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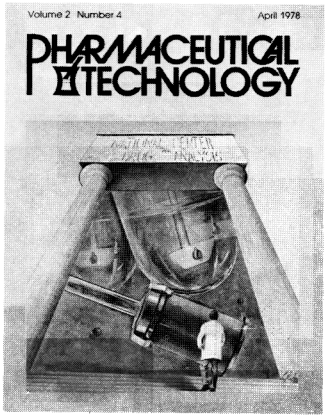

The cover: *The National Center for Drug Analysis has evolved techniques that ensure agreement between results obtained from different dissolution-testing apparatuses. Their guidelines are set forth in the article beginning on page 40. Cover art by Lon Levin.*

ARTICLES

DEPARTMENTS

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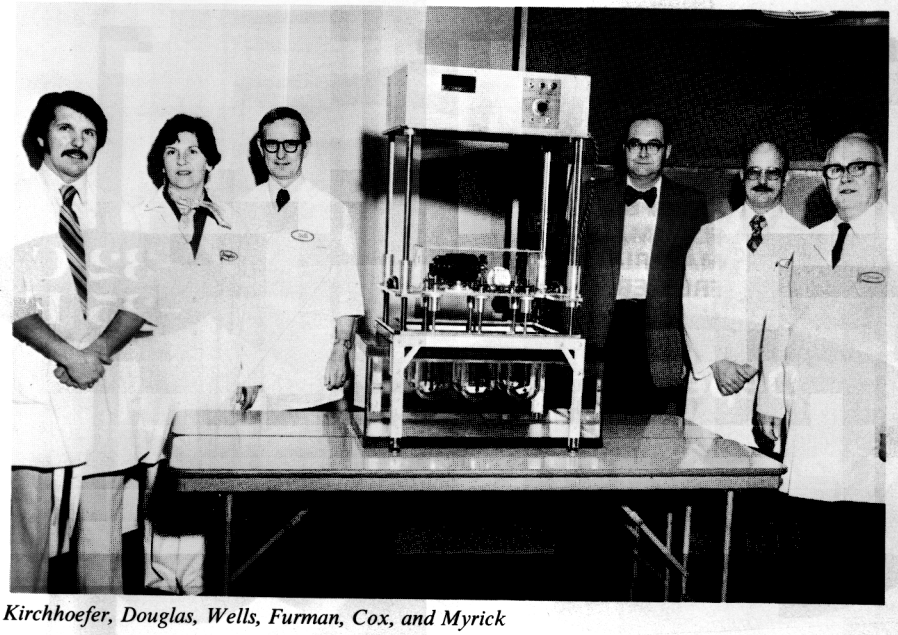
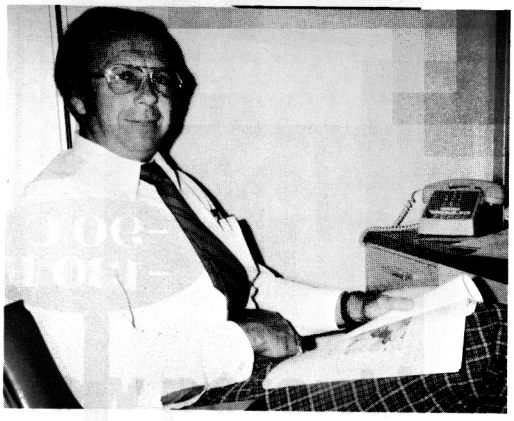
Clyde E. Wells is a research chemist in the Methods Research Branch of the National Center for Drug Analysis. He received his BS degree in chemistry from Louisiana State University in 1956. After serving two years in the army and working two years in an industrial laboratory, he joined the Food and Drug Administration in Seattle, and transferred to the center in 1967.



Kirchhoefer, Douglas, Wells, Furman, Cox, and Myrick



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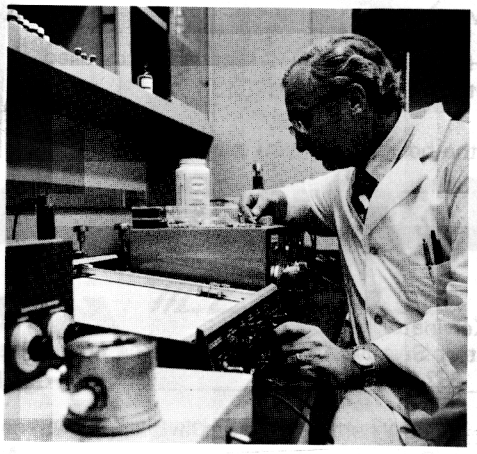
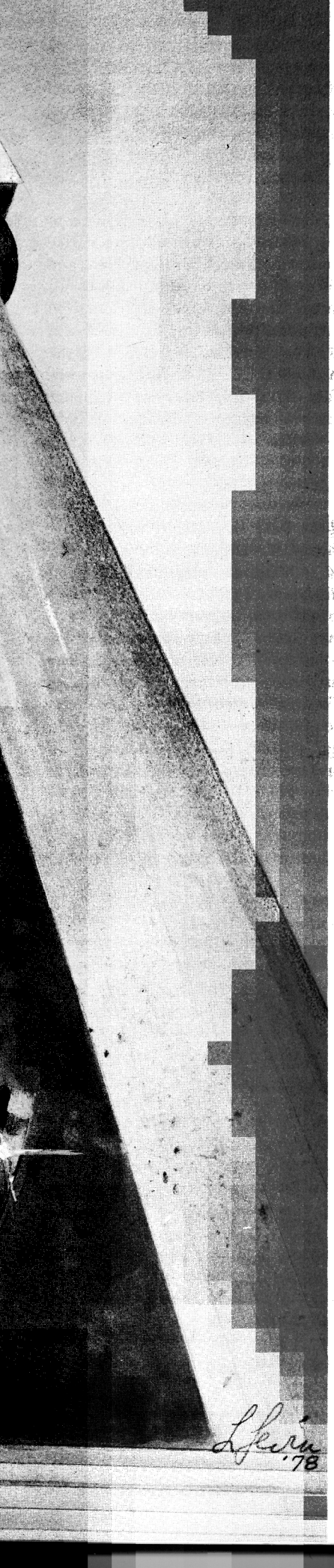




Guidelines for dissolution testing

DON C. COX, CAROL C. DOUGLAS, WILLIAM B. FURMAN, ROSS D. KIRCHHOEFER, JAMES W. MYRICK, and CLYDE E. WELLS

IN A GUEST EDITORIAL recently written for *Pharmaceutical Technology,* Gene Knapp explains why FDA has become involved in dissolution testing.[1] Briefly, the agency feels that in vitro dissolution testing can help pinpoint formulations that may present potential bioequivalence problems. The agency further believes that once a formulation has been shown to be bioavailable, dissolution testing is of great value in assuring lot-to-lot bioequivalence.

Of the many dissolution apparatuses that have been proposed for in vitro testing of solid drug-dosage forms, FDA has chosen to concentrate on three: the USP rotating-basket apparatus,[2] the USP paddle apparatus,[3] and the rotating-filter apparatus.[4] As Dr. Jerome P. Skelly recently pointed out, the agency's experience has largely been limited to these three apparatuses.[5] The former two have achieved official recognition by the USP, and fairly large data bases exist for them.

Skelly also stated that different laboratories may have difficulty in obtaining similar results when conducting dissolution tests on the same lot of tablets.[5] This potential lack of agreement is disturbing for at least two reasons. First, from a scientific viewpoint, if laboratories cannot be expected to agree on the results of a dissolution test, then an in vitro–in vivo correlation obtained by one laboratory cannot be generalized as being valid in all laboratories. Second, differences between dissolution results obtained in industrial laboratories and those obtained in agency laboratories raise problems in the making of regulatory decisions.

The National Center for Drug Analysis (NCDA) has been conducting routine dissolution tests as well as research into in vivo–in vitro correlations for the last seven years. During this time, techniques have been evolved that assure agreement in results obtained in our laboratory from dissolution apparatuses of widely differing characteristics. Many of the critical factors in conducting such tests with the USP basket or USP paddle methods have been identified, and it is the purpose of this article to set forth guidelines for conducting dissolution tests in accordance with the best of our current knowledge.*

In vitro dissolution testing as applied to solid-dosage drug forms measures the amount of drug dissolved in a known volume of liquid medium at a predetermined time, using a specified apparatus designed to carefully control the parameters of dissolution testing. The amount of drug dissolved may be determined at one time or at several successive times depending upon the type of information needed. Most compendial monographs that include such a test state that a certain percentage of the drug in the solid-dosage form shall be dissolved in so many minutes. Thus, one determination with respect to time is usually all that is required. Determining the amount of drug dissolved at several different times gives information on the rate of dissolution from the solid-dosage form, the maximum amount of drug that will dissolve, and the points in time when the rate of dissolution changes. Precise, standardized technique and equipment are needed in either procedure if these determinations are to be reproducible.

General Considerations

All portions of the apparatus that come in contact with the tablet or capsule or with the dissolution medium – baskets, paddles, vessels, etc. – must be inspected for cleanliness before each test is begun.

In general, the dissolution test is performed on six tablets or capsules at a time. It is important that a transparent water bath be used so as to allow visual monitoring of the dissolution process. The dissolution medium is deaerated, and the correct volume of medium is placed in each dissolution vessel and brought to 37°C before the test begins. The solid-dosage forms are immersed in the medium at time zero and subjected to the test, using the rotation speed and type of stirrer specified. Aliquots taken at the time(s) called for in the methodology being used are filtered and analyzed for drug content. Thus, we have a general outline of what is to be accomplished.

Deaeration

In our laboratory, deionized water is routinely used to prepare large batches of dissolution medium. Water emerges from the deionizer below room temperature and under pressure, and thus will be supersaturated with air when it is used to prepare the medium. If such medium used in the test is 37°, during the test the excess air will come out in the form of tiny bubbles that collect on the sides of the vessel, on the surface of the stirring mechanism, and on the surface of the solid-dosage form under test. The dissolution rate may be affected because air bubbles collecting on the surface of the solid-dosage forms or particles may cause them to float and will prevent contact between the product being tested and the medium.

Air may be partially removed by boiling and cooling the water, by spraying the water into a large vessel under vacuum, or by other means. If a large quantity of deaerated medium is allowed to stand at room temperature, it will eventually reequilibrate with air at room temperature and thus will again be in a supersaturated state at 37°. If a large amount of medium has been prepared previously, it is best to test it just prior to use as follows: place a portion of the medium in a dissolution vessel and bring its temperature to 37°; stir the medium with the basket or paddle – as required by the method – at the rotation speed and for the length of time specified in the method. If an excess of air is present, the stirrer (basket or paddle) will acquire a silvery appearance due to the collection of air. Air from supersaturated water is not to be confused with large bubbles created when air from the atmosphere is trapped in the medium as the solid-dosage form and basket are immersed.

Temperature and Vibration

Temperature of the dissolution medium in the vessels should be checked before the test is started. Though the water-bath temperature may measure 37°, the medium in the vessels will require time to equilibrate with it.

A dissolution apparatus is used with a constant-temperature bath. If the constant-temperature bath has a vigorous circulation device and if the dissolution apparatus is mounted on top of the bath, vibration from the circulation device may be directly transmitted to the dissolution vessels through the plate that supports them. Additional vibration may be transmitted to the vessels through the surrounding water. These sources of vibration must be reduced to a minimum.

The following apparatus configuration is recommended: replace metal constant-temperature baths with tanks made of glass or clear plastic; mount a small heater-circulator device on a separate support so that immersion of the heater-circulator element in the water bath constitutes the only contact between the device and the dissolution apparatus; make sure the heater-circulator device does not rest on or come into contact with the side of the tank. The

* To arrange for the loan of a videotape recording demonstrating critical steps of the dissolution test, contact Dr. Thomas Layloff, Director, NCDA, 1114 Market St., Rm. 1002, St. Louis, Mo. 63101.

device should provide only gentle stirring of the water in the bath, and streams of circulating water should not be directed at any of the vessels.

The dissolution apparatus should be set on a sturdy bench, and no other source of vibration should be placed on this bench.

Volume

The amount of drug dissolved is determined from its concentration in the dissolution medium; therefore, the total volume of dissolution medium present in the system at the time the sample is withdrawn must be known. Relatively large volumes – in the range of 500–1000 ml – are used in dissolution testing. These volumes are usually measured by graduated cylinder.

Graduated cylinders that are to be used to dispense dissolution medium into dissolution vessels should be calibrated by weight before being used. The error that arises from taking the medium to the mark, which is attributable to the large diameter of graduated cylinders, has been estimated from experience to be 0.5%–1.0% for 750–900 ml when measured in a 1000-ml graduated cylinder. If the volume measurement is made at 37°, the expansion of water will cause additional error. The maximum error as a result of expansion would be close to 0.4%.

Certain dissolution procedures require taking of more than one aliquot at prescribed time intervals. The procedure being followed may or may not require that the analyst replace the removed aliquot with fresh dissolution medium. If the volume removed is not replaced, the volume of the remaining dissolution medium is reduced in a stepwise fashion. If the volume removed in each aliquot is replaced, the drug in the dissolution medium remaining in the vessel is diluted in a stepwise fashion. In either case, the volume of each aliquot must be taken into account when calculating the analytical values at all sampling times except the first. It is therefore desirable to minimize the uncertainty in the volumes taken (or replaced) so as to avoid excessive cumulative error in the calculations. The devices (syringe, pipette, etc.) used to remove (or replace) aliquots should introduce no more than 1% uncertainty into the value of the volume of medium remaining in the dissolution vessel throughout the test.

Rate of Agitation, Time(s) of Aliquoting, and Concentration Gradients

The rate of agitation and time(s) of aliquoting will be specified in the dissolution-test methodology. Ideally these parameters will have been selected on the basis of some correlation with in vivo data.

The rate of agitation, usually from 50 to 150 rpm, will govern how quickly a solid-dosage form will disintegrate and/or dissolve in a specified volume of dissolution medium. From the time the drug begins to dissolve until dissolution is complete, concentration gradients are present within the dissolution vessel. These concentration gradients depend on the rate of agitation: as the rate of agitation is increased, the gradient becomes less pronounced.

If the time(s) of aliquoting is such that the drug is dissolving quickly when the aliquot is taken, special attention should be given to the location in the vessel from which the aliquot is removed. The concentration of dissolved drug will be highest near the bulk of undissolved drug and lowest at the points of lowest agitation in the vessel. Both extremes should be avoided, if possible, when taking aliquots. These locations will be found along the boundaries of the dissolution medium, near any remaining bulk of the solid-dosage form, and close to the stirrer.

Standard Solutions

In the analysis, the filtrate will be compared to a standard solution in virtually all cases. The composition and pH of the medium used for the standard solution should be a very close approximation to those of the aliquot under test. It is difficult, in many cases, to weigh an amount of standard material accurately and be assured that that amount will dissolve in the dissolution medium. The common practice is to dissolve a relatively large amount of standard material in a small amount of water-miscible solvent. An aliquot of this stock standard solution is diluted to a final volume with the dissolution medium. The presence of a small amount of water-miscible solvent in the standard solution should have no effect on the analysis. To confirm this assumption, several standard solutions of different known strengths should be prepared in the water-miscible solvent. Each of these standard solutions should be diluted in the dissolution medium such that each final solution has the same drug content. Each final solution will, however, have a different concentration of the water-miscible solvent, and analysis of these solutions will therefore demonstrate the effect, if any, of the water-miscible solvent.

Manual Aliquoting and Filtration

In filtering the aliquots taken for analysis, the common practice is to discard the first portion of filtrate. This practice washes the filter free of interferences and saturates the filter with drug so that none is removed from the portion of filtrate collected for analysis. The amount of filtrate to be discarded must be determined experimentally and then checked periodically thereafter. The amount of filtrate that must be discarded may change when one begins to use a new batch of the filter material, whether one is using a membrane filter, filter paper, cotton, etc. Different drugs adsorb to different degrees on these materials, and an experiment to determine the correct volume of filtrate to be discarded must be conducted for each drug and each type of filtration material to be used.

The common practice in taking manual aliquots involves the drawing of dissolution medium from the vessel with a syringe that is fitted with either a stainless-steel cannula or a glass tube butted against the end with rubber tubing. The cannula is removed, a filter holder (an adapter that holds a membrane filter) is fitted to the syringe, and a predetermined volume of filtrate is discarded (the remainder being collected in a suitable flask). From 3 to 6 min are required to withdraw and filter six aliquots.

It is obvious that aliquots cannot be drawn and filtered instantaneously and that there exists some uncertainty as

to the time that the aliquot is taken. The problem is further complicated if the solid-dosage form is still dissolving when the aliquot is removed. In many instances, an almost perfectly clear aliquot will be obtained because the undissolved particles are distributed on the bottom of the vessel and on the top of the solution. This situation will present itself more often with the basket than with the paddle and is most desirable because, if no particles are drawn from the midpoint of the solution, the rate of dissolution is zero for the solution in the syringe. In other instances, however, the aliquot drawn up into the syringe will contain particulate matter from the tablet being tested. If so, the turbulence created by the action of the syringe will accelerate dissolution of any undissolved drug present in the particles. Moreover, the particles drawn up into the syringe will almost never be representative of those left behind in the dissolution vessel. Particles drawn up into the syringe will continue to dissolve until the solution is filtered. Thus, the taking of manual aliquots involves compromise.

Certain methods call for replacement of dissolution medium. In practice, 10–50 ml, representing from 1% to 10% of the bulk of the solution, will usually have been drawn out. Such volumes have little effect on the dissolution rate in the bulk of the solution if the test is being carried out under unsaturated conditions. The major consideration is that the volume replaced must have had time to mix with the bulk of the solution before the next aliquot is taken.

If the aliquot, taken from the medium at 37°, is replaced with fresh dissolution medium at room temperature, the temperature of the dissolution medium in the kettle is lowered momentarily. The fresh dissolution medium will have a slightly greater density and will tend to fall through the larger volume in the kettle, causing unwanted turbulence. It is therefore recommended that, if the method calls for replacing the medium, the fresh dissolution medium should be preheated to 37°.

When conducting a dissolution profile, one must take aliquots from each vessel at the time intervals specified in the method. The best analytical technique is to use a fresh, clean, dry syringe and cannula for each aliquot. This technique requires many syringes and cannulas, however, and the chore of cleaning and drying the glassware becomes burdensome. It would be preferable to use the same syringe and cannula to take all the aliquots sequentially from a given vessel. In doing so, we must accept a slight decrease in the accuracy of the determinations, since a small amount of the previous aliquot will remain on the wall and plunger of the syringe and on the cannula wall, and this liquid will contaminate the next aliquot when it is drawn up into the syringe and cannula. One should therefore select syringes that will empty as completely as possible when the plunger is fully depressed.

A simple experiment will show how much of a given aliquot is retained in the syringe and cannula after the syringe plunger has been fully depressed. Weigh the dry syringe and cannula (weight A). Take an aliquot of dissolution medium, disconnect the cannula and let it drain, and weigh the filled syringe and drained cannula (weight B). Reconnect the cannula to the syringe, depress the syringe plunger, disconnect the cannula and let it drain, and weigh the emptied syringe and drained cannula (weight C). If

$$\frac{100 \text{ (weight C)}}{\text{weight B} - \text{weight A}}$$

is less than 2%, sequential contamination of the next aliquot will be small enough to ignore, and the same syringe and cannula may be used to take sequential aliquots from a given vessel with negligible effect on the test results.

Because of the design of certain filter holders (adapters that hold membrane filters), it may take a surprisingly large volume to adequately rinse out the old volume. Thus it is best to use a different filter holder for each aliquot unless experimentation shows that little error is introduced by using the same filter holder for a given vessel throughout a dissolution profile and that no filter clogging occurs.

Automated Aliquoting

Use of automated aliquoting systems is growing in our laboratory. In these flow-through systems, filtering of the dissolution medium takes place at the point of entry into the system. The filtered solution travels (at the discretion of the analyst) from the point of collection either into AutoAnalyzer cups (Technicon, Incorporated), or to an automated analytical system, or to waste, or back to the dissolution vessel. Filters of various materials and filtering ability are available. These systems may be conveniently used with all of our dissolution equipment.

Depending on the volume of aliquot necessary for analysis, the aliquot is collected over a period of 30–60 sec. This time period will be equally divided before and after the specified time of interest so that an averaging effect will take place. The lag time between filtration and collection is taken into account, and the system may be flushed at the discretion of the analyst before the aliquot is collected. By using pump tubes of the same pump rate and transfer tubing of the same length, it is possible to simultaneously obtain six aliquots within 10 sec of the specified time of interest. Under ideal conditions, it is possible to synchronize these aliquots within 2–3 sec of each other.

The filters may partially clog with repeated use. One can often foresee this problem by noting the volumes collected. If they decrease or vary with respect to one another, it is time to change the filters.

Because the volumes collected are small (circa 3 ml), an automated analysis of the drug content is necessary. The automated aliquoting devices are poorly suited for manual analysis of aliquots.

Though filters may clog and volumes collected are small, the use of automated devices is superior to manual collection of aliquots for profile work. Less manipulation is necessary, and the aliquots are collected at more precise time intervals.

Quality Control

Development of a simple, reliable procedure to measure and control the quality of results from a dissolution test is a desired but elusive goal. The use of standards, such

as the salicylic acid disks proposed by the USP, or the implementation of proficiency-testing regulations as proposed by FDA, may help in reaching this goal. At present, however, NCDA cannot recommend a total program of quality control for dissolution testing.

Quality control of all steps in the analytical portion of the procedure is possible and should be implemented. In other words, commencing with the withdrawal and filtration of the aliquot, all steps are similar to those of any routine chemical analysis. The following recommendation is intended to provide quality control of all analytical steps that follow the actual dissolution process.

A quality-control composite should be prepared from a sample that dissolves fairly quickly and that will reliably release 100% of the drug present. One tablet or capsule weight of powdered composite should be taken up in the volume of dissolution medium used for the test and shaken on a mechanical shaker, and an aliquot should be taken for analysis as specified in the dissolution test. The purpose of this test is to monitor the precision of the technique and method used to analyze the dissolution aliquots, and the results should be interpreted as they would be for any such quality-control sample.

Apparatus

In our laboratory, we routinely use either baskets or paddles as dissolution stirrers. These stirrers are used with two machines of different design, the FDA unit and the Hanson unit. Aliquots are taken manually or by an automated device. Techniques will change somewhat depending on which combination of stirrer, dissolution apparatus, and aliquoting method is being used.

Speed Control

Machines with variable speed control should be adjusted to the lower end of the specified tolerance just before the test is started. For example, if 100 rpm is specified for the test, the machine should be adjusted for 98–99 rpm at the beginning. The reason for adjusting variable-speed machines in this manner is that the speed tends to creep upward during the test. It is difficult to satisfactorily compensate for the drift by adjusting the control during the test. It is usually better to take the drift into account as described. The machine will rarely drift above the upper tolerance during a test run of 1–2 hr.

Staggered Tests

As discussed earlier, a finite time is required in order to take aliquots and collect filtered portions of them. If the dissolution test is started by immersing all six tablets or capsules simultaneously, the time from immersion of tablet or capsule number one to collection and filtration of its aliquot will be shorter than that for the remaining tablets or capsules. The last tablet or capsule will be in contact with dissolution medium for a substantially longer period than will the first.

One way to equalize the time between immersion of each tablet or capsule and the aliquoting-filtration step is to stagger the immersion time of each tablet or capsule (at 1- or 2-min intervals, for example). This interval gives the analyst time to complete the aliquoting-filtration step for each tablet or capsule before drawing the aliquot from the next vessel.

It is convenient to stagger dosage-form immersion when one is using the paddle method: at the desired intervals, the solid-dosage forms are simply dropped into the vessels and allowed to settle on the bottom. Staggered immersion is not always conveniently accomplished when one is using the basket method, however. With the old-model Hanson apparatus, it is possible to lower the baskets one at a time and then engage the clutch. It is much more difficult to follow this procedure with the new Hanson model because the shafts are held by O rings and do not slide up and down easily. Neither is it possible to stagger the initial dosage-form immersion with the FDA machines in the usual fashion.

The following optional procedure is suggested when the time of immersion must be staggered but the apparatus design will not permit the lowering of individual basket-shaft assemblies. Preheat the dissolution medium to 37° in a separate constant-temperature bath. Load the six baskets with tablets or capsules, lower them into empty vessels, and commence rotation. At 1- or 2-min intervals, pour the required amounts of the preheated medium into each vessel in a manner that will not subject the tablet or capsule to physical shock. A long-stemmed funnel of reasonably large diameter, arranged so as to deliver the stream down the side of the vessel, serves well. If the volume is added in 30–45 sec after time zero and the aliquot is taken and filtered after time x, then the first delay in time is partially canceled by the second delay in time. Although this procedure has been used successfully at NCDA, it is not common practice in our laboratory.

USP Basket Method

The description of the USP basket method in the *USP XX Comment Proof* specifies that the basket shaft shall be centered within 0.2 cm of the center line of the vessel; that the basket shall rotate without significant wobble; and that, after centering, the bottom of the basket shall be 2 cm from the bottom of the vessel (see Figure 1). A cover plate with a center porthole and other holes is placed over the vessel. Shaft rotation is maintained within ±5% or 2 rpm, whichever is less. Temperature is maintained at 37° ±0.5°.

In the basket method, according to the *USP XX Comment Proof,* aliquots are supposed to be drawn from the space midway between the surface of the dissolution medium and the top of the basket and not less than 1 cm from the vessel wall. This specification is inadequate. The first problem occurs when one is using 500 ml of dissolution medium, because the medium surface level and the top of the basket are nearly equal. At this stage, the specification is difficult to meet. After a suitable aliquot is removed and the test is continued (e.g., for digitoxin tablets), the medium level is below the top of the basket, and the specification becomes impossible to meet. The second problem arises from the words "not less than 1 cm from

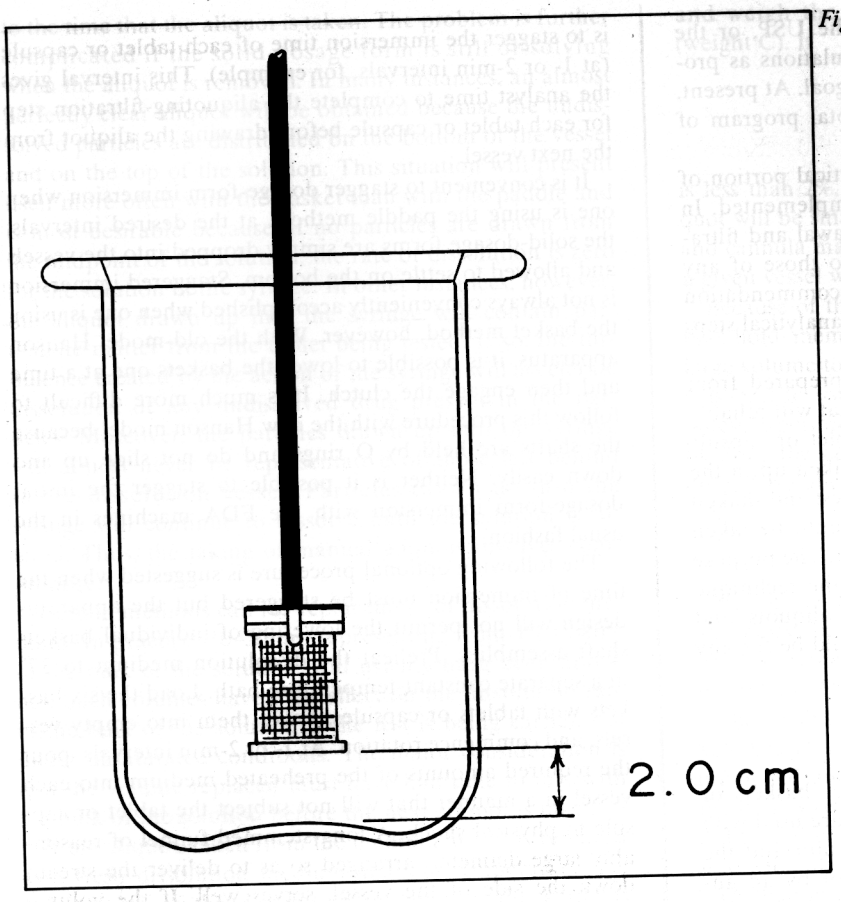


Figure 1: USP rotating-basket apparatus.

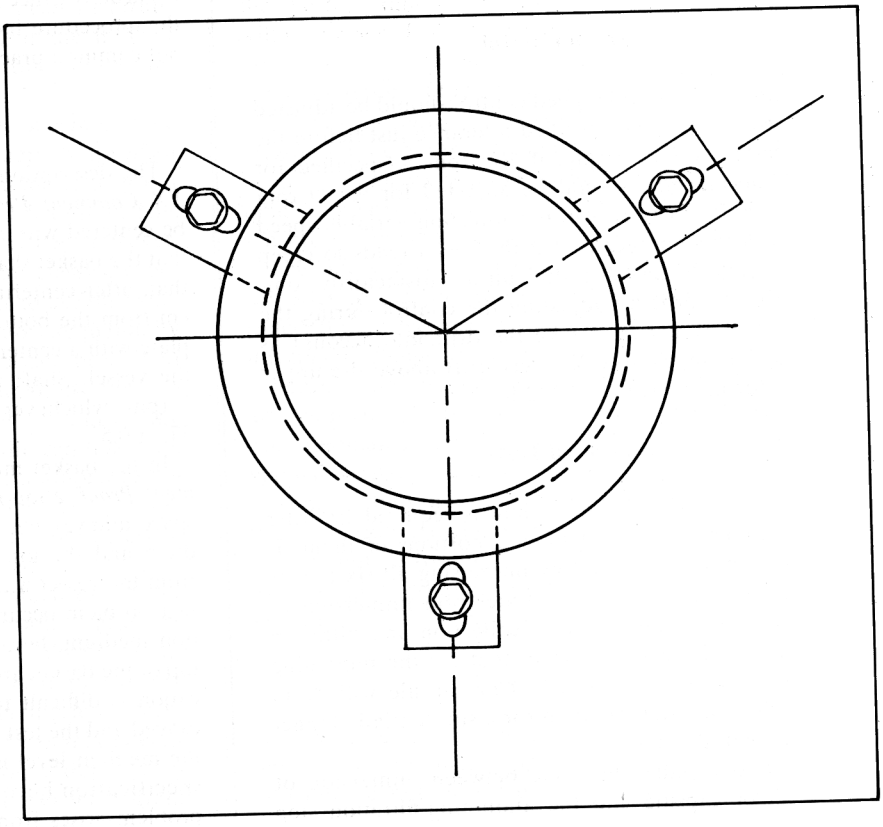


Figure 2: Use of fingers to center dissolution vessel on stirrer shaft for basket and paddle methods.

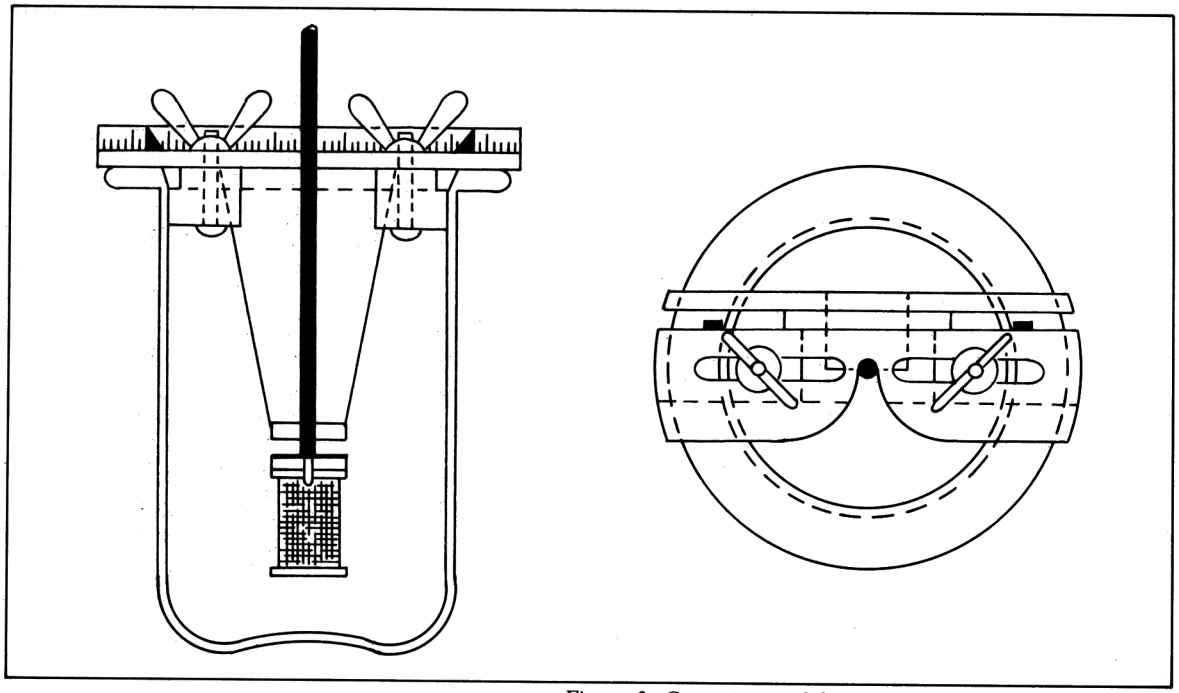


Figure 3: Centering tool for USP rotating-basket apparatus.

the vessel wall." The specification allows sampling from all points more than 1 cm from the vessel wall. If one must sample at or below the upper level of the basket, the specification presumably permits the tip of the aliquoting device to scrape against the side of the basket.

Therefore, NCDA recommends the following: aliquots should be withdrawn from the point that is midway between the surface of the dissolution medium and the bottom of the vessel and midway between the cylindrical edge of the basket and the wall of the vessel. Note that the point of sampling changes if the volume of dissolution medium in the vessel is diminished, i.e., if there is no replacement of fresh medium after an aliquot is taken.

Maintaining the center line of the vessel within 0.2 cm of the basket shaft calls for a precise method of adjusting the vessel to its proper position and locking it in place. We have modified our Hanson units as follows: the spring-loaded clips that are provided by Hanson to hold the vessels in place are removed and discarded; three fingers fabricated from aluminum are mounted around each vessel as shown in Figure 2 (a slot is provided in each finger to allow motion toward or away from the vessel); the vessel is centered (see below) on the stirrer shaft, the fingers are moved forward to pass under the lip of the flask and to touch the outer curved surface of the flask, and the fingers are tightened in place; each vessel is numbered and marked to allow its return to the correct position in the dissolution apparatus.

A tool for centering the basket shaft within the specified tolerance is now available (see Figure 3). The shafts should first be centered in the holes located in the plate that supports the vessels in the dissolution machine. The vessels are then inserted into the holes in the plate, centered with respect to the shafts, and locked into position with the fingers that are provided in equipment modified according to NCDA specifications.

Basket wobble can be created by a wobbling shaft, by a bent shaft, or by the basket's bottom being out of line with the top of the basket (caused by pulling the basket off the shaft too quickly). The shaft or basket should be replaced if the wobble is significant. An adequate supply of true shafts and baskets should be on hand, and those which are not true should be collected for repair. The clips should hold the basket to the shaft firmly. Shafts should be stored in a pipette rack when not in use, and care should be exercised in handling and storing the baskets. Baskets with burrs or other defects should not be used.

As vessels and baskets are not of uniform height, each basket must be individually adjusted to a position 2 cm from the bottom of its vessel. The vessels are then marked and used with their respective basket-shaft assembly in the same position each time. Adjustment should take place after the shafts have been centered. It is not sufficient to sight along the basket-shaft assemblies to see whether they appear to be even in height. Because of variation from vessel to vessel, the basket-shaft assemblies, when properly adjusted, are rarely uniform in height above a reference such as the bench top.

In making the adjustment on the Hanson unit, the head is set at a convenient working height, preferably as close to the bottom plate as possible. The shafts are then pulled down until each basket rests on the bottom of its vessel. The shafts are marked 2 cm below the ends of the chucks and then pushed back to the mark. Alternatively, one may

fabricate spacers 2 cm thick from corks or rubber stoppers, and these can be used to adjust the height of each basket.

In order to make the adjustment on the FDA machine, one must lower the head until it rests either on a block of wood or on the bottom plate. The shafts are lowered until each basket rests on the bottom of its vessel, and the set screws are tightened on the shafts. The head is then raised, a 2-cm spacer (such as a rubber stopper cut to 2 cm) is placed on the block or bottom plate, and the head is lowered to rest on the spacer. Another technique is to mark the shafts at the 2-cm point in a fashion similar to that described for the Hanson unit.

A nylon bearing for the center port of the cover plate, and spring clips to hold the cover plate and vessel in place are provided with the Hanson machines. The center nylon bearing should not be used as it may introduce further vibration and often causes the shaft to be pulled down during the test because of binding. On equipment modified according to NCDA specifications, the aluminum fingers provide an accurate centering action, a function not offered by the spring clips.

These steps apply when one is using the old-style (green) Hanson apparatus: when starting a test, disengage all six clutches; turn the motor on; lower basket number one into the medium; engage clutch number one within 5–10 sec after immersion of basket number one; lower basket number two and engage clutch number two, etc. The time from immersion of basket number one to engagement of clutch number six should be less than 1 min. For all six tablets or capsules, time zero is defined as the time the clutch is engaged on basket number one.

These steps apply to the new-style (blue) Hanson apparatus and to the FDA apparatus: when starting a test, turn the motor off; engage all six clutches on the Hanson apparatus; lower all six baskets simultaneously into their respective vessels (i.e., lower the head of the apparatus, not each basket-shaft assembly individually); turn the motor on within 5–10 sec after immersion of the baskets. Time zero is defined as the time the motor is switched on.

In all instances, the baskets should remain in motion while the analyst is taking aliquots. Turn the motor off or disengage the clutches only after the final aliquot has been taken.

The following procedure is recommended when one is using glass syringes to remove aliquots and membrane-filter devices to carry out subsequent filtration: at the prescribed time of sampling, begin drawing up the aliquot from vessel number one into syringe number one; lay syringe number one aside and immediately draw up the aliquot from vessel number two into syringe number two, and so forth (all six aliquots should be taken within 1 min); after all six aliquots are withdrawn, attach the membrane-filter devices and proceed to filter the content of syringe number one, then that of syringe number two, and so forth (all six aliquots should be filtered within 3 min — i.e., within 4 min from the time the first aliquot is removed). If the method requires the addition of fresh dissolution medium to replace the volume removed by aliquoting, this addition should take place after filtered portions of all six of the previous aliquots have been collected.

The location of the solid-dosage forms in the baskets should be noted just after beginning the test. Tablets should be on the bottom of the basket. Capsules should be near the top of the basket. If some of the solid-dosage forms being tested are near the top and others are on the bottom, the dissolution rate may be affected by location. It has been observed, for example, that a tablet will occasionally be suspended on an air bubble directly under the disk to which the basket is clipped. The air bubble is trapped under the disk when the basket-shaft assembly is lowered into the medium. Results for such suspended tablets are usually considerably lower than are results for tablets located on the bottom of the basket. Results from suspended tablets should be rejected.

USP Paddle Method

Solid-dosage forms that tend to float should be weighted with metal that is inert to the medium. A common practice used with capsules is to select a metal drill bit of slightly larger diameter than the capsule and to wrap several turns of inert wire around the drill bit to form a helix. The drill bit is removed from the helix, and the capsule is inserted into the helix and dropped into the vessel. There should be minimal movement of the solid-dosage form under the paddle until disintegration occurs. Causes of movement should be found and eliminated, if possible, as excessive movement of the solid-dosage form gives higher dissolution results.

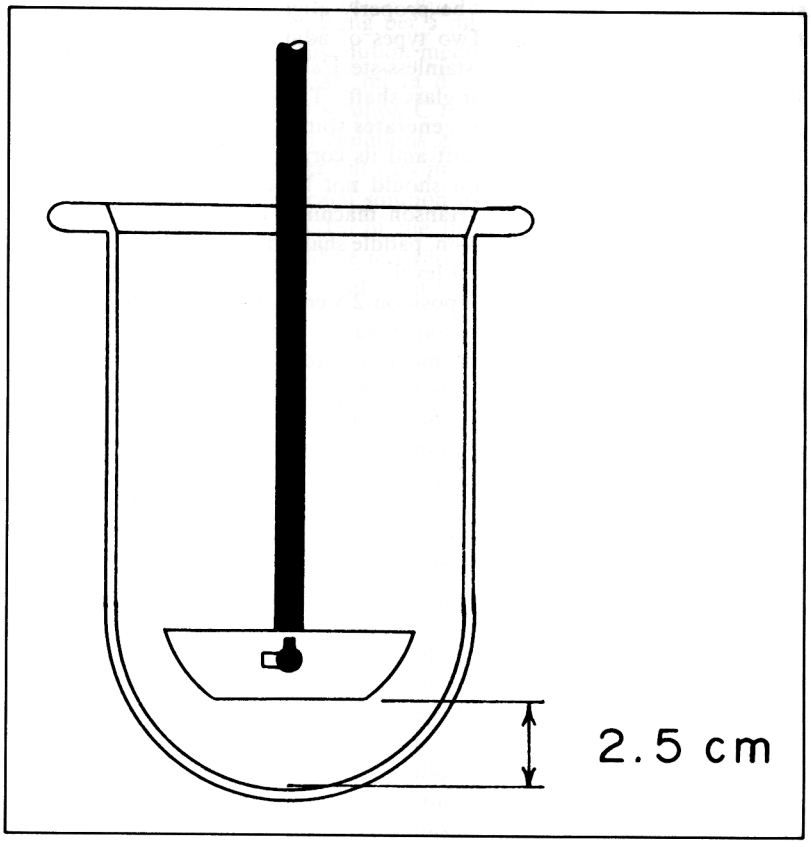
The paddle methodology in the *USP XX Comment Proof* specifies that the paddle shaft shall be centered within 0.2 cm of the center line of the vessel, that the shaft shall rotate without perceptible wobble, and that the bottom of the paddle shall be 2.5 $\pm$0.2 cm from the lowest inner surface of the vessel (see Figure 4). A cover plate with a center porthole and other holes is used. Shaft rotation is maintained within 4% of the nominal value. Temperature is maintained at 37° $\pm$0.5°. No instructions for drawing aliquots are provided. We recommend the following procedure: draw the aliquots from the point that is midway between the surface of the dissolution medium and the upper edge of the paddle and midway between the stirrer shaft and the wall of the vessel. Note that the point of sampling changes if the volume of dissolution medium in the vessel is diminished, i.e., if there is no replacement of fresh medium after an aliquot is taken.

It is imperative that the paddle shafts be vertical, that the vessels be resting on a horizontal plane, and that the vessels be centered properly. Special care should be taken to see that these conditions are met.

The plate which holds the vessels is leveled, using a carpenter's level for measurement. Check the paddle shafts for verticality by placing the edge of the blade of a combination square with level against the shaft and noting the displacement of the bubble in the handle of the square. Alignment tools are used to center the paddle shafts in the same way that they are used in centering the basket shafts.

Paddle wobble may arise from several sources. The paddle shaft may itself be bent or misaligned in its chuck, while on the older Hanson and FDA machines, a ¼-in. adapter must be used with the ⅜-in. paddle shaft, and the

Figure 4: USP paddle apparatus.



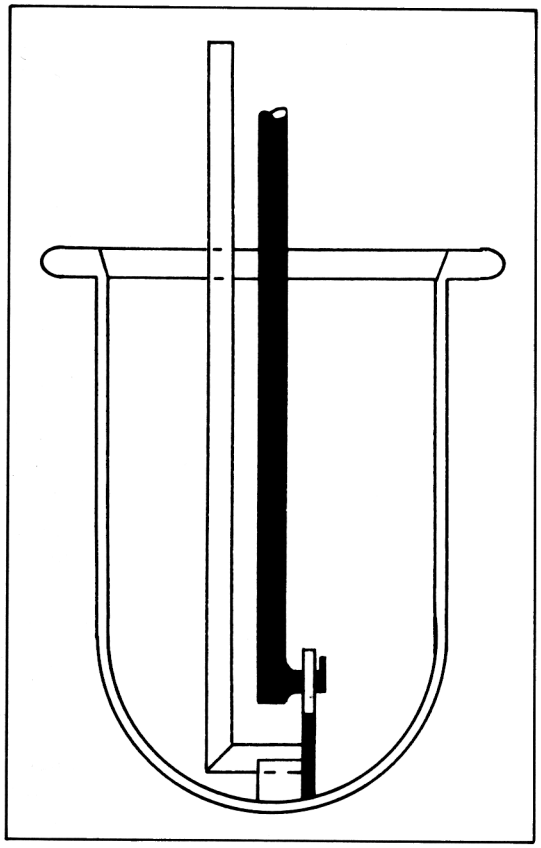


Figure 5: Spacer tool used to adjust height of paddle.

sleeve of the adapter may not be properly aligned with the axis of the paddle shaft. Two types of adapters are available, one for the coated stainless-steel shafts from Hanson Corporation and one for glass shafts. The Hanson adapter-and-shaft combination generates some wobble, but much less than the glass shaft and its corresponding adapter. This latter combination should not be used in dissolution testing. The newer Hanson machines can be converted to accommodate the ⅜-in. paddle shafts directly, thus reducing wobble to its lowest level.

The paddles are adjusted to a position 2.5 cm from the bottom of the vessel in much the same way as the basket is adjusted, except that the placement is made with an NCDA-developed spacer tool (see Figure 5). Once the shafts are properly centered, this tool will locate the paddle correctly in relation to the lowest point on the inner surface of the vessel. As the paddles tend to become loose on the shafts, a Teflon washer may be inserted between the paddle and shaft to provide the tension required to keep the paddle in the correct horizontal position during the test. Such washers may be cut from sheets of Teflon or from bottle-cap liners made of Teflon.

Ideally, the upper portion of each vessel would be perfectly cylindrical, and its bottom would be a perfect hemisphere. These vessels are currently being manufactured by Kimble Products of Owens-Illinois; they are made one at a time by manually blowing a molten mass of glass into a mold. As a result, the vessels are not uniform with respect to weight, inside diameter, and inside curvature. We have found statistically significant differences in dissolution rates when the same product is tested in different vessels. At present, FDA and USP are working with Kimble to develop suitable vessel specifications. Meanwhile, the inside surface of each vessel must be carefully inspected for abnormalities. The flange must be perpendicular to the walls of the vessel, and the lowest point in the vessel must be in line with the vertical axis of the paddle.

When starting a test, turn on the motor and, if necessary, engage the clutches. Stagger the introduction of solid-dosage units at 1- or 2-min intervals, and use the same interval in the aliquoting step described below. With all six paddles rotating in their dissolution medium, drop tablet or capsule number one into vessel number one, and call this time "time zero" for unit number one. After the interval, drop tablet or capsule number two into vessel number 2, and call this time "time zero" for unit number two, and so forth. When taking aliquots, allow the paddles to remain in motion. Turn the motor off or disengage clutches only after the final aliquot has been removed.

The following procedure is recommended when one is using glass syringes to remove aliquots and membrane-filter devices for subsequent filtration: at the prescribed sampling time, begin to draw the aliquot from vessel number one into syringe number one; attach a membrane-filter device to syringe number one and collect a portion of the filtered aliquot from syringe number one; if the method so requires, add fresh dissolution medium to vessel number one to replace the volume removed in the aliquot; after the predetermined 1- or 2-min interval has passed, repeat the sequence with vessel number 2, and so forth. The comments made earlier regarding temperature and shaft rotation in variable-speed machines using the basket method apply equally to the paddle method.

Laboratory Procedures

The foregoing discussion has touched on all the critical aspects of dissolution testing that we have identified to date. We have found it useful to reduce this rather general discussion to a set of specific laboratory procedures for use by chemists and technicians, and we offer these procedures below.

Preliminary Experiments

Deaeration of Medium

Note: This test is optional. It should be run, at the discretion of the analyst, when the deaerated medium has been allowed to stand at room temperature long enough to permit partial reequilibration of the medium with the atmosphere.

1. Transfer the amount of deaerated medium specified in the method into a dissolution vessel, place the vessel in the apparatus, and allow the medium to assume the temperature of the water bath (37°).
2. Start the motor, engage the clutch, and allow the stirrer (paddle or basket) to rotate at the speed given in the method for the time required in the test.
3. Observe the stirrer and the walls of the vessel. There should be no air bubbles.

Calibration of Vessel Used to Dispense Medium into Dissolution Vessels

1. Select the vessel (usually a graduated cylinder).
2. Fill the vessel with water to the mark that represents the volume of dissolution medium called for in the method.
3. Deliver the water in the vessel into a tared beaker, and, from the weight of the delivered medium, calculate its volume. The tolerance of the calculated volume is 1%, e.g., ±5 ml in 500 ml.

Calibration of Vessel(s) Used to Aliquot (and Replace) Dissolution Medium

Note: Other experimental plans of equivalent accuracy and precision may be substituted.

1. Select vessels – usually a syringe for removal of the aliquot and, if required, a graduated cylinder for replacement of the aliquot with fresh medium.
2. Place the required volume of dissolution medium in a tared vessel, weigh the vessel, and calculate the net weight of the medium.
3. Remove aliquots as directed in the method, using the vessel selected in step 1.
4. Replenish the volume with fresh medium, if required by the method, using the vessel selected in step 1.
5. Reweigh the tared vessel and, from the net weight, calculate the final volume. The tolerance is 1% of the final volume, e.g., ±9 ml in 900 ml.

Example 1. The initial volume of medium is 500 ml. At 15, 30, 45, and 60 min, a 25-ml aliquot is removed for analysis. After each aliquot is taken at 15, 30, and 45 min, 25 ml of fresh dissolution medium are added to replace the volume of the aliquots removed.

Calculate. A 1% uncertainty in volume of dissolution medium during the test allows for a medium volume of 500 ±5 ml. Therefore, cumulative error in aliquoting and replacing medium should not exceed 5 ml.

Experiment. (Run at room temperature.) Place 500 ml of medium in a tared vessel, weigh it, and calculate the net weight of the medium. Employing the devices selected for use in the method (syringe, pipette, graduated cylinder, etc.), remove three 25-ml aliquots and replace them with three 25-ml portions of fresh medium. Reweigh the vessel and from the net weight of the medium calculate the final volume. The tolerance is 495–505 ml.

Example 2. The initial volume of dissolution medium is 500 ml. At 30 and 60 min, a 100-ml aliquot is removed for analysis. The volume of dissolution medium taken at 30 min is not replaced.

Calculate. A 1% uncertainty in volume of dissolution medium at 60 min equals 400 ±4 ml. Therefore, cumulative error in aliquoting (only one aliquot in this instance) should not exceed 4 ml.

Experiment. (Run at room temperature.) Place 500 ml of medium in a tared vessel, weigh it, and calculate the net weight of the medium. Employing the device selected for use in the method (syringe, pipette, etc.), remove one 100-ml aliquot. Reweigh the vessel and from the net weight of the medium calculate the final volume. The tolerance is 396–404 ml.

Effect of Organic Solvent in Standard Solutions

Note: Ignore this section if it is possible to prepare the standard solution by directly dissolving the standard in the dissolution medium without the aid of an organic solvent.

1. Prepare three stock standard solutions of the drug in the organic solvent so that the ratios of their concentrations are 1:2:4 and so that the intermediate concentration is equal to that proposed for use in the method.
2. Prepare dilutions of each stock standard solution in dissolution medium so that the final concentration of each is equal to 100% of the anticipated amount of drug at the 100% dissolution level.
3. Analyze each solution as directed in the method. The tolerance is 99%–101% recovery.

Example 1. Tablets labeled as containing 5 mg of drug are to be tested in 500 ml of dissolution medium (water). One-hundred-percent dissolution will yield a concentration of 10 mg of drug per liter. The drug is difficult to dissolve in water but is readily soluble in alcohol. We want to prepare our standard solution by dissolving 10 mg of drug, accurately weighed, in 5 ml of alcohol and diluting it to 1 L with dissolution medium.

Experiment. Prepare three stock standard solutions in alcohol: solution A containing 5 mg of drug per 5 ml; solution B containing 10 mg per 5 ml; and solution C containing 20 mg per 5 ml. Dilute 5 ml of solution A to 500 ml in dissolution medium (solution X); 5 ml of solution B to 1000 ml in dissolution medium (solution Y); and 5 ml of solution C to 2000 ml in dissolution medium (solution Z). Solutions X, Y, and Z all contain 10 mg of drug per liter but vary in alcohol content.

Analyze each solution as directed in the method. The tolerance is 1% of the theoretical amount; i.e., 9.9–10.1 mg/L should be recovered. If the influence of the alcohol exceeds 1%, a different organic solvent should be selected and tested.

Effect of Filtration Step — Part 1

Note: If a small amount of organic solvent is present in the standard solution (see previous section), the results from Effect of Filtration Step — Part 1 may be substantially different than those from Effect of Filtration Step — Part 2.

1. Prepare a standard solution, in dissolution medium, equivalent to the 100% dissolution level.
2. Filter a portion of the standard solution through the proposed filtration device and collect the filtrate in 5-ml portions.
3. Analyze each 5-ml portion of filtrate, using the unfiltered standard solution as the reference standard solution. The results should approach a final, reproducible value.
4. The tolerance is 99%–101% recovery. Make a note of the volume of filtrate that should be discarded before the portion for analysis is collected.

Effect of Filtration Step — Part 2

1. Subject a capsule or tablet to the dissolution test for the period of time specified in the method.
2. Remove a portion of the dissolution medium and mix it thoroughly.
3. Filter the solution and collect the filtrate in 5-ml portions.
4. Analyze each 5-ml portion of filtrate using the unfiltered standard solution (previous section, step 1) as the reference standard solution. The results should approach a final, reproducible value.
5. Make a note of the volume of filtrate that must be discarded in order to obtain the correct result.

Effect of Filtration Step — Part 3

Note: This section applies only when one is conducting a dissolution profile (i.e., a dissolution test in which aliquots are taken at more than one time), and only when one wishes to reuse a given filtration device to filter all the sequential aliquots from a given vessel. If a fresh filtration device is to be used for each aliquot from a given vessel, this section may be ignored.

This is a severe test, for the extreme changes in sequential concentrations specified below are never encountered in practice. Hence, the tolerances are set rather widely.

1. Using dissolution medium as the solvent, prepare a standard solution equivalent to the 100% dissolution level.

2. Using the optimum filtration technique (which was determined in the Effect of Filtration Step – Part 1), prepare a filtered portion of the standard solution (solution A).
3. Using the same filtration device and the same technique, prepare a filtered portion of blank dissolution medium (solution B).
4. Using the same filtration device and the same technique, prepare another filtered portion of the standard solution (solution C).
5. Analyze solutions A, B, and C, using the unfiltered standard solution (step 1) as the reference standard solution.
6. The tolerance for solution A is 99%–101% recovery. The tolerance for solution B is that no more than 5% of the concentration of solution A shall be found. The tolerance for solution C is 95%–101% recovery. If the tolerances for solutions B or C are exceeded, there may be excessive dead volume in the filtration device, and it may be necessary to discard larger volumes of filtrate before collecting a portion for analysis.

Procedure for USP Rotating-Basket Apparatus

Inspection and Alignment of Apparatus

1. Inspect baskets, shafts, and vessels for cleanliness.
2. Select the gear drive or adjust the speed control to obtain the revolution speed specified in the method. Turn on the motor drive. Measure the shaft revolutions per minute by manual count or by a revolution-counting device. Allow the machine to run for the time specified in the dissolution-test procedure. At that time, again measure the shaft revolutions. The tolerance for deviation from the speed specified in the method is ±5% or 2 rpm, whichever is less.
3. Measure the temperature of the water bath. The tolerance is 37° ±0.5°. Make sure that vibration from the circulation device in the water bath is not transmitted to the dissolution medium in the vessels, either directly – through the plate supporting the vessels – or indirectly – through the water surrounding them. Do not mount the circulation device on the bath. The use of a transparent water bath is recommended.
4. Inspect the baskets for deformation, burrs, or other defects.
5. Inspect the shafts for straightness. Install the shafts, turn on the motor, engage the clutches, and measure the amount of wobble by placing a runout gauge against each shaft just above the spring clips. The tolerance is 1 mm (0.04 in.).
6. Level the entire apparatus. Adjust the head on its support so that the shafts are exactly vertical. Use a square with a bubble level to check the verticality of each shaft.
7. Using the alignment tool, adjust the position of the drive head so that the shafts are as nearly centered as possible in the six holes in the plate that supports the vessels.
8. Repeat steps 6 and 7 until no further adjustments are needed.
9. Place the vessels in their holes. Use the alignment tool to center each vessel with respect to the vertical axis of its shaft. The tolerance is 2 mm. Tighten the fingers against the vessel to prevent movement during the test. Mark each flask so that it can be replaced in exactly the same position.
10. Adjust each basket-shaft assembly so that the basket is 2 cm above the inner floor of the vessel. The tolerance is 2 mm. Mark each shaft so that it can be returned to the correct height.

Starting the Test

1. Measure the temperature of the medium in each dissolution vessel. The tolerance is 37° ±0.5°.
2. Load the baskets with capsules or tablets. Proceed to step 3 or 4.
3. Old-style (green) Hanson apparatus.
   a. Disengage all six clutches.
   b. Turn the motor on.
   c. Lower basket number one into the medium.
   d. Engage clutch number one within 5–10 sec of immersion of basket number one.
   e. Lower basket number two into the medium.
   f. Engage clutch number two within 5–10 sec of immersion of basket number two.
   g. Repeat steps e and f for basket-shaft assemblies three through six.
4. New-style (blue) Hanson apparatus and FDA apparatus.
   a. Turn the motor off.
   b. Engage all six clutches on the Hanson apparatus.
   c. Lower the head and submerge all six baskets in the medium.
   d. Turn the motor on within 5–10 sec of baskets' immersion.

Location of Tablets

1. Examine the position of each tablet in its basket.
2. Reject results from tablets that are suspended from air bubbles. Analyze additional tablets to compensate for rejected data.

Taking Aliquots

1. Do not turn the motor off and do not disengage the clutches. Draw the aliquots from the point midway between the surface of the dissolution medium and the bottom of the vessel and midway between the cylindrical edge of the basket and the wall of the vessel.
2. Draw an aliquot from vessel number one.
3. Draw an aliquot from vessel number two.
4. Repeat step 3 for vessels three through six.
5. Filter aliquot number one.
6. Filter aliquot number two.
7. Repeat step 6 for aliquots three through six.
8. If required, add fresh medium, preheated to 37°, to replace the volume removed in the aliquots.

Procedure for USP Paddle Apparatus

Inspection and Alignment of Apparatus

1. Inspect paddles, shafts, and vessels for cleanliness.
2. Select the gear drive or adjust the speed control to obtain the revolution speed specified in the method. Turn on the motor drive. Measure the shaft revolutions per minute by manual count or by a revolution-counting device. Allow the machine to run for the time specified in the dissolution test. At that time, again measure the shaft revolutions. The tolerance for deviation from the speed specified in the method is ±4% or 2 rpm, whichever is less.
3. Measure the temperature of the water bath. The tolerance is 37° ±0.5°. Make sure that vibration from the circulation device in the water bath is not transmitted to the dissolution medium in the vessels, either directly – through the plate supporting the vessels – or indirectly – through the water surrounding them. Do not mount the circulation device on the bath. The use of a transparent water bath is recommended.
4. Inspect paddle-shaft assemblies for defects. If the paddle is loose on the shaft, cut a small washer from a sheet of Teflon and place it between the shaft button and the paddle socket to provide the needed friction. Adjust each paddle so that it's exactly perpendicular to its shaft. The shorter edge of the paddle faces down.
5. Inspect the shafts for straightness. Install shafts, start motor, engage clutches, and measure the amount of wobble by placing a runout gauge against each shaft just above the paddle. The tolerance is 1 mm (0.04 in.).
6. Level the entire apparatus. Adjust the head on its support so that the shafts are exactly vertical. Use a square with a bubble level to check the verticality of each shaft.
7. Using the alignment tool, adjust the position of the drive head so that the shafts are centered as exactly as possible in the six holes in the plate that supports the vessels.
8. Repeat steps 6 and 7 until no further adjustments are needed.
9. Place the vessels in their holes. Use the alignment tool to center each vessel with respect to the vertical axis of its shaft. The tolerance is 2 mm. Tighten the fingers against the vessel to prevent movement during the test. Mark each flask so that it can be replaced in exactly the same position.
10. Using the spacer tool, adjust each paddle-shaft assembly so that each paddle is 2.5 cm above the inner floor of its vessel. The tolerance is 2 mm. Mark each shaft so that it can be returned to the correct height.

Starting the Test

1. Measure the temperature of the medium in each dissolution vessel. The tolerance is 37° ±0.5°.
2. Turn on the motor and engage all six clutches.
3. Drop tablet or capsule number one into vessel number one at a point near the wall of the vessel.
4. After a selected, precisely timed interval, drop tablet or capsule number two into vessel number two at a point near the wall of the vessel.
5. Repeat step 4 for tablets or capsules three through six.

Taking Aliquots

1. Do not turn the motor off and do not disengage the clutches. Draw the aliquots from the point midway between the surface of the dissolution medium and the upper edge of the paddle and midway between the stirrer shaft and the wall of the vessel.
2. Draw an aliquot from vessel number one.
3. Filter the aliquot from vessel number one.
4. If required by the method, replace the volume withdrawn from vessel number one with fresh dissolution medium preheated to 37°.
5. After the selected, precisely timed interval, draw an aliquot from vessel number two.
6. Filter the aliquot from vessel number two.
7. If required by the method, replace the volume withdrawn from vessel number two with fresh dissolution medium that has been preheated to 37°.
8. Repeat steps 5, 6, and 7 for aliquots three through six.

Conclusion

Dissolution tests are critical and difficult to carry out properly. If one is to obtain correct results, care and attention must be given to those aspects that have been identified as crucial. It is our hope that other scientists will share their findings and techniques so that dissolution testing may be advanced to a reproducible and reliable scientific procedure.

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