



## Extending the quality and applicability of pharmaceutical dissolution testing

*The efficacy of most pharmaceutical products requires their dissolution and subsequent absorption into the bloodstream. Consequently, in vitro testing techniques that reliably reflect this aspect of behaviour are crucial to clinical success. Dissolution testing already underpins both the development and quality control of solids dosage forms and is now on the radar of those developing products for inhaled drug delivery. We take a look at recent innovations in this vital area of pharmaceutical analysis.*

Dissolution testing (or Drug Release testing in the case of non-oral dosage forms) is used routinely by the pharmaceutical industry to steer formulation design and to control product quality for solid dosage forms, suspensions and transdermal patches, though not, as yet, for orally inhaled products (OIPs). Since the dissolution rate of a solid oral dosage is widely recognised as a Critical Quality Attribute (CQA), appropriate testing is especially important for tablets and hard gelatine capsules, which remain the most widely used drug delivery vehicles. As a result, dissolution testing enjoys a central position in pharmaceutical analysis.

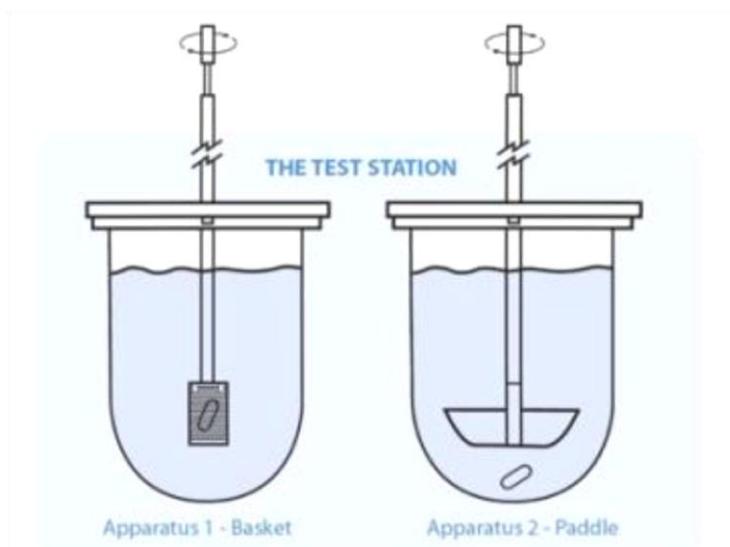
Adding value at points throughout the entire drug development cycle, dissolution testing enables:

- characterisation of APIs
- development, selection and optimisation of formulations
- the study of drug-release mechanisms
- batch-to-batch consistency
- stability monitoring
- the demonstration of bioequivalence between formulations

The technique has been instrumental in the development of more sophisticated solid dosage products with controlled release profiles: some tablets now combine both short- and long-term action. Sensitive enough to distinguish out-of-specification manufactured batches, dissolution data can also be used to demonstrate equivalence following changes in formulation or in support of claims of parity in a generic product.

### **Dissolution testing practice**

The two most widely used methods for solids dosage dissolution testing cover most industry needs and are classed by the USP as: Apparatus 1, the basket method; and, Apparatus 2, the paddle method.



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

Testing procedures are relatively straightforward. The tablet is either held in a basket or dropped into the vessel depending on the approach adopted. The user sets hydrodynamic test conditions by defining the speed of rotation of the paddle or basket, and determines the testing temperature which is kept constant. Samples taken during the course of the dissolution process are analysed to give a profile that characterises the product.

Calibration is a periodic requirement to verify system performance and ensure data integrity. It is a topic that continues to fuel considerable debate among those involved in dissolution testing despite the fact that both the techniques and apparatus used are well established. In the simplest of terms there are two possible approaches to calibration:

- to mechanically verify those dimensions of the apparatus that dictate performance to defined tolerances, **and/or**
- to chemically verify the performance of the system with a standard tablet under well-defined conditions

Historically, chemical calibration has been the norm. However, the advent of better engineered test apparatus coupled with increasing recognition of the variability associated with testing of the standard tablets has shifted emphasis towards mechanical calibration. After considering all of the available evidence, over a period of almost a decade, the regulators in the form of the FDA (Food and Drug Administration) have concluded that “an appropriately enhanced mechanical calibration method executed according to a written procedure” is an acceptable, alternative approach to the standardised tablets employed in the *Apparatus Suitability* procedure described in USP <711>.

Changes to the regulatory framework began in earnest in October 2005, when mechanical calibration was endorsed by the FDA and an in-house procedure was developed.<sup>1</sup> Subsequently, the ASTM added the procedure to its Standard E 2503-07, published in April 2007.<sup>2</sup> In October that same year the USP issued new draft guidance, to run in parallel with Chapter 711, the USP chapter relating to dissolution testing. This advice recommended that performance verification testing (PVT) with standardised tablets (chemical calibration) should remain as an assessment of the assembly, its operating environment and lab procedure as a whole (essentially a performance qualification [PQ]). However, it also recommended that enhanced mechanical calibration should be used for operational

qualification (OQ) and some parts of installation qualification (IQ)<sup>3</sup>. This view was reiterated in Version 2 published March 22, 2010.<sup>3</sup>

In January 2010, the FDA officially republished its guidance document<sup>4</sup> to incorporate the work discussed in its 2007 draft guidance. This most recent guidance states that, if properly executed, an enhanced mechanical calibration procedure will satisfy the cGMP requirements in lieu of chemical tablet calibration.

### **Enhanced mechanical calibration (EMC)**

This switch to enhanced mechanical calibration, with its emphasis on a more extensive mechanical assessment and tighter acceptance tolerances, is in part a result of better manufacturing practice. It is now possible to manufacture a dissolution test vessel, lid and stirring elements that deliver the precision required to consistently produce results within extremely tight tolerances. Systems such as the DIS-EMC Dissolution Tester from Copley Scientific employ modern engineering techniques to support enhanced mechanical calibration, reducing the traditional dependence on time-consuming, and often unreliable, chemical methods.

During dissolution testing it is the test station where the tablet is held (see figure 1) that has the most potential to contribute variation.<sup>5</sup> Enhanced mechanical calibration requires strict control of equipment dimensions as well as of the spatial relationships between critical elements of the test setup. Periodic monitoring of test parameters such as temperature of the dissolution medium, rotation speed, and volume must also be carried out.



**Figure 2: The vacuum formed EMC Dissolution Vessel and EMC Test Station (Copley Scientific)**

Pictured in figure 2, the new DIS-EMC Dissolution Vessel is vacuum formed rather than being extruded. This production method guarantees an internal diameter tolerance and blemish-free spherical radius of +/- 0.13 mm, improving on traditional figures of +/- 2 mm.<sup>6</sup> A precision-ground shaft for the stirring element, and friction-free bearings in the lid, cut tolerances relating to wobble, verticality and centering by a half. Overall, engineering improvements within the complete setup help deliver dimensional tolerances that better, by a factor of 2, those specified by the FDA.

Better engineered apparatus, such as this, in combination with simpler, more reliable calibration, delivers greater reproducibility and consequently more sensitive measurement, with less calibration effort. This is a major step forward.

### **Dissolution testing for orally inhaled products (OIPs)**

While dissolution testing for solids dosage forms is being refined towards better productivity and accuracy, dissolution testing for other forms such as orally inhaled products (OIPs) is still in its infancy. As yet there is no regulatory requirement or established pharmacopoeial technique for dissolution testing of orally inhaled products (OIPs)<sup>7</sup> but its obvious relevance has generated a significant amount of interest among developers of inhaled drugs that deposit powders in the lung. Characterising and controlling the dissolution rate of actives, particularly those designed for systemic therapy, enables tailoring of formulation properties, dosing levels and dosing frequencies, ultimately delivering improved drug efficacy. Clearly, there are close parallels with solids dosage testing. Within a recent USP Pharmacopoeial Forum review<sup>8</sup>, it is recognised that dissolution testing may support the development of new OIPs by expanding our understanding of inhaled drug delivery. Recent work presented by GlaxoSmithKline contrasting the dissolution profile of a long-acting beta agonist with that of an inhaled corticosteroid exemplifies this view and highlights industrial interest in the topic<sup>9</sup>.

Just as with a solid dosage form, the therapeutic effect of an inhaled powder is realised by dissolution. By necessity powders delivered to the lung are extremely fine<sup>8</sup>, so it is often assumed that dissolution rates are rapid enough to have little impact on the overall process of drug delivery. However, the trend towards systemic drug delivery via the pulmonary route may mean that this assumption becomes less easy to rationalise, especially for larger molecule drug entities. The desire to control the release rate of both systemic and locally acting therapies strengthens the impetus to refine OIP performance through the modification of particle properties such as size, shape or crystal habit to control *in vivo* release rate.

### **The challenges of dissolution testing for inhalable formulations**

From a practical viewpoint, *in vitro* dissolution testing for inhalable products should be able to distinguish between samples in a way that replicates trends found *in vivo*. Testing must also take account of the delivery characteristics of OIPs.

The required simulation of pulmonary behaviour presents multiple challenges in dissolution testing. Perfectly designed for absorption but with fluid levels in the region of 10 to 20 ml/100 m<sup>2</sup>, the surface of the lungs does not present an ideal environment for dissolution - such small amounts of liquid are likely to be stagnant, further inhibiting the process. In addition, the exact composition of the aqueous fluids and surfactants lining the respiratory tract is not accurately known, complicating the selection of a test medium.

Analysis is further complicated by the fact that during inhaled drug delivery just a portion of the emitted dose enters the lung, typically material in the sub five micron fraction; larger particles are ingested. Dissolution testing of the whole dose is therefore inappropriate. A better aim is to access the dissolution profile of only those particles that will deposit in the lung. This is exactly what researchers at The University of Texas at Austin have done when developing a dissolution test for OIP formulations based on the standard USP Apparatus 2 Method (see figure 1)<sup>9</sup> already used for other dosage forms, resulting in an approach not dissimilar to USP Apparatus Method 5 (Paddle over Disk)

### **Introducing a technique for OIP dissolution testing**

To capture a suitably representative sample for OIP dissolution testing the University of Texas team have designed the Next Generation Impactator (NGI) dissolution cup and membrane holder (see figure 3).



**Figure 3: NGI dissolution cup and membrane holder (Copley Scientific, UK)**

A system of choice for routine aerodynamic particle size distribution (APSD) measurement, the NGI multistage cascade impactor separates the emitted dose from an OIP into sized fractions, capturing each fraction in a collection cup. There are usually seven cups in total.

Mirroring the dimensions of a standard NGI cup, the modified NGI dissolution cup fits neatly into positions 2 through 7 in a standard NGI cup tray and is used in the same way as routine APSD measurement cups. It includes a 50 mm removable insert in the impaction area where the sample is collected. Simply by inserting the NGI dissolution cup at the stage of choice it is possible to collect all particles of a certain size and below for subsequent dissolution testing, using methods identical to those routinely adopted for APSD measurement.

Following collection, the insert is removed from the cup and covered with a pre-punched 55 mm diameter polycarbonate membrane, which is secured in place with the membrane holder supplied. This forms a sealed, sandwich-like disc that can be placed in a conventional dissolution tester under appropriate operating conditions, and processed using solid dosage dissolution techniques (see figure 4).



**Figure 4: NGI membrane holder in position in the vessel of a standard USP Apparatus 2**

Key to the success of the device, is the thin (~6 micron) polycarbonate membrane which outperforms its cellulose acetate prototype. The polycarbonate is robust with non-tortuous cylindrical pores of well-defined size that enable the free diffusion of both the dissolved drug and dissolution media under relevant hydrodynamic conditions. During testing it neither swells nor creates air bubbles.

A modified version of this novel solution is now commercially available for those wishing to access dissolution testing information to innovate more sophisticated inhaled formulations. A full case study demonstrating its application can be read in the article 'Dissolution testing for inhaled drugs'

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## **Conclusion**

Dissolution testing is widely and routinely employed within the pharmaceutical sector for suspensions, transdermal patches and, of course, tablets and capsules. The apparatus and associated methodologies are well-established but continued to be refined, both in terms of the practicalities of use and applicability.

For those implementing Quality by Design the dissolution rate of a solid dosage product is typically a Critical Quality Attribute (CQA), underlining the need for sensitive and reliable data. Here, better engineering coupled with greater understanding of the limitations of chemical testing has promoted a shift towards enhanced mechanical calibration - a simpler, more robust technique for verifying that performance lies within the tolerances expected by the regulators. New FDA guidance released in 2010 confirms the acceptability of enhanced mechanical calibration for satisfying cGMP requirements, with chemical tablet calibration now retained principally for performance verification testing.

For orally inhaled products there are as yet no regulatory requirements for dissolution testing although the relevance of the technique is clear. The idea of tailoring the release profile of drugs delivered via the pulmonary route, is perhaps both daunting and exciting in equal measure. Test equipment manufacturers have already begun to respond to the potential demands for dissolution testing equipment for OIPs, building on the substantial body of knowledge already available for other dosage forms. The development of a specially adapted NGI cup for dissolution testing is an elegant solution that enables those working at the cutting edge of dry powder inhaler development to access what could prove to be vital information for more sophisticated formulation.

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