

DISSOLUTION TESTING TODAY: HOW ADVANCED MANUFACTURING TECHNIQUES ARE IMPROVING CALIBRATION

Improvements in the precision of the machine tools and metrology techniques used to manufacture and qualify modern day dissolution testers are making enhanced mechanical calibration a reality. Tony Copley discusses the importance of the latest developments.

During the past few years, 'calibration' has generated considerable discussion amongst those organizations involved in dissolution testing. Currently, the method adopted by the United States Pharmacopeia (USP) in their *Apparatus Suitability Test* — and still the accepted practice within the industry — is to calibrate dissolution testers on a regular basis using a combination of mechanical checks and performance verification tablets, formerly known as dissolution calibrators. A number of concerns, however, have been raised about the latter because of the wide acceptance ranges and variability of results generated by the reference standard tablets used. Consequently, a Performance Verification Test (PVT) based on salicylic acid RS tablets is no longer a requirement and there is a move towards using an enhanced form of mechanical calibration as a possible alternative, or at least as a precursor in support of chemical calibration using prednisone RS tablets.

It has long been recognized that dissolution vessel dimensions and irregularities are major factors in results variability, but improvements in the precision of the machine tools and metrology techniques used to manufacture and qualify modern-day dissolution testers means that enhanced mechanical calibration is now a reality. Advanced engineering techniques enable the manufacture of dissolution test vessels, lids and stirring elements to within tight tolerances, minimizing equipment-associated variance. Such enhancements would have been impossible in the 1970s when the dissolution tester was first introduced.

Demonstrating Apparatus Suitability

As well as being an integral part of formulation development for understanding the mechanisms of drug release, dissolution testing of solid dosage forms such as tablets and capsules, is an essential aspect of quality control (QC). It bridges the gap between in vivo and in vitro product performance, and ensures both product and process consistency. The dissolution rate of a dosage is widely recognized as a critical quality attribute and now, with the widespread integration of Quality by Design (QbD) principles into pharmaceutical formulation, development and manufacturing cycles, dissolution testing must satisfy a wider field of expectation and become more clinically relevant.

There are several alternative methods for conducting dissolution tests, but the two used most widely, which cover the majority of the industry's needs, are classed by the USP as: Apparatus 1, the basket method; and, Apparatus 2, the paddle method. To demonstrate apparatus suitability, FDA current good manufacturing practice (cGMP) regulations require dissolution apparatus to be calibrated every 6 months, following major change, or after an instrument move. See CFR 211.160(b)(4) and 211.68.¹

Dissolution Calibration: A Brief History

Historically, both chemical and mechanical methods of calibration have been used to regulate dissolution apparatus. In 1978, Chapter 711 of the USP described the use of calibrator tablets, requiring the disintegration and

Calibration parameter	PDG harmonized pharmacopeial specifications (USP, EP, JP)	FDA recommendations based on ASTM standard
Shaft wobble	Rotates smoothly without significant wobble	≤1.0 mm total runout
Shaft verticality	N/A	Bubble must be within the lines of bubble level (≤0.5° from vertical)
Basket wobble	±1 mm runout	≤1.0 mm total runout
Vessel/shaft centring	≤2.0 mm from centre line	≤1.0 mm from centre line measured at an upper and lower position
Vessel verticality	N/A	≤1.0° from vertical
Height check/basket depth	25 ± 2 mm	25 ± 2 mm
Rotational speed	±4% from target	±2 rpm from target

Table I: Mechanical calibration parameters: dissolution rotating basket apparatus.



Figure 1: A modern-day dissolution tester (Copley DIS-EMC 6000) with enhanced mechanical calibration features.

non-disintegration of a 50-mg prednisone tablet (Upjohn) and a 300-mg salicylic acid tablet (Hoffman LaRoche) respectively.² The relatively straightforward, although time-consuming, nature of this method quickly made chemical calibration the main choice for laboratories.

In 1979, the use of a 10-mg prednisone tablet had been adopted by the Center for Drug Evaluation and Research (CDER) Division of Pharmaceutical Analysis in St. Louis, MO (DPA) because of its high sensitivity to dissolved gases in the medium and to vessel centering for the paddle method (Apparatus 2). As a result, in 1999 the USP finally replaced the 50-mg disintegrating calibration tablet, which had been discontinued by Upjohn in 1997, with a 10-mg tablet manufactured by the University of Maryland at Baltimore (UMAB).²

In 1999, a Pharmaceutical Research and Manufacturers of America (PhRMA) dissolution committee proposed that chemical calibration could be replaced by mechanical calibration.³ At that time, the USP argued that the two methods were complementary and insisted on both for dissolution apparatus qualification.⁴ Since 2000, however, several collaborative studies have shown that, with time, chemical calibration suffers from a great deal of variability in the dissolution measurement system.² This can be because

- results for the UMAB 10-mg tablet are less stable so tend to be lower with the paddle method than with the basket method²

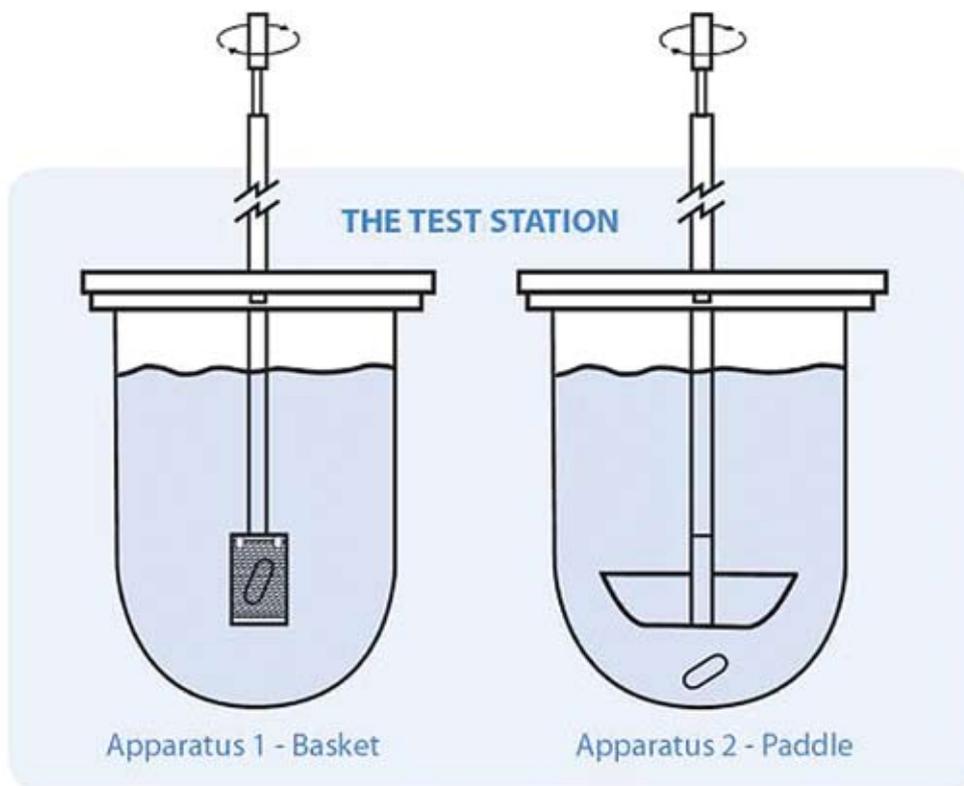
- cover a wider range across laboratories, forcing the USP to extend accepted limits for both Apparatus 1 and 2⁵
- the USP Salicylic Acid Tablet was found to be insensitive to perturbations of both USP Apparatus 1 and 2⁶
- the USP degassing procedure, required to prevent results being affected by the formation of bubbles around a tablet as a result of dissolved gases, is time consuming. Consequently, it is often replaced by different degassing methods across laboratories.^{7,8}

While these issues with PVTs were being discussed, dissolution tester manufacturers continued to significantly improve the specifications relating to the glassware and other components, making mechanical calibration a real factor in the reduction of dissolution test variables (Figure 1).

In October 2005, FDA endorsed mechanical calibration and an in-house procedure was developed.⁹ Subsequently, the ASTM added the procedure to its Standard E 2503-07, published in April 2007.¹⁰ In October that same year, the USP issued its own draft guidance, to run in parallel with Chapter 711, recommending that while performance verification testing should remain as an assessment of the assembly, its operating environment and lab procedure as a whole (essentially a performance qualification [PQ]), enhanced mechanical calibration should be used for operational qualification (OQ) and some parts of

Figure 2: USP Apparatus 1 (the basket) and 2 (the paddle).

Table II: Mechanical calibration parameters: dissolution rotating paddle apparatus.



Calibration parameter	PDG harmonized pharmacopeial specifications (USP, EP, JP)	FDA recommendations based on ASTM standard
Shaft wobble	Rotates smoothly without significant wobble	≤1.0 mm total runout
Shaft verticality	N/A	Bubble must be within the lines of bubble level (≤0.5° from vertical)
Vessel/shaft centring	≤2.0 mm from centre line	≤1.0 mm from centre line measured at an upper and lower position
Vessel verticality	N/A	≤1.0° from vertical
Height check/basket depth	25 ± 2 mm	25 ± 2 mm
Rotational speed	±4% from target	±2 rpm from target

References

1. FDA, Centre for Drug Evaluation and Research (CDER), The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 — Current Good Manufacturing Practice (CGMP), January 2010.
2. FDA, Centre for Drug Evaluation and Research (CDER), The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 — Current Good Manufacturing Practice (CGMP), *Draft Guidance*, October 2007.
3. www.dissolutiontech.com/DTresour/899Art/RecentInnov.html
4. www.dissolutiontech.com/DTresour/200articles/200art1.html
5. www.usp.org/referenceStandards/useAndStorage/calibrators.html
6. M. Oates, et al., “Dissolution Calibration: Recommendations for Reduced Chemical Testing and Enhanced Mechanical Calibration,” *Pharmacopeial Forum*, **26**(4), 1149–1151 (2000).
7. T. Moore, “Dissolution Testing: A Fast Efficient Procedure for Degassing Dissolution Medium,” *Dissolution Technologies* **3**(2), 3–5 (1996).
8. Z. Gao, et al., Effects of Deaeration Methods on Dissolution Testing in Aqueous Media: A Study Using a Total Dissolved Gas Pressure Meter,” *J. Pharmaceut. Sci.* **95**(7), 1606–1613 (2006).
9. FDA, Mechanical Qualification of Dissolution Apparatus 1 and 2, June 2006.
10. ASTM, Standard E 2503-07, Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus, April 2007.
11. USP, Toolkit Dissolution Procedure: Mechanical Calibration and Performance Verification Test, October 2007.
12. M.R. Liddell, et al., “Evaluation of Glass Dissolution Vessel Dimensions and Irregularities,” *Dissolution Technologies*, **14**(1), 28–33 (2007).
13. www.copleyscientific.co.uk

installation qualification (IQ). This view was reiterated in Version 2 published 22 March 2010.¹¹ Finally, in January 2010, FDA officially republished its guidance document to incorporate the work discussed in its 2007 draft guidance.^{1,2} This states that, if properly executed, an enhanced mechanical calibration procedure will satisfy the cGMP requirements in lieu of chemical tablet calibration.¹

Enhanced Mechanical Calibration

Forty years ago, dissolution testing equipment was relatively crude, but thanks to the application of today’s advanced engineering techniques enhanced mechanical calibration (EMC) now delivers results that are robust enough to meet industry standards. It is the test station where the tablet is held during testing (Figure 2) that has the most potential to contribute variation.

EMC requires strict control of the dimensions of, and the spatial relationships between, critical elements of the dissolution tester. Test parameters

such as rotation speed, and volume and temperature of the dissolution medium must also be monitored periodically. Tables I and II detail the harmonized Pharmacopeial Discussion Group (PDG) and FDA requirements for mechanical calibration for basket and paddle apparatus, respectively.

The dissolution vessel and lid, and the stirring element have the most influence on dissolution results. Controlling these, while maintaining stirring speed, media composition and temperature within tight limits, minimizes variability in test results that may be contributed to the instrument itself. Today, the application of new vacuum-forming techniques together with advanced engineering methods allows the production of vessels with superior dimensions. This, in turn, has provided a platform for the development of a new lid and stirring element.

EMC Dissolution Vessel

Mechanical calibration can suffer from variability because the dimensions of dissolution testing vessels

Figure 3a: The vacuum formed EMC Dissolution Vessel (Copley Scientific).

Figure 3b: The EMC Test Station (Copley Scientific).



3a

may differ widely. Traditionally, they are made individually using manual glass-blowing techniques starting with extruded glass tubing and the vessels are notoriously difficult to reproduce. One study, for example, found multiple irregularities and enormous differences between inside diameters, and height and radius measurements of vessels from five different suppliers. Variations of up to 18% in the volumes of the vessels' hemispheric regions were found to occur even across samples from the same supplier.¹²

The new EMC Dissolution Vessel (Figure 3) is vacuum formed. Rather than being extruded, the glass blank is first heated to 2000 °C before being shrunk in a vacuum onto a precision-ground stainless steel mandrel. This production method guarantees an internal diameter tolerance and blemish-free spherical radius of ± 0.13 mm (compared with the traditional unit's ± 2 mm).¹³

EMC Lid and Interchangeable Stirring Element

Having resolved the issues of irregularity between vessels, the design of a dissolution vessel lid and stirring element with equal performance was relatively straightforward. Friction-free bearings in the lid and a precision-ground shaft for the stirring element enable a 50% reduction in tolerances relating to wobble, verticality and centering. Within a complete setup these improvements deliver dimensional tolerances that better those specified by FDA as shown in Tables I and II by a factor of two.



3b

QC Dissolution Testing

Knowing how a pharmaceutical dosage is affected by each source of variability associated with dissolution test equipment enables tighter control. This can result in more meaningful dissolution data and lead to better QbD decisions. By employing state-of-the-art precision engineering equipment manufacturers are able to minimize instrument variation. Improvements in the manufacture of dissolution test vessel, lid and stirring element now produce results that consistently lie within very tight tolerances. This has made enhanced mechanical calibration of equipment possible, reducing dependence on potentially unreliable, and often time consuming, chemical methodologies. **Pharma**

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For more information

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