Back to Basics: Dissolution Testing 2: The Rotating Basket Method (Apparatus 1)

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This is the fourth in a series of articles introducing the basics of aspects of research techniques that may be required for the development and evaluation of controlled release technologies.

Introduction

This is the second in a series of articles covering the basic principles of operations required for various dissolution apparatus configurations. The rotating basket method, commonly called "Apparatus 1," is the topic of this article, which focuses on the proper execution of the dissolution test to ensure accurate, reproducible, and reliable results are generated.

As mentioned in the first article, the dissolution test consists of two primary components: 1) sample preparation on the dissolution apparatus; and 2) analytical finish performed primarily with spectrophotometric or liquid chromatographic analytical instrumentation. This article concentrates on the basket dissolution apparatus, evolution and compendial requirements of the rotating basket apparatus, testing procedure, and performance qualification and calibration.

Until the 1960s the disintegration test was used to ensure that dosage forms would reduce to small particles rapidly when immersed in simulated gastric fluid. It was felt at the time that disintegration indicated that a drug was available for absorption in the GI tract and, therefore, reflected bioavailability. However, continuing studies proved that disintegration had very little to do with bioavailability, and the need for a dissolution test became apparent. During the 1950s and 1960s, a number of basket and stirring devices were developed, and numerous papers were published on the benefits of dissolution testing. Eventually, the rotating basket method for dissolution, generally credited to M. Pernarowski in 1968 (1), became widely accepted as a suitable apparatus for dosage form evaluation.

The rotating basket was incorporated in USP XVIII in 1970 as the first official dissolution test. Notably, this early apparatus had a concave vessel bottom that later evolved into the hemispheric bottom vessel that is used today. The basket apparatus was useful for submerging floating dosage forms such as encapsulated products. Other typical products tested with the rotating basket include swelling dosage forms, bead formulations, coated and uncoated tablets, suppositories, and a variety of immediate and modified release formulations.

The Rotating Basket Apparatus

The rotating basket apparatus consists of a 316 stainless steel shaft and basket and a 1,000 mL glass vessel (Figure 1). The basket is attached to the shaft by three retention clips. Other means of attachment, including O-rings, have been used, but they do not meet USP requirements, and they have demonstrated lower results (2). Therefore, validation should be conducted to show that an O-ring attachment is equivalent to the official clip attachment on a product-by-product basis.

The basket apparatus was harmonized between the European (2.9.3), Japanese (15), and U.S. (<711>) Pharmacopeias. The International Conference on Harmonisation (ICH) produced common technical documents to standardize dissolution methods

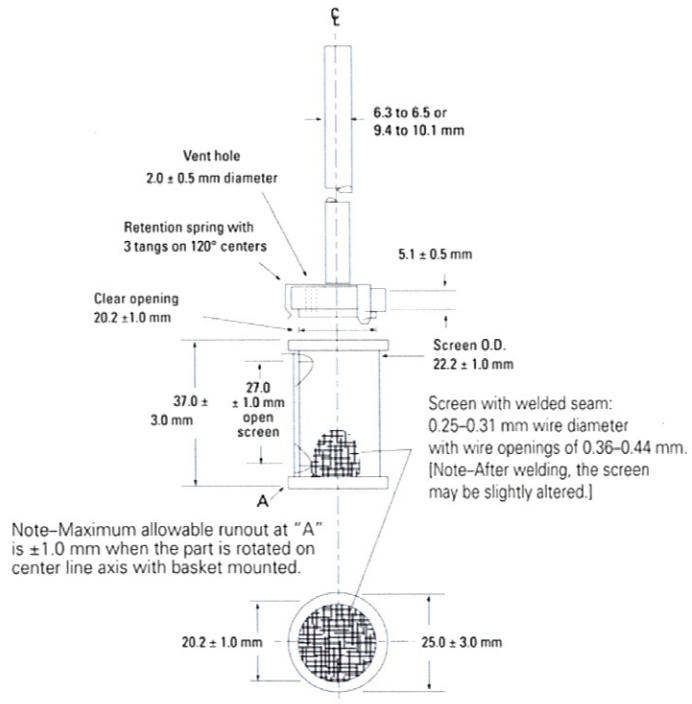

Figure 1. *USP basket stirring element.*

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and procedures, providing a simplified and consistent process for the submission and approval of drug standards throughout the world. However, we must be mindful that the various pharmacopeias have different specifications for the mesh dimensions of the basket. A single harmonized specification exists today that encompasses two different basket mesh sizes, specifically the 40-mesh basket from the EP and USP and the 36-mesh basket from the JP. The mesh number reflects the number of openings per linear inch (25.4 mm) of woven screen. In the opinion of these authors, the baskets are not equivalent and should be properly validated within the regions of their use. If a difference in results is observed between the baskets, the dimensions of the basket should be included in the dissolution procedure. Preliminary studies indicate slightly lower test results for USP Prednisone Tablets with the 36-mesh baskets (3).

The baskets are quite fragile and require proper handling and care. Baskets should be rinsed immediately after use, dried, and stored properly. They should not be allowed to roll around in a drawer where they may be dented or misshapen. Baskets should always be attached and detached from the shaft by holding the upper rim of the basket. Otherwise, improper handling will damage the basket, and it will not maintain its cylindrical shape. To ensure consistent dissolution performance, a damaged or corroded basket must never be used.

Additional baskets designs have been developed and justified for special dosage forms that have shown performance issues when tested with the standard compendial baskets. These include variations in mesh number from 10-µm to 10-mesh, slotted baskets for suppository testing, large baskets to handle veterinary bolus tablets, and mini-baskets for use with 200-mL vessels.

The Rotating Basket Procedure

When executing the rotating basket dissolution test, a series of steps should be routinely performed during each test. These steps may be included in a general dissolution standard operating procedure (SOP), as they are often not included in a specific test method for a particular product.

- Prior to the start of the test, the analyst should evaluate the dissolution apparatus, vessels, baskets, and shafts to ensure that they are clean and dry.
- The analyst is responsible for the verification of physical parameters prior to the start of a test, especially if the vessel, shaft, or basket components have been moved or exchanged.
- Media must be properly prepared according to the method and thoroughly deaerated. Dissolved gasses that have not been removed will form bubbles in the mesh of the basket during the test, which will change the performance of the basket. Lower profiles or test results may be observed due to blocked apertures in the wire cloth of the basket.
- Media must be delivered to the vessel while maintaining a volumetric accuracy of ±1%. For a typical dissolution test with 900 mL and a required volumetric accuracy of ±9 mL, appropriate Class A volumetric glassware is required, which may exclude most graduated cylinders.
- The media must reach 37.0°C in each vessel prior to the start of the test. If the media is barely within the lower range, 36.5°C, the temperature will drop below the range when the cold steel shafts and baskets are lowered into the media.
- Media temperature must be measured and recorded for each vessel at a minimum before and at the end of each dissolution test to verify that the temperature of the media has been maintained properly (Figure 2).

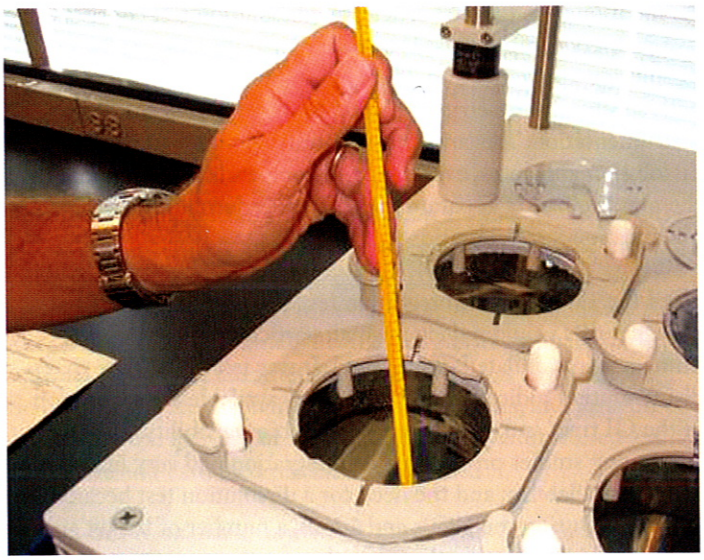

Figure 2. *Temperature measurement.*

Table 1. Dissolution apparatus specifications

Parameter	ICH Harmonized Specifications (USP, EP, JP) (5)	FDA (DPA-LOP.002) (6)	ASTM (E2503-07) (7)
Basket/paddle depth	25 ± 2 mm	25 ± 2 mm	25 ± 2 mm (or within 8% of desired height)
Rotational speed	±4% of specified rate	±2 rpm of target	Within 2% or ±2 rpm of stated rate (use larger)
Shaft wobble	No significant wobble	≤1.0 mm total runout	≤1.0 mm total runout
Shaft verticality	Not measured	≤0.5° from vertical	Within bubble
Basket wobble	±1 mm	≤1.0 mm total runout	≤1.0 mm total runout
Vessel/shaft centering	NMT 2 mm from center axis	≤1.0 mm from center line	≤1.0 mm from center line
Vessel verticality	Not measured	≤1.0° from vertical from 2 positions 90° apart	≤1.0° from vertical from 2 positions 90° apart
Vessel plate level	Not measured	Not measured	Not measured
Performance verification test	USP Prednisone Tablets RS	Not measured	Not measured

- Prepare all sampling materials if sampling manually or automatically, including fresh filters and measuring equipment that is clean and dry. Prepare fresh, clean, dry, and properly labeled vials or test tubes for each sample time point.
- Handle all dosage units with gloved hands or protective tweezers that will not scratch or crack capsules or the coating on tablets. Moisture and oils on the skin will affect the performance of many dosage forms prior to the start of the dissolution test.
- If weights are required for documentation, expose the dosage forms to as little humidity as possible.
- Do not place dosage units in the basket until you are ready to begin the test (Figure 3). Suspending the dosage units in the basket above the dissolution apparatus for a lengthy period prior to the test could expose the dosage unit to high humidity levels, which may alter the performance of the dosage unit.
- Have all documentation materials nearby to record temperatures and times and to note visual observations taken during the test.
- Record the times at which the baskets are lowered into the media and when each of the samples is pulled from the vessel.
- Visually inspect the baskets for bubble formation. There should not be a bubble under the basket, which may occur when starting the test with wet or dirty baskets. While many capsules may be seen floating in the top of the basket, tablets should not be trapped in the top of the basket with an air bubble, which may delay the dissolution of the tablet coating.
- Samples should be pulled within 2% of the time that the test begins. In other words, samples must be pulled for a 30-min time point within ±36 sec of the 30-min time point. If all six samples are started at the same time, then all six samples must be pulled and filtered within this window of time. Automated sampling equipment is often used to obtain, filter, and document sampling accuracy.

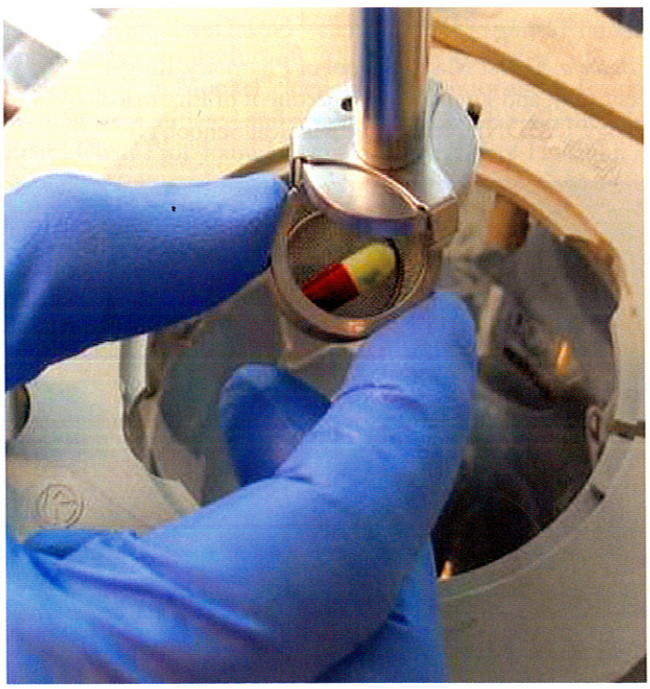

Figure 3. *Placing the basket on the shaft.*

- The filter stops the dissolution process and clarifies the sample for analytical measurement. Only validated filters should be used that remove all undissolved particles from the sample and do not bind the drug substance after conditioning with a specified amount of sample-containing medium.
- The dissolution samples are ready for analytical measurement once they have cooled to room temperature.

Qualification: Chemical vs. Mechanical

All dissolution apparatus used for testing within a cGMP environment should be properly qualified. The dissolution test is a test of the performance of the drug product, and therefore, qualification testing should include a periodic performance qualification (PQ) in addition to the standard installation and operational qualifications (IQ and OQ). The USP prescribes the use of the Performance Verification Test with USP Prednisone Tablets RS, but this is not a requirement of the harmonized dissolution chapters.

Mechanical qualification of the dissolution apparatus has been proposed by the U.S. Food and Drug Administration (FDA) in a draft Guidance for Industry. This proposal suggests an alternative approach to the use of USP Performance Tablets in calibrating a dissolution apparatus (4). Table 1 contains the specifications that the dissolution apparatus must maintain to meet mechanical calibration standards. The frequency of measurement and documentation of these parameters will be the responsibility of laboratories choosing mechanical qualification practices.

If the mechanical calibration procedure is used, additional documentation is required to verify the dimensions for each individual vessel, basket, and basket shaft used in the laboratory. Additional operational checks must also be documented at the time of each test for baskets to ensure that they are not corroded misshapen, deformed, or frayed and are free from residue. Vessels must be documented to ensure they are free from residue, cracks, scratches, and pits. Vessel temperature must be taken, and vibration must be evaluated.

In the next "Back to Basics" article the paddle apparatus, "Apparatus 2", will be discussed.

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