ROLES OF DISSOLUTION TESTING

Dissolution testing plays a key role during the drug product development and commercial manufacturing. During the development stages of a drug product, dissolution testing is used to evaluate the rate of drug release from formulations and assess their stability and formulation changes. In addition, it is employed to establish an *in vitro–in vivo* correlation (IVIVC) in order to predict bioavailability or bioequivalence of drug products. For release of drug products, dissolution testing is used to ensure manufacturing and product consistency. For instance, for an immediate-release (IR) product, a single-point release criterion is often used, such as, "Q" = 80% in 30 min. In certain circumstances, a complete dissolution profile comparison rather than a single-point assessment is used (Food and Drug Administration CDER 1997). Dissolution testing is also used in granting biowaivers of low strengths and for postapproval manufacturing changes. The BCS guidance (Food and Drug Administration CDER 2015) employs dissolution testing to demonstrate rapid dissolution of immediate-release solid oral dosage forms so that a biowaiver can be granted.

The continued use of dissolution as a quality control tool is based on the belief articulated by United States Pharmacopeia (USP) that the dissolution test is in general overly sensitive to formulation differences. As a result, dissolution tests used for quality control emphasize the selection of discriminatory media and conditions. In comparison, dissolution tests for predicting bioavailability/bioequivalence require the choice of biorelevant media and conditions. Although it is desirable to have a single dissolution test that can be applied for both evaluation of *in vivo* performance and assurance of product consistency, identifying such a dissolution test remains a significant challenge, particularly for dosage forms containing poorly soluble drugs (Brown et al. 2004; Zhang and Yu 2004).

FORMULATION OF LOW SOLUBILITY DRUGS

Definition of Low Solubility

The U.S. Food and Drug Administration (FDA) issued a Guidance for Industry covering the BCS in August 2000 and revised it in May 2015 (Food and Drug Administration CDER 2015). The BCS is a scientific framework for classifying a drug substance on the basis of its equilibrium aqueous solubility and intestinal permeability (Amidon et al. 1995). When combined with the *in vitro* dissolution characteristics of a drug product, the BCS takes into account three major factors: solubility, intestinal permeability, and dissolution rate. These three factors govern the rate and extent of oral drug absorption for IR solid oral dosage forms (Food and Drug Administration CDER 2015). The BCS defines four classes of drug substances on the basis of their solubility and permeability characteristics.

	High Solubility	**Low Solubility**
High permeability	Class I	Class II
Low permeability	Class III	Class IV

From the BCS guidance, the criterion for high solubility uses the ratio of the highest strength to the minimum aqueous solubility in the pH range of 1–6.8 at 37°C ± 1°C. This ratio has a unit of volume and is referred to as the dose solubility volume. It is the volume needed to dissolve the strength across the entire pH range. If the dose solubility volume is ≤250 mL, the drug substance is considered highly soluble. However, if the dose solubility volume is >250 mL, the drug substance is considered poorly soluble. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 oz.) of water.

The permeability classification is based indirectly on the extent of intestinal absorption of a drug substance in humans and directly on measurements of the rate of mass transfer across the human