intestinal membrane. A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 85% or higher. Otherwise, the drug substance is considered to be poorly permeable.

An IR drug product is characterized as a *rapidly dissolving* product when not less than 85% of the labeled amount of the drug dissolves within 30 min using USP Apparatus 1 at 100 rpm or USP Apparatus 2 at 50 rpm (at 75 rpm when appropriately justified) in a volume of 500 mL or less with each of the following media: (a) acidic media, such as 0.1 N HCl or USP-simulated gastric fluid (SGF) without enzymes; (b) a pH 4.5 buffer; and (c) a pH 6.8 buffer or USP-simulated intestinal fluid (SIF) without enzymes. Otherwise, the drug product is considered to be a slowly dissolving product.

We will use the BCS definition to define low solubility drugs. However, we recognize that the BCS definition is conservative because it is used to waive regulatory bioequivalence studies for Class I drugs (Yu et al. 2002). There are two reasons why the BCS definition for solubility is too conservative. The first reason is because of the need to show high solubility across the range of pH from 1.0 to 7.5. On the basis of the ionizable groups, the solubility of weak bases is higher in the stomach than that in the small intestine. A low solubility at high pH may not be a barrier to absorption of weak bases because the absorption may be complete before the drug enters the low solubility, high pH GI region. On the other hand, low solubility at low pH may not be a problem of weak acids as high solubility and high permeability at distal small intestine are sufficient for their complete absorption. For example, many nonsteroidal anti-inflammatory drugs, although classified as low solubility according to the BCS, have the bioavailability over 90% (Yazdanian et al. 2004).

The second reason is that for the low solubility drugs, the *in vitro* aqueous solubility is not reflective of the *in vivo* gastrointestinal (GI) tract solubility. The solubility of lipophilic drugs is generally better in an *in vivo* environment because of the presence of bile salts or lecithin micelles. Recent studies have shown that solubility in biorelevant medium can be 1.1–160 times greater than the aqueous solubility of BCS Class II drugs, ranging from griseofulvin to danazol (Takano et al. 2006).

Formulation of Low Solubility Drugs

Some drugs classified as low solubility drugs on the basis of *in vitro* measures of aqueous solubility may have acceptable *in vivo* solubility because of either pH dependence or solubility in GI fluids. If these drugs with acceptable *in vivo* solubility are BCS Class II (Food and Drug Administration CDER 2015), they would then be expected to have acceptable oral bioavailability from standard solid oral dosage forms. For BCS Class II drugs that are shown to have low bioavailability owing to their poor solubility and inability to dissolve rapidly, the selection of formulation is often of great importance in developing a successful product for oral administration of Class II drugs. The bioavailability of these drugs can be improved by several formulation approaches. The most common method of increasing solubility (either a weak acid or weak base) is to induce salt formation. Even if the salt formation has no significant effect on the solubility, the salt dissolution rate will often be enhanced owing to the difference in the pH of the thin diffusion layer surrounding the drug particle. The dissolution rate can also be increased by reducing the size of solid drug particles, which leads to an increased surface area available for dissolution. A typical micronization method such as an air-jet mill can reduce the particle size to 2–5 μm. Further reduction requires the use of ball-milling media in aqueous suspension (Merisko-Liversidge et al. 2003). This technology can reduce the crystalline particle size to 100–250 nm, providing a considerable increase in dissolution rate.

Another method of improving bioavailability for these poorly soluble drugs is to prepare an amorphous formulation, since an amorphous form allows faster dissolution of the drug in comparison to its corresponding crystalline form. An amorphous formulation is prepared by incorporating