The following steps are crucial for designing a dissolution test for poorly soluble drug products:

1. Classification and characterization
    - Measure solubility as a function of pH
    - Classify a drug substance according to BCS
    - Consider formulation factors
2. Determination of appropriate medium and volume
3. Selection of appropriate dissolution apparatus and operating speed
4. Determination of appropriate acceptance criteria

CLASSIFICATION AND CHARACTERIZATION

The first step is to know the BCS classification of the drug and use this information to help design formulations and evaluate the possibility of IVIVC. For a poorly soluble drug dosed in an immediate-release product, the disintegration of the dosage form is generally rapid and the oral drug absorption is mainly limited by dissolution rate and/or permeation rate (permeability), where permeation rate refers to the flux of drug across the intestinal membrane. The rate of dissolution and the uptake rate of permeation determine the concentration of drug in the GI tract. However, the concentration in the GI tract is also limited by the solubility of the drug. When the rate of dissolution is far more than the uptake rate of permeation, the drug concentration in the GI fluid approaches its solubility limit. Therefore, poor dissolution can be caused either by particle size (r) and/or solubility (C_s). To emphasize the importance of solubility, Yu (1999) referred to the dissolution/solubility-limited case as solubility-limited absorption. The dissolution/particle size-limited case is still called dissolution-limited absorption. As a result, permeability, solubility, and/or dissolution can limit the absorption of poorly absorbable drugs.

For poorly soluble drugs with dissolution-limited absorption, the formulation approach commonly used to overcome slow dissolution is to increase surface area by reducing the particle size. The *in vitro* dissolution testing can be predictive of evaluating the effect of particle size reduction. However, a very small particle size could complicate the development of a dissolution test as small particles can pass through filters and subsequently dissolve. In this situation, the use of small pore filters, centrifugation, ultracentrifugation, or high wavelength UV detection may be needed (Brown et al. 2004).

For poorly soluble drugs with solubility-limited absorption, possible formulation approaches are to use amorphous materials, lipid formulations, or one of the other technologies stated earlier. These formulation technologies and their potential failure modes will affect the selection of a dissolution test. In formulations using amorphous materials, a possible conversion of amorphous to crystalline state during the dissolution testing should be considered. An example of such an issue is the troglitazone data presented by Dressman and Reppas (2000). Troglitazone dissolution in the fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) is predictive of the food effect observed in *in vivo* pharmacokinetic studies. However, the dissolution profile in FaSSIF demonstrates a maximum. This maximum is due to recrystallization of the drug substance during the dissolution process into a less soluble crystalline form. This peak was not seen in the FeSSIF dissolution medium, indicating the role of medium components on the rate of nucleation of the less soluble form.

For lipid-based formulations where the drug is in solution, dissolution testing is not used to evaluate drug dissolution. Instead, it is employed to measure product capsule disruption and possible drug emulsification or precipitation on dilution. Nevertheless, if *in vitro* sink condition is maintained, the precipitation that might occur *in vivo* will not be observed *in vitro*. Therefore, we need to be cautious when we develop dissolution testing for lipid-based formulations.