

## **Dissolution Apparatus – History and Sources of Variability**

Dissolution testing is used as an in vitro surrogate in formulation development and bioequivalence. Dissolution tests are also used as quality control measures for most solid dosage form drugs. Dissolution failures have long accounted for >10% of drug recalls. The Division of Pharmaceutical Analysis (DPA) laboratory has been involved with improving dissolution testing for over 30 years. Although many improvements have occurred, an additional understanding of the source of variability and hydrodynamics within the dissolution apparatus is needed.

### **Instrumentation**

The USP has 7 different apparatus that can be used for dissolution testing although most tablets and capsules use Apparatus 1 or 2 also known as basket and paddle. These two apparatus were developed through the 1960s and adopted by the USP in the 1970s. Before use, several parameters are calibrated or checked such as Vessel, Basket, and Paddle Dimensions, Shaft Vertical Alignment, Basket and Paddle Shaft Wobble, Vessel/Shaft Centering, Basket and Paddle Depth, Vibration Rotational Speed and Vessel Medium Temperature. These parameters affect the hydrodynamics within the vessels. USP has criteria for some of these mechanical calibration parameters, and PhRMA suggested more stringent criteria after conducting a collaborative study in 1998.

### **USP Calibrator Tablets**

In addition to mechanical calibration, chemical calibration of apparatus is usually done every 6 months, if a unit is moved or when a major change has been made to instrumentation. In 1978 the a 50-mg prednisone tablet (Upjohn) and a 300-mg salicylic acid tablet (Hoffman LaRoche) became official USP disintegrating and nondisintegrating chemical calibration tablets respectively. Prior to this time, laboratories relied on minimal mechanical calibration criteria to make sure their apparatus was set up properly. In 1979 DPA discovered a commercially available 10-mg prednisone tablet that was extremely sensitive to dissolved gasses in the medium and vessel centering for the paddle method (Apparatus 2). DPA used these as an in-house calibrator tablet for about 20 years. In 1997 when Upjohn discontinued the 50-mg Prednisone tablet, USP replaced it with a 10 mg Prednisone tablet manufactured at UMAB similar in formulation to the in-house DPA calibrator tablet. Unlike the original 10-mg DPA tablets which are stable over a number of years, the newer USP 10-mg Tablets tends to give lower dissolution results with the paddle method over time. DPA and a PhRMA collaborative study have found that the USP Salicylic Acid Tablets are operationally insensitive to perturbations of Apparatus 1 and 2. Acceptance criteria for the 10-mg Prednisone Tablet are based on a collaborative study and tend to be wide to accommodate data from multiple laboratories (27–48% range for the current lot for Apparatus 2 and 53-77% for Apparatus 1).

### **Degassing**

Sometimes dissolved gasses can cause bubbles to form around a dosage form which can affect the results of a dissolution test. To eliminate this source of variability, medium are degassed. The degassing procedure in the USP (vacuum filtration at 41°C, then cooling to 37°C before use) can be time consuming so some labs use alternative techniques including helium sparging. The calibrator tablets are sometimes used to ensure sameness between these alternative techniques and the USP method for degassing.

Other factors that can influence Dissolution Results:

- Sampling probe size when automatic sampling is used,
- Method of tablet or capsule introduction into medium including the use of sinkers (devices designed to make tablets or capsules sink to the bottom of the vessel),
- Basket Construction: some vendors have “clips” to hold on the basket and others have o-rings.