amprenavir (**26**). Fosamprenavir was developed to address the poor solubility and therefore the poor bioavailability of amprenavir.