(2040) Disintegration and Dissolution of Dietary Supplements

INTRODUCTION

This general chapter is provided to determine compliance with the disintegration and dissolution standards for dietary supplements where stated in the individual monographs.

For the purposes of this chapter, dietary supplement dosage forms have been divided into three categories: Vitamin–Mineral Dosage Forms, Botanical Dosage Forms, and Dietary Supplements Other Than Vitamin–Mineral and Botanical Dosage Forms. Vitamin–Mineral Dosage Forms includes articles prepared with vitamins, minerals, or combinations of these dietary ingredients (e.g., USP dietary supplements Class I to Class VI, described below). Botanical Dosage Forms comprises formulations containing ingredients of botanical origin, including plant materials and extracts. Dietary Supplements Other Than Vitamin–Mineral and Botanical Dosage Forms encompasses dietary supplements formulated with lawfully recognized dietary ingredients that are different from those pertaining to the two foregoing categories (e.g., amino acids, chondroitin, and glucosamine).

Where a dietary supplement represents a combination of the categories mentioned above, and there is a difference between the requirements for the individual categories, the more stringent requirement applies.

Dissolution testing as described in this chapter is a quality-control tool to enable the performance of dietary supplements to be routinely assessed.

DISINTEGRATION

This test is provided to determine whether dietary supplement tablets or capsules disintegrate within the prescribed time when placed in a liquid medium at the experimental conditions presented below. Compliance with the limits on Disintegration stated in the individual monographs for dietary supplements is required except where the label states that the products are intended for use as troches, are to be chewed, or are designed as extended-release dosage forms. In the case of tablets, the condition of dissolution is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core.

Apparatus

Apparatus A—Use the Apparatus described under Disintegration (701) for tablets or capsules that are not greater than 18 mm long. For larger tablets or capsules, use Apparatus B.

Apparatus B—The apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 53 mm and not more than 57 mm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 15 mm below the surface of the fluid and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become submerged. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-Rack Assembly—The basket-rack assembly consists of three open-ended transparent tubes, each 17.5 ± 2.5 mm long and having an inside diameter of 32.0 to 34.6 mm and a wall 2.0 to 3.0 mm thick; the tubes are held in a vertical position by two plastic plates, each about 97 mm in diameter and 7.5 to 10.5 mm in thickness, with three holes, each about 33 to 34 mm in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is a 2.5-mm (325-inch) W. and M. gauge wire cloth having a plain square weave. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plastic plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.

Disks—Each tube is provided with a perforated cylindrical disk 15.3 ± 0.15 mm thick and 31.4 ± 0.13 mm in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Seven 3.15 ± 0.1-mm holes extend between the ends of the cylinder, one of the holes being spaced on a 4.2 ± 0.1-mm radius from it. All surfaces of the disks are smooth.

Procedure

Uncoated Tablets—Place 1 tablet in each of the tubes of the basket and, if prescribed, add a disk to each tube. Operate the apparatus, using water or the specified medium as the immersion fluid, maintained at 37 ± 2°. At the end of 30 minutes, lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Plain Coated Tablets—Place 1 tablet in each of the tubes of the basket and, if the tablet has a soluble external sugar coating, immerse the basket in water at room temperature for 5 minutes. Then, if prescribed, add a disk to each tube, and operate the apparatus, using water or the specified medium as the immersion fluid, maintained at 37 ± 2°. At the end of 30 minutes, lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not fewer than 16 of the total of 18 tablets tested disintegrate completely.

1 An apparatus and disks meeting these specifications are available from Varian Inc., 3000 Weston Parkway, Cary, NC 27513, or from laboratory supply houses.

2 The use of automatic detection employing modified disks is permitted where the use of disks is specified or allowed. Such disks must comply with the requirements for density and dimensions given in this chapter.
Delayed-Release (Enteric-Coated) Tablets—Place 1 tablet in each of the six tubes of the basket, and if the tablet has a soluble external sugar coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 0.5°C as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS, maintained at 37 ± 0.5°C, as the immersion fluid for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Buccal Tablets—Apply the test for Uncoated Tablets. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets—Apply the test for Uncoated Tablets. At the end of the time limit specified in the individual monograph, all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Hard Shell Capsules—Apply the test for Uncoated Tablets, using as the immersion fluid, maintained at 37 ± 0.5°C, a 0.05 M acetate buffer prepared by mixing 2.99 g of sodium acetate trihydrate and 1.66 mL of glacial acetic acid with water to obtain a 1000-mL solution having a pH of 4.50 ± 0.05. Attach a removable wire cloth, as described under Basket-Rack Assembly, to the surface of the upper plate of the basket-rack assembly. At the end of 30 minutes, lift the basket from the fluid, and observe the capsules: all of the capsules disintegrate except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not fewer than 16 of the total of 18 capsules tested disintegrate completely.

Soft Shell Capsules—Proceed as directed under Rupture Test for Soft Shell Capsules.

Use of Disks—

VITAMIN–MINERAL DOSAGE FORMS—Add a disk to each tube unless otherwise specified in the individual monograph.

BOTANICAL DOSAGE FORMS—Omit the use of disks unless otherwise specified in the individual monograph.

DIETARY SUPPLEMENTS OTHER THAN VITAMIN–MINERAL AND BOTANICAL DOSAGE FORMS—Omit the use of disks unless otherwise specified in the individual monograph.

NOTE—The use of disks for enteric-coated tablets is not permitted.

RUPTURE TEST FOR SOFT SHELL CAPSULES

Medium: water; 500 mL.

Apparatus—Use Apparatus 2 as described under Dissolution (711), operating at 50 rpm.

Time: 15 minutes.

Procedure—Place 1 capsule in each vessel, and allow the capsule to sink to the bottom of the vessel before starting rotation of the blade. Use sinkers if the capsules float. Observe the capsules, and record the time taken for each capsule shell to rupture.
DISSOLUTION CONDITIONS FOR FOLIC ACID

NOTE—Perform this test under light conditions that minimize photo degradation.

Medium: water; 900 mL. If the units tested do not meet the requirements for dissolution in water, test 6 additional dosage units for dissolution in a medium of 900 mL of 0.05 M pH 6.0 citrate buffer solution, prepared by mixing 9.5 mL of 0.1 M citric acid monohydrate and 40.5 mL of 0.1 M sodium citrate dihydrate in a 100-mL volumetric flask, diluting with water to volume, mixing, and adjusting to a pH of 6.0 by using either 0.1 M hydrochloric acid or 0.1 M sodium hydroxide solution.

Apparatus 1: 100 rpm, for capsules.
Apparatus 2: 75 rpm, for tablets.
Time: 1 hour.

NOTE—Compliance with the dissolution requirements for folic acid does not exempt the product from dissolution testing of the pertinent index vitamin or the corresponding index mineral.

DISSOLUTION CONDITIONS FOR INDEX VITAMINS AND INDEX MINERALS

Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 1: 100 rpm, for capsules.
Apparatus 2: 75 rpm, for tablets.
Time: 1 hour.

For formulations containing 25 mg or more of the index vitamin, riboflavin, use the following conditions:

Medium: 0.1 N hydrochloric acid; 1800 mL.
Apparatus 1: 100 rpm, for capsules.
Apparatus 2: 75 rpm, for tablets.
Time: 1 hour.

NOTE—Compliance with dissolution requirements for the pertinent index vitamin or index mineral does not exempt the product from dissolution testing of folic acid, if present.

SELECTION OF INDEX VITAMINS AND INDEX ELEMENTS

Compliance with the dissolution requirements for dietary supplements representing combinations of water-soluble vitamins (Water-Soluble Vitamins Capsules and Water-Soluble Vitamins Tablets) and combinations of oil- and water-soluble vitamins (Oil- and Water-Soluble Vitamins Capsules and Oil- and Water-Soluble Vitamins Tablets) is determined by measuring the dissolution of a single index vitamin from the water-soluble vitamins present. Riboflavin is the index vitamin when present in the formulation. For formulations that do not contain riboflavin, pyridoxine is the index vitamin. If neither riboflavin nor pyridoxine is present in the formulation, the index vitamin is niacinamide (or niacin), and in the absence of niacinamide (or niacin), the index vitamin is thiamine. If none of the above four water-soluble vitamins is present in the formulation, the index vitamin is ascorbic acid.

Compliance with the dissolution requirements for dietary supplements representing combinations of minerals (Minerals Capsules and Minerals Tablets) is determined by measuring the dissolution of only one index element. Iron is the index element when present in the formulation. For formulations that do not contain iron, the index element is calcium. If neither iron nor calcium is present, the index element is zinc, and in the absence of all three of these elements, magnesium is the index element.

Compliance with dissolution requirements for dietary supplements representing combinations of water-soluble vitamins and minerals (Water-Soluble Vitamins with Minerals Capsules and Water-Soluble Vitamins with Minerals Tablets) and combinations of oil- and water-soluble vitamins and minerals (Oil- and Water-Soluble Vitamins with Minerals Capsules and Oil- and Water-Soluble Vitamins with Minerals Tablets) is determined by measuring the dissolution of one index water-soluble vitamin and one index element, designated according to the respective hierarchies described above.

PROCEDURES

In the following procedures, combine equal volumes of the filtered solutions of the 6 individual specimens withdrawn, and determine the amount of folic acid or the index vitamin or element dissolved, based on the average of 6 units tested. Make any necessary modifications including concentration of the analyte in the volume of test solution taken. Use the Medium for preparation of the Standard solution and dilution, if necessary, of the test solution.

Folic Acid—Determine the amount of C₁₉H₁₉N₇O₆ dissolved by employing the procedure set forth in the Assay for folic acid under Oil- and Water-Soluble Vitamins with Minerals Tablets, in comparison with a Standard solution having a known concentration of USP Folic Acid RS in the same Medium.

Niacin or Niacinamide, Pyridoxine, Riboflavin, and Thiamine—Determine the amount of the designated index vitamin dissolved by employing the procedure set forth in the Assay for niacin or niacinamide, pyridoxine, riboflavin, and thiamine under Water-Soluble Vitamins Tablets.

Ascorbic Acid—Determine the amount of C₂₀H₂₀O₈ dissolved by adding 10 mL of 1.0 N sulfuric acid and 3 mL of starch TS to 100.0 mL of test solution, and titrating immediately with 0.01 N iodine VS. Perform a blank determination, and make any necessary correction.

Iron, Calcium, Magnesium, and Zinc—Determine the amount of the designated index element dissolved by employing the procedure set forth in the appropriate Assay under Minerals Capsules.

TOLERANCES

The requirements are met if not less than 75% of the labeled content of folic acid and not less than 75% of the labeled content of the...
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index vitamin or the index element from the units tested is dissolved in 1 hour.

**Botanical Dosage Forms**

Compliance with dissolution requirements necessitates the testing of 6 dosage units individually, or testing 2 or more dosage units in each of the 6 vessels of the dissolution apparatus, and measuring the dissolution of one or more index/marker compound(s) or the extract specified in the individual monograph.

**PROCEDURES**

Combine equal volumes of the filtered solutions of the 6 or more individual specimens withdrawn, and use the pooled sample as the test solution. Determine the average amount of index or marker compound(s) or the extract dissolved in the pooled sample by the Procedure specified in the individual monograph. Make any necessary modifications, including concentration of the analyte in the volume of the test solution taken. Use the Medium for preparation of the Standard solution and dilution, if necessary, of the test solution.

**INTERPRETATION**

*Pooled Sample*—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of the index or marker compound(s) or the extract dissolved from the pooled sample conform to the accompanying acceptance table. The quantity, \( Q \), is the amount of dissolved index or marker compound(s) or the extract specified in the individual monograph, expressed as a percentage of the labeled content so that these values and \( Q \) are in the same terms.

**Acceptance Table for a Pooled Sample**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number Tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>( S_1 )</td>
<td>6</td>
<td>Average amount dissolved is not less than ( Q + 10% )</td>
</tr>
<tr>
<td>( S_2 )</td>
<td>6</td>
<td>Average amount dissolved ((S_1 + S_2)) is equal to or greater than ( Q + 5% )</td>
</tr>
<tr>
<td>( S_3 )</td>
<td>12</td>
<td>Average amount dissolved ((S_1 + S_2 + S_3)) is equal to or greater than ( Q )</td>
</tr>
</tbody>
</table>

**Dietary Supplements Other Than Vitamin–Mineral and Botanical Dosage Forms**

Unless otherwise stated in the individual monographs for dietary supplement dosage forms in this category, compliance requires the testing of 6 individual units, measuring the dissolution of the dietary ingredient as the average of the 6 units tested.

**PROCEDURES**

Combine equal volumes of the filtered solutions of the 6 specimens withdrawn, and use the pooled sample as the test solution. Determine the average amount of dietary ingredient dissolved in the pooled sample by the Procedure specified in the individual monograph. Make any necessary modifications, including concentration of the analyte in the volume of the test solution taken. Use the Medium for preparation of the Standard solution and for dilution, if necessary, of the test solution.

**TOLERANCES**

Because of the diversity of chemical characteristics and solubilities of dietary ingredients pertaining to this category, general tolerances cannot be established. See individual monographs for Tolerances.