Guidelines for dissolution testing: an addendum

DON C. COX, WILLIAM B. FURMAN, TERRY W. MOORE, and CLYDE E. WELLS

Reprinted from PHARMACEUTICAL TECHNOLOGY February 1984

Guidelines for dissolution testing: an addendum

DON C. COX, WILLIAM B. FURMAN, TERRY W. MOORE, and CLYDE E. WELLS

THE DISSOLUTION TEST was in a state of flux when "Guidelines for Dissolution Testing" was published in 1978.[1] Although most of the elements affecting test reproducibility had been identified by that time, criteria for adequate control of these elements were not well defined. The guidelines served to elucidate some of these criteria. Since that article was published, however, several changes have been made in the USP's general chapter on dissolution,[2] and manufacturers of dissolution equipment have steadily improved their products. This addendum to the guidelines addresses those changes and improvements.

Deaeration

USP XX's third supplement states that "dissolved gases [in the dissolution medium] . . . may change the results of the test. In such cases, dissolved gases should be removed prior to testing." To determine whether or not dissolved gas changes test results, dosage units should be tested at least twice — once in a medium with a high gas concentration and once in a medium with a low gas concentration. If the results change appreciably, a gas concentration should be found below which test results are unaffected.

The equilibrium concentration of dissolved gases in dissolution media can be controlled in several ways. The simplest and most convenient way is to equilibrate the medium with air under a low, regulated pressure. To prepare medium for routine dissolution tests in the laboratory of the National Center for Drug Analysis (NCDA), bubbles of air are passed upward through approximately 20 L of medium at a pressure of 140–150 mm Hg for 15–20 min. Detailed directions for this procedure are available from the authors on request.

After atmospheric pressure has been restored over the medium, disturbing the partially deaerated medium should be avoided as far as is possible. The medium is now siphoned into volumetric flasks, and the contents of the flasks are heated to 37 °C. The contents are transferred to the dissolution vessels just before the test is started. This deaeration process is carried out daily.

Temperature

The 1978 guidelines stated that the temperature of the water bath should be kept at 37.0 °C. In reality, the contents *of the vessels* should be kept at 37.0 °C. To do so, the temperature of the water bath should be set at about 37.5 °C for glass vessels and at 38.0 °C to 38.5 °C for plastic vessels. Note that these values apply only if fitted covers are used, because the temperature of the medium is harder to control if the vessel is uncovered.

Volume

Volumetric flasks (500 ml and 900 ml) marked "to contain — to deliver" are now commercially available; such flasks allow convenient and accurate addition of the desired volume of dissolution medium to each vessel. To minimize reequilibration of the medium with the atmosphere before the test is started, these flasks should be prepared and used as described in the section discussing deaeration, above.

Manual Aliquoting and Filtration

Manual techniques are no longer recommended if more than one aliquot must be taken from a dissolution vessel. When a cannula or glass tube is inserted into the medium, the flow of the medium is disturbed. The extent of this disturbance is governed by the size of the cannula or tube, the depth to which it is inserted, and its location with respect to the vessel wall.[3,4] The magnitude of change in the test results will depend upon the physical characteristics of the dosage unit. When Apparatus 2 (the paddle) is used, for instance, flow disturbances readily influence dosage units that disintegrate quickly, release their drug content slowly, and produce dense particles that remain on the bottom of the vessel. By contrast, dosage units whose particles circulate throughout the medium are relatively immune to such disturbances.

At the very least, flow disturbances are difficult to control when manual aliquots are taken, making results obtained from all aliquots except the first difficult to reproduce. Automated aliquoting is thus highly recommended under the circumstances described here.

Automated Aliquoting

In NCDA's laboratory, continuous-flow systems are often used to take aliquots of dissolution medium and analyze them

automatically. The filter is no longer placed in the medium at the point at which the medium is drawn into the flow stream of the automatic analyzer; this decision was made because, when the filter was placed in the dissolution medium, its bulk disturbed the flow of the medium.[3,4] Current NCDA procedure is to insert a thin glass tube similar to a melting-point capillary into the medium. The filter is mounted on top of the tube above the surface of the medium. The lower end of the tube is placed at a defined location in the vessel, that is, at a point midway between the vessel wall and the stirring element and midway between the top of the stirring element and the surface of the medium. With this method, baffling action in the medium is slight and is reproducible from vessel to vessel.

Quality Control

NCDA has not yet formulated a total program of quality control for dissolution testing. A simple, reliable procedure for measuring and controlling the quality of results from a dissolution test remains a desired but elusive goal. USP calibrators fail to warn of minor but significant deviations from Apparatus 2 test specifications.[5] Nevertheless, the USP disintegrating calibrator shows promise for measurement of Apparatus 1 suitability.[6]

Staggered Tests

Although desirable for ease in manual aliquoting, staggered tests are not always feasible. With Apparatus 1 in particular, staggered tests have never been convenient. In NCDA's laboratory, dosage units are immersed simultaneously when the basket is used. After the test time has elapsed, aliquots are taken from all six vessels as quickly as possible. The aliquots are then filtered — also as quickly as possible.

If Apparatus 2 has clutches for its individual paddles, the tests may be staggered conveniently; without clutches, however, it is difficult to stagger the tests because of the USP requirement that stirring shall not commence until the dosage unit reaches the bottom of the vessel. Not all six-spindle dissolution drives are equipped with clutches. When a clutchless drive is used with the paddle method in the NCDA laboratory, immersion of the dosage units is staggered at timed intervals with all of the paddles rotating. Although this procedure deviates from *USP XX* directions, it provides better reproducibility than does using clutches or lowering each paddle into the medium after introduction of each dosage unit. If any sample appears to fail the USP test requirements, however, the analysis is repeated using an apparatus with clutches so that *USP XX* directions for testing may be followed exactly.

USP Basket and Paddle Methods

Both Apparatus 1 and 2 — basket and paddle — now use round-bottom dissolution vessels. The tolerance for the nominal rotational rate is ±4%, and the axis of the stirring element (basket or paddle) must coincide within 2 mm with the vertical axis of the vessel. The bottom of the stirring element is placed 25 mm (±2 mm) from the bottom of the vessel. Centering tools and depth gauges are now available commercially and should be used to align stirring elements precisely in the vessels. Manufacturers now provide test apparatus with acceptable means to hold the vessels in place once the alignments have been completed.

Basket shafts with diameters of 6.35 mm (0.25 in.) or 9.5 mm (0.375 in.) are currently available. In the NCDA laboratory, the larger shafts are used exclusively: these shafts are interchangeable with the paddle shafts and are, perhaps more importantly, less susceptible to warp. In addition, the paddle blade now passes through the diameter of the shaft and is an integral part of the stirring element for Apparatus 2. Engineering drawings of both stirring elements appear in the compendia, so one can readily determine if stirring elements meet USP specifications.

Vessels

Since 1978, the uniformity of dissolution vessels has been substantially improved. Glass and plastic vessels that pass USP specifications are now available. Nevertheless, on a few occasions distinct differences have resulted from using glass and plastic vessels with Apparatus 2, even though both types of vessel passed USP specifications and their surfaces did not adsorb the drug.[7] For this reason, it is good practice to record the manufacturer and type of vessel with the analytical results.

Currently, USP specifies that the vessel be cylindrical with a hemispherical bottom. Its overall height can range from 160 mm to 175 mm, its inside diameter from 98 mm to 106 mm. Strictly speaking, plastic vessels are not cylindrical but instead have sides that taper slightly from top to bottom; however, the physical dimensions of plastic vessels from the same manufacturer are uniform from one vessel to the next. The dimensions of glass vessels tend to be more variable, so, whenever possible, NCDA uses plastic dissolution vessels for routine dissolution tests. Recovery experiments should be conducted first to make certain that plastic vessels neither adsorb the drug nor release interfering substances into the dissolution medium. Details of these experiments are available from the authors on request.

Position Effect

The position of a dosage unit in the dissolution environment can affect the rate at which the drug dissolves. Unless the positions of the tested units are closely reproduced, results obtained from these units will reflect this variation. For example, when Apparatus 1 is used to test a tablet, the tablet is enclosed in the relatively small volume of the basket at the beginning of the test. The action of lowering the basket into the medium forces the tablet to tumble upward in the basket. Occasionally, a bubble of air is trapped under the top of the basket. In some instances, the tablet actually becomes attached to the air bubble and is suspended at the top of the basket at the beginning of the test. Results for such suspended tablets are considerably lower than results for tablets located on the bottom of the basket and should be rejected.[1] A solution to this problem with Apparatus 1 has been suggested,[8] but it has not been implemented by USP.

A position effect is also associated with Apparatus 2 and is seen with a small but troublesome minority of tablet samples that pass through the NCDA laboratory. Ideally, when a tablet is dropped into the dissolution vessel it should come to rest on the bottom of the vessel and should be centered with respect to the vessel's vertical axis. In practice, however, the tablet often settles some distance away from the center, and the fluid flow generated by the paddle is seldom great enough to move it. Nonetheless, the fluid flow is sufficient to move the particles formed as the tablet disintegrates. Lighter particles are lifted and circulated in the medium, while heavier particles stay in the bottom of the vessel where they rotate around the vessel's vertical axis.

Noncentered tablets are in a region of high fluid flow; they disintegrate faster and tend to give higher results than do cen-

tered tablets. If a tablet disintegrates rapidly — within one or two minutes — the result is not noticeably influenced by the tablet's position. If tablet disintegration is slow — in excess of five minutes — the results can be affected dramatically. In extreme cases, ranges of 30% to 50% of label claim have been observed in the results of six tablets.

This addendum does not offer an acceptable solution to the position problem. A wide range in results from slowly disintegrating tablets is an indication of the position effect. In such cases, greater weight should be given to results obtained from well-centered tablets because such tablets give more reproducible results with Apparatus 2.

Research on USP Apparatus 2

The results of NCDA's laboratory research on USP Apparatus 2 are being published as a series of papers.[5,7,9-12] Other literature references and useful discussion of the dissolution test may be found in William Hanson's text.[13]

References

1. Cox, D.C., Douglas, C.C., Furman, W.B., Kirchhoefer, R.D., Myrick, J.W., and Wells, C.E., "Guidelines for Dissolution Testing," *Pharm. Technol.*, Vol. 2, No. 4, 1978, pp. 41–53.
2. *USP XX*, 3rd. suppl., Rockville, Maryland, The United States Pharmacopeial Convention, Inc., 1982, pp. 310–311.
3. Wells, C.E., "Effect of Sampling Probe Size on Dissolution of Tableted Drug Samples," *J. Pharm. Sci.*, Vol. 70, 1981, pp. 232–233.
4. Savage, T.S., and Wells, C.E., "Automated Sampling of In Vitro Dissolution Medium: Effect of Sampling Probes on Dissolution Rate of Prednisone Tablets," *J. Pharm. Sci.*, Vol. 71, 1982, pp. 670–673.
5. Cox, D.C., Furman, W.B., Thornton, L.K., Moore, T.W., and Jefferson, E.H., "Systematic Error Associated with Apparatus 2 of the USP Dissolution Test III: Limitations of Calibrators and the USP Suitability Test," *J. Pharm. Sci.*, Vol. 72, 1983, pp. 910–913.
6. Thakker, K.D., Naik, N.C., Gray, V.A., and Sun, S., "Fine-Tuning of Dissolution Apparatus for the Apparatus Suitability Test Using the USP Dissolution Calibrators," *Pharmacopeial Forum*, Vol. 6, 1980, pp. 177–185.
7. Cox, D.C., and Furman, W.B., "Systematic Error Associated with Apparatus 2 of the USP Dissolution Test V: Interaction of Two Tableted Prednisone Formulations with Glass and Plastic Vessels," *J. Pharm. Sci.*, in press.
8. Sarapu, A.C., and Clark, L., Jr., "Elimination of Tablet Air Entrapment Using USP1 Rotating-Basket Dissolution Apparatus," *J. Pharm. Sci.*, Vol. 69, 1980, p. 129.
9. Cox, D.C., and Furman, W.B., "Systematic Error Associated with Apparatus 2 of the USP Dissolution Test I: Effects of Physical Alignment of the Dissolution Apparatus," *J. Pharm. Sci.*, Vol. 71, 1982, pp. 451–452.
10. Cox, D.C., Wells, C.E., Furman, W.B., Savage, T.S., and King, A.C., "Systematic Error Associated with Apparatus 2 of the USP Dissolution Test II: Effects of Deviations in Vessel Curvature from That of a Sphere," *J. Pharm. Sci.*, Vol. 71, 1982, pp. 395–399.
11. Cox, D.C., Furman, W.B., and Page, D.P., "Systematic Error Associated with Apparatus 2 of the USP Dissolution Test IV: Effect of Air Dissolved in the Dissolution Medium," *J. Pharm. Sci.*, Vol. 72, 1983, pp. 1061–1064.
12. Cox, D.C., and Furman, W.B., "Collaborative Study of the USP Dissolution Test for Prednisone Tablets with Apparatus 2," *J. Pharm. Sci.*, in press.
13. Hanson, W.A., *Handbook of Dissolution Testing*, Springfield, Oregon, Pharmaceutical Technology Publications, 1982.