Recommended Methodology for Classifying a Drug Substance and for Determining the Dissolution Characteristics of a Drug Product

The following approaches are recommended for classifying a drug substance and determining the dissolution characteristics of an IR drug product according to the BCS.

Determining Drug Substance Solubility Class

An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH conditions. The pH-solubility profile of the test drug substance should be determined at 37°C ± 1°C in aqueous media with a pH in the range of 1–6.8. A sufficient number of pH conditions should be evaluated to accurately define the pH-solubility profile within the pH range of 1–6.8. The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance to include pH = pKa, pH = pKa + 1, pH = pKa − 1, and at pH = 1 and 6.8. A sufficient number of pH conditions should be determined for both ionizable and non-ionizable compounds. A minimum of three replicate determinations of solubility in each pH condition is recommended. Depending on study variability, additional replicates may be necessary to provide a reliable estimate of solubility.

Standard buffer solutions described in the USP are considered appropriate for use in solubility studies. If these buffers are not suitable for physical or chemical reasons, other buffer solutions can be used with justification. Solution pH should be verified (measured and adjusted to the target pH if required) after addition of the drug substance to a buffer. Solution pH should also be measured at the end of the equilibrium solubility study.

Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification supporting the ability of such methods to predict equilibrium solubility of the test drug substance. The concentration of the drug substance in selected buffers (or pH conditions) should be determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products.[8] If degradation of the drug substance is observed as a function of buffer composition and/or pH, it should be reported. The solubility class should be determined by calculating the volume of an aqueous medium sufficient to dissolve the highest strength in the pH range of 1–6.8. A drug substance should be classified as highly soluble when the highest strength is soluble in ≤250 mL of aqueous media over the pH range of 1–6.8. In other words, the highest strength divided by 250 should be less than or equal to the lowest solubility observed over the entire pH range of 1–6.8.

For drug products where the highest single dose administered is higher than the highest strength, additional information may be necessary. If the solubility classification is likely to change with the highest single dose as criterion, additional PK dose proportionality information in a wide dose range covering the therapeutic dose range will be necessary.

[8] Refer to the guidance for industry *Submitting Documentation for the Stability of Human Drugs and Biologics*.