

Innovations in dissolution testing

Tony Copley
Managing Director,
Copley Scientific

Having been directly involved in the evolution of dissolution testing since its introduction in the early 1970s and variously representing Hanson, Van Kel, Sotax and Erweka prior to developing our own range of dissolution testers in 2002, I would have to say that advances in dissolution testing technology have been one of the biggest breakthroughs in solid dosage form testing over the last decade.

How accurate are current tests?

It is widely acknowledged that the rate at which a tablet or capsule dissolves (the dissolution rate) is critical to its therapeutic effectiveness, or in modern 'pharma' speak is a Critical Quality Attribute in its *in vitro* characterisation. Unfortunately, as with any *in vitro* test, the accuracy of the results is only as good as the instrument used to conduct it — the more variables in the apparatus, the more variables in the results.

A number of studies have been conducted recently by both the FDA and United States Pharmacopeia (USP) to identify different sources of mechanical variation within the USP Dissolution Apparatus that lead to variability in results. This has resulted in calls from both regulators and industry alike for a tightening of the original mechanical specifications relating to Dissolution Testers (laid down in the USP) to ensure that those tolerances that are critical to the process are maintained within known limits and policed by a process described as an enhanced mechanical calibration.

Such suggested 'enhancements' would not have been possible in the 1970s when the dissolution tester was first introduced. Fortunately, improvements in the precision of the machine tools and metrology techniques used to manufacture and qualify the modern-day dissolution

tester mean that, today, enhanced mechanical calibration is not only a possibility, but a reality.

Limiting variability

Based on our own research, we quickly recognised that the critical elements of a dissolution tester and therefore the most likely to affect the accuracy of results were the ones making up the actual test station — namely the dissolution vessel itself, the dissolution vessel lid and the stirring element appertaining to it.

It follows that if we can control the dimensions of these critical elements and their spatial relationship with each other, and then ensure that the speed of the stirring element and the composition and temperature of the dissolution media are maintained within equally tight limits, then any instrument's contribution to test method variability would be minimised.

The dissolution community has long recognised that one of the major problems with respect to results variability relates to vessel dimensions and irregularities. We determined from the outset of our new product development project that if we were able to resolve the problems arising from the vessel, then the problems emanating from the other elements of the test station — the stirring element and the vessel lid — could be easily solved. Traditionally, dissolution vessels have been made individually using manual glass blowing techniques from extruded glass tubing having a nominal tolerance of ± 2 mm. Unfortunately, even by using 'specially selected' tubing, it is simply not possible to obtain the tolerances (twice as tight as those specified) desired using this technique.

We found that the solution was to vacuum-form the vessel as opposed to extrude it. In this method, the glass blank employed to produce our dissolution vessel is first heated to 2000 degrees before being vacuum-

formed by shrinking it on to a precision ground stainless steel mandrel. Having resolved the problems relating to the dissolution vessel, it was then a relatively simple matter to design a dissolution vessel lid and stirring element to match it. We have used the results of our research to develop our new tablet dissolution tester, which was launched earlier this year.

Where do we go from here?

The subject of calibration continues to stimulate considerable discussion amongst those organisations involved in dissolution testing. Currently, the method of calibration adopted by USP in Chapter 711, and still the accepted practice with the industry, has been to calibrate dissolution testers on a 6-monthly basis, using a combination of mechanical checks and performance verification reference tablets (formerly known as dissolution calibrators) to establish apparatus suitability.

Performance verification testing (PVT) is time-consuming, and concerns have been raised in some quarters about the wide acceptance ranges and variability of the results generated by the reference tablets used.

Current FDA and International Pharmaceutical Federation thinking would suggest the use of enhanced mechanical calibration as an alternative to PVT. Other sources, including USP themselves, argue that there is still a place for PVT testing on the grounds that it is not possible to pick up every variable through mechanical means alone. Dirty flow cells and analyst error are typical examples.

I have no doubt that this debate will rumble on for some time to come. Either way, enhanced mechanical calibration, either standalone or as a precursor to PVT, can only be beneficial in reducing instrument induced variability and thereby improving the accuracy of results. **PTE**