Drug solutions in these fluids should be incubated at 37°C for a period that is representative of in vivo drug contact with these fluids, for example, one hour in gastric fluid and three hours in intestinal fluid. Drug concentrations should then be determined using a validated stability- indicating assay method. Significant degradation (>5%) of a drug in this study could suggest potential instability.

Determining Drug Product Dissolution Characteristics and Dissolution Profile Similarity[7]

Dissolution testing should be carried out in USP Apparatus 1 (typically at 100 rpm) or USP Apparatus 2 (typically at 50 rpm, or at 75 rpm when appropriately justified) using 500 mL (or 900 mL with appropriate justification) of the following dissolution media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. For gelatin capsules and tablets with gelatin coating, Simulated Gastric and Intestinal Fluids USP (with enzymes) can be used.

The dissolution testing apparatus used in this evaluation should conform to the requirements in USP (<711> Dissolution) and FDA's guidance on Mechanical Calibration of Dissolution Apparatus 1 and 2.[11] Selection of the dissolution testing apparatus (USP Apparatus 1 or 2) during drug development should be based on a comparison of in vitro dissolution and in vivo PK data available for the product. The USP Apparatus 1 (*basket method*) is generally preferred for capsules and products that tend to float, and USP Apparatus 2 (*paddle method*) is generally preferred for tablets. For some tablet dosage forms, in vitro (but not in vivo) dissolution may be slow due to the manner in which the disintegrated product settles at the bottom of a dissolution vessel. In such situations, USP Apparatus 1 may be preferred over Apparatus 2, or alternatively, rotation speed for Apparatus 2 may be modified with justification. If the testing conditions need to be modified to better reflect rapid in vivo dissolution (e.g., use of a different rotating speed), such modifications can be justified by comparing in vitro dissolution with in vivo absorption data (e.g., a relative BA study using a simple aqueous solution as the reference product).

A minimum of 12 dosage units of the test and reference drug product for each strength should be evaluated to support a biowaiver request. Samples should be collected at a sufficient number of intervals to characterize the entire dissolution profile of the drug product (e.g., 5, 10, 15, 20, and 30 minutes).

When comparing the test and reference products, dissolution profiles should be compared using a similarity factor (f2).

$$f2 = 50 \bullet \log \{[1 + (1/n)\Sigma t\, n\, (Rt - Tt)2] - 0.5 \bullet 100\}$$

The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent of dissolution between the two curves; where n is the number of time points, Rt is the dissolution value of the reference batch at time t, and Tt is the dissolution value of the test batch at time t.

[11] See the guidance for industry *The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2—Current Good Manufacturing Practice (CGMP).*