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15th November 2019

REPORT on

Measurement of Disintegration Time of Jorveza® 1 mg Schmelztabletten

Professor Geoffrey Lee, Ph.D.

Abstract

Jorveza 1 mg Schmelztabletten disintegrate in a simulated saliva fluid within less than 60 seconds as determined by the USP < 701 > Disintegration Test.

I: INTRODUCTION

1. I have been requested by Bird & Bird LLP, Maximiliansplatz 22, 80333 Munich, Germany, to determine the disintegration behaviour of the commercial drug product *Jorveza 1 mg Schmelztabletten* in simulated saliva fluid. The product is marketed by Dr. Falk Pharma GmbH, Leinenweberstrasse 5, 79108 Freiburg, Germany. Bird & Bird also provided me with the European patent EP 2 482 822 B1. This patent relates to orally administered corticosteroid compositions, and in particular orally dispersing tablets. In Claim 2 the patent discloses that orally dispersing tablets may disintegrate within 60 seconds in simulated saliva fluid when tested using the USP *< 701 >* disintegration test. This information was taken into account for the performance of the present disintegration tests.

II: TO MY PERSON

2. From 1993 until October 2019 I was Chair and Head of the Division of Pharmaceutics at the University of Erlangen, Germany. The subject of

Pharmaceutics encompasses the conception, formulation, development, production, testing and biopharmaceutical behaviour of drug products and medical devices. I have taught most aspects of this subject over the past 25 years and possess therefore broad knowledge of the development and testing of drug products.

III: THE TESTED DRUG PRODUCT

3. *Jorveza 1mg Schmelztabletten* were tested from:

Lot Number: L19001A
Expiry Date: 02/2021

Figure 1: Photographs of Packaged *Jorveza 1 mg Schmelztabletten* with lot number and expiry date.

The tablets were commercially available and I obtained them from a pharmacy. The product was stored in accordance with the manufacturer's storage instructions in the unopened state at room temperature until tested.

IV: THE DISINTEGRATION TEST

4. The disintegration tester used was the PharmaTest PTZ AUTO 2EZ 'Vollautomatischer Zerfallszeit Testsystem' certified to conform with both the USP and EP Pharmacopeias:

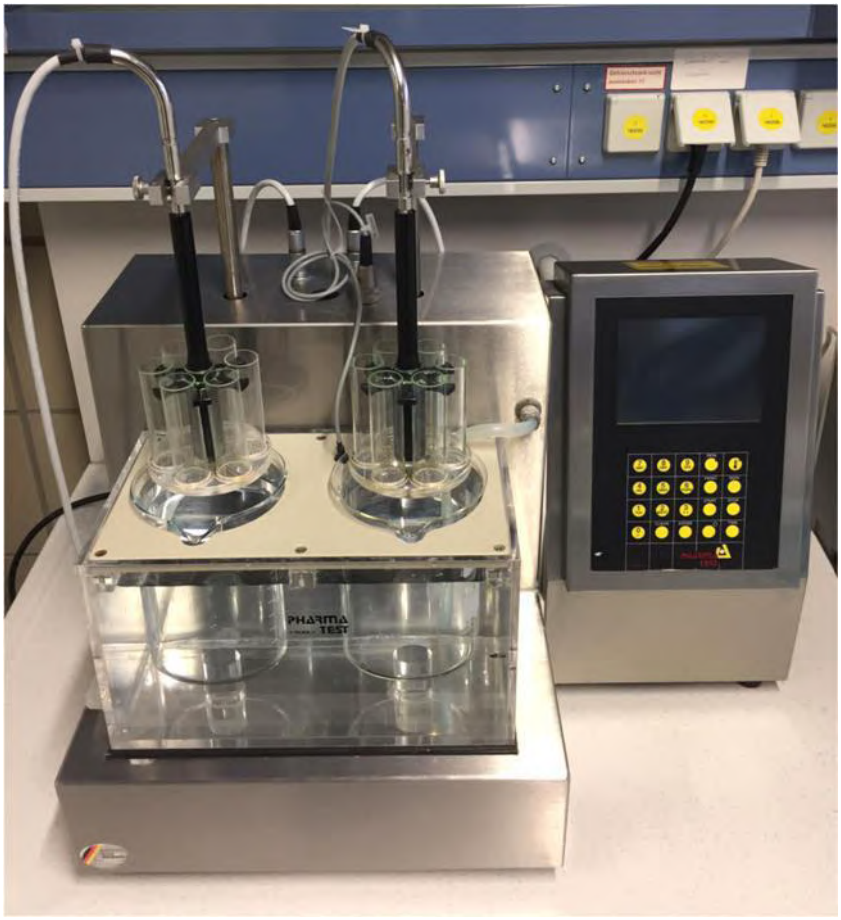

Figure 2: Photograph of Disintegration Tester (empty).

5. Six tablets of *Jorveza 1 mg* were tested for disintegration according to the *USP < 701 > Disintegration* chapter (August 1, 2008) (see **Appendix C**). The disintegration tester conformed exactly to the Apparatus description of < 701 >. The Basket-Rack Assembly conformed exactly to the description in < 701 >. The procedure used was that of 'Uncoated Tablets' under the following conditions:

i) Immersion fluid = simulated saliva fluid (see below);
ii) Immersion fluid temperature = 37 °C;
iii) Immersion fluid volume: as specified in 'Apparatus' of < 701 >, lines 11-17 .
iv) 1 tablet placed in each of the six tubes of the basket;
v) no disk;
vi) operating time set to 60 seconds, i.e. turn-off at 60 seconds.

6. The 6 tablets were placed in the pre-warmed disintegration tester and the apparatus was started (t = 0). A video film of the upper surface of the tubes was

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taken to document the disintegration behaviour of the tablets. This was also observed directly by eye to determine if the tablets disintegrated before the apparatus ceased after 60 seconds' run time.

V: SIMULATED SALIVA FLUID

7. As already mentioned above, Claim 2 of EP 2 482 822 B1 requires the use of simulated saliva fluid as the immersion fluid for the disintegration test. On searching for simulated saliva fluids I came across the publication 'Simulated Biological Fluids with Possible Applications in Dissolution Testing' by Marques, M., Loebenberg, R. and Almukainzi, M., *Dissolution Technologies*, August (2011), a publication coming from the US Pharmacopeia, i.e. the same organization that issued *USP < 701 > Disintegration* chapter. Table 10 of this publication discloses 5 different compositions for simulated saliva (SS), of which SS 5 had been used to monitor drug release from oral fast-dissolving films (see also: Mashru, R., Sutariya, V., Sankalia, M., Parikh, P. Development and evaluation of fast-dissolving film of salbutamol sulphate, *Drug Devel. Ind. Pharm.* 31: 25-34 (2005). This straightforward composition used in a similar test was therefore used in the current disintegration experiments:

Substance	Sodium chloride	Monobasic potassium phosphate KH_2PO_4	Dibasic sodium phosphate K_2HPO_4	pH
Amount [g/L]	8.00	0.19	2.38	6.8

The other compositions of SS 1 to SS 4 in Table 10 had been used for applications other than dissolution or disintegration, viz corrosion of dental alloys, effects of tobacco smoke, interactions with mouth rinses and dentifrices, or dialysis of drugs and salivary components. These compositions were considered therefore not to be suitable for the current tablet disintegration test.

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VI: RESULTS

8. The disintegration behaviour could be successfully determined. **Appendix A** shows a series of ten still photographs taken from the video which depicts the dissolution behaviour of one representative tablet as time progresses up to 60 seconds (turn-off point). These photographs illustrate three points:

i) the end point of disintegration can be determined with clarity;

ii) all of the 6 tablets had disintegrated before 60 seconds;

iii) judged visually, all six tablets had disintegrated at t = 50 seconds.

9. I note that *< 701 >* defines 'complete disintegration' 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'*. According to this definition, the *Jorveza 1 mg Schmelztabletten* showed complete disintegration within less than 60 seconds.

10. I note further that the tablets showed no difficulties of floatation during the disintegration process. The use of a disk was not therefore considered to be necessary.

11. The complete disintegration of the tablets of *Jorveza 1 mg Schmelztabletten* in the simulated saliva fluid is also evident from the photographs given in **Appendix B** which illustrate the behaviour of all six tubes after various times up to 60 seconds. All six tablets had fully disintegrated after 60 s. No residue is visible on the screen at the end of the experimental run.

V: CONCLUSIONS

12. The following conclusions are drawn from these measurements:

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i) the disintegration behaviour of *Jorveza 1 mg Schmelztabletten* in simulated saliva fluid could be successfully determined according to *USP < 701 >*;

ii) the end point of disintegration could be clearly identified;

iii) all of the 6 tablets tested in one experimental run had disintegrated before 60 seconds;

iv) the disintegration times of the six tablets were all less than 50 seconds.

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APPENDIX A

Series of still photographs taken from the video which depicts the dissolution behaviour of one representative tablet as time progresses up to 60 seconds.

A1) t = - 10 s (before start)

A2) t = 0 s (start point of first immersion)

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A3) t = 9 s

A4) t = 19 s

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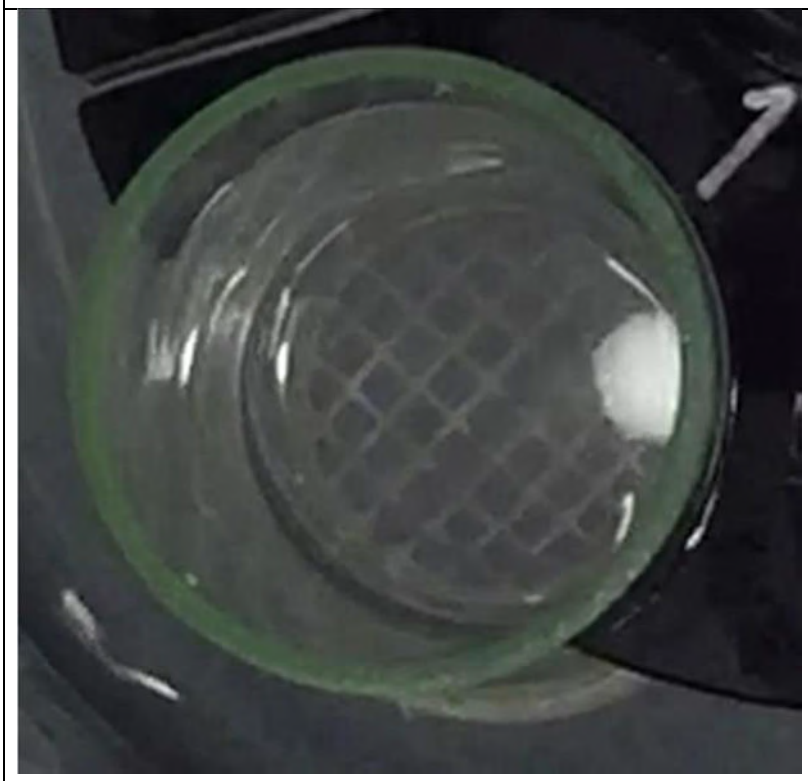
A5) t = 29 s



A6) t = 39 s

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A7) t = 45 s

A8) t = 49 s

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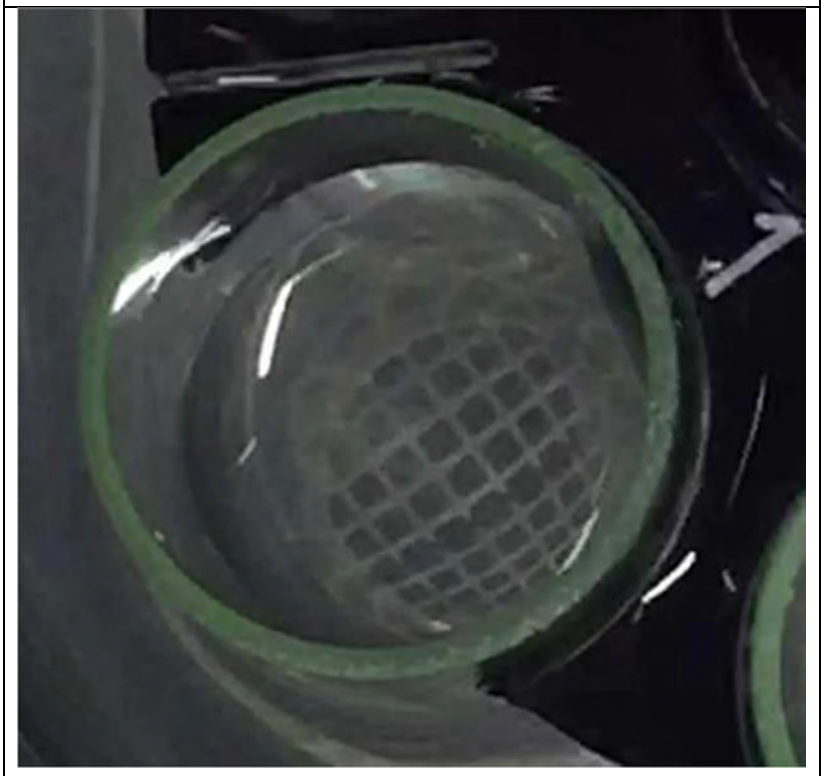
A9) t = 53 s



A10) t = 60 s

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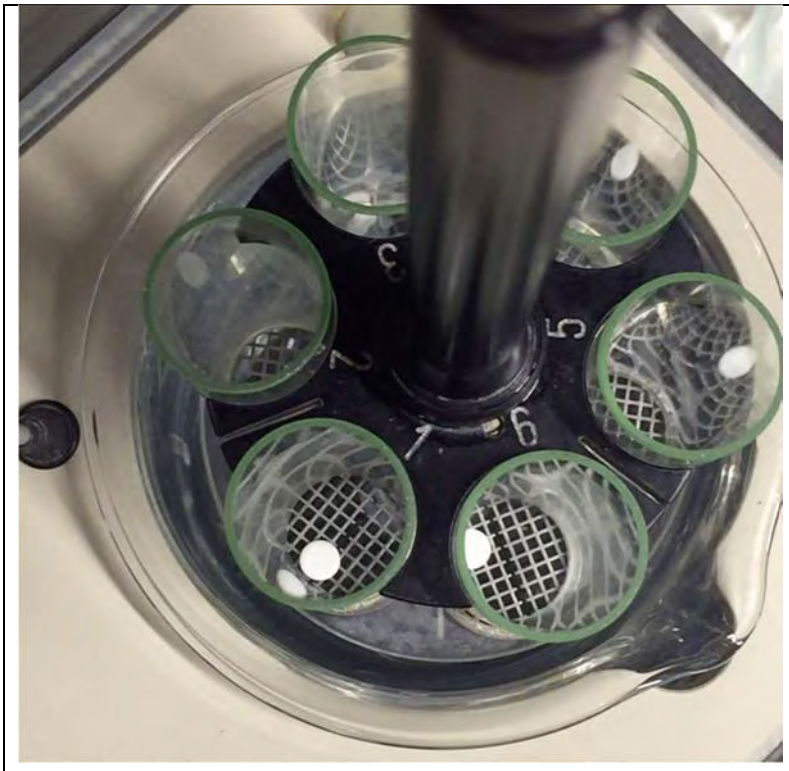
APPENDIX B

Series of still photographs taken from the video which depicts the dissolution behaviour of all six tablets contained in the disintegration tester.



B1) t = - 10 s (before start)

B2) t = 45 s

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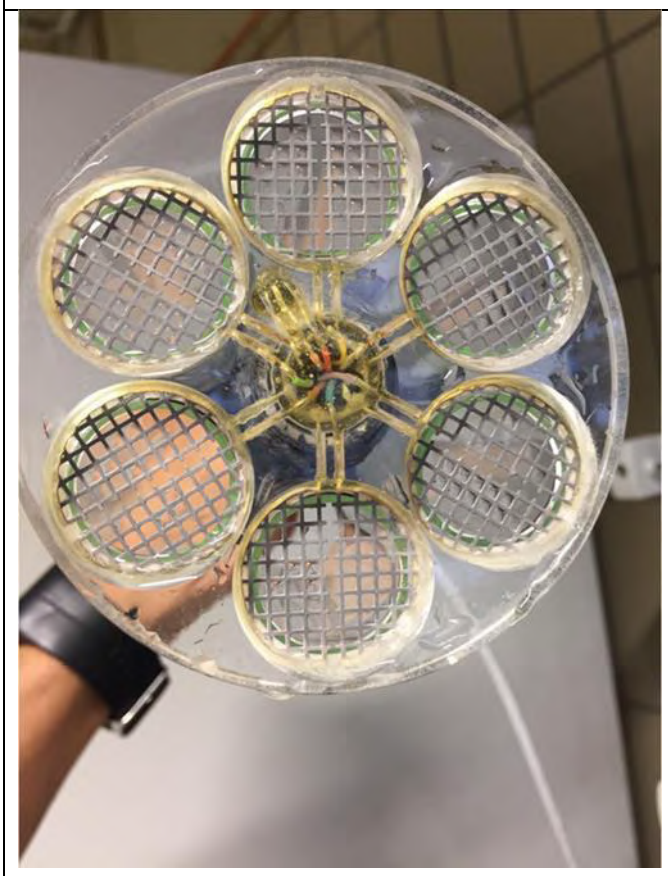
B3) t = 60 s



B4) End of experiment; screen at rack base.

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Change to read:

⟨701⟩ DISINTEGRATION

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia.* The texts of these pharmacopeias are therefore interchangeable, and the methods of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* may be used for demonstration of compliance instead of the present general chapter. These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter.

Portions of the present general chapter text that are national *USP* text, and therefore not part of the harmonized text, are marked with symbols (✦✦) to specify this fact.

This test is provided to determine whether 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 is required except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as extended-release dosage forms or delayed-release dosage forms. Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.✦

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration 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

The apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker, 138 to 160 mm in height and having an inside diameter of 97 to 115 mm 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 six open-ended transparent tubes, each 77.5 ± 2.5 mm long and having an inside diameter of 20.7 to 23 mm and a wall 1.0 to 2.8 mm thick; the tubes are held in a vertical position by two plates, each 88 to 92 mm in diameter and 5 to 8.5 mm in thickness, with six holes, each 22 to 26 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 woven stainless steel wire cloth, which has a plain square weave with 1.8- to 2.2-mm apertures and with a wire diameter of 0.57 to 0.66 mm. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

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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. The basket-rack assembly conforms to the dimensions found in *Figure 1*.

Disks—The use of disks is permitted only where specified or allowed ✦in the monograph. If specified in the individual monograph,✦ each tube is provided with a cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable transparent plastic material having a specific gravity of between 1.18 and 1.20. Five parallel 2 ± 0.1-mm holes extend between the ends of the cylinder. One of the holes is centered on the cylindrical axis. The other holes are centered 6 ± 0.2 mm from the axis on imaginary lines perpendicular to the axis and parallel to the axis and parallel to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centers of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of 1.6 ± 0.1 mm, and its bottom edges lie at a depth of •1.5 to 1.8 mm•(RB 2008-08-01) from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length of 9.4 ± 0.2 mm, and its center lies at a depth of 2.6 ± 0.1 mm from the cylinder's circumference. All surfaces of the disk are smooth. If the use of disks is specified ✦in the individual monograph✦, add a disk to each tube, and operate the apparatus as directed under *Procedure*. The disks conform to dimensions found in *Figure 1*[1].

[1]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 dimension given in this chapter.

PROCEDURE

✦**Uncoated Tablets**—✦Place 1 dosage unit in each of the six tubes of the basket and, if prescribed, add a disk. Operate the apparatus, using ✦water or✦ the specified medium as the immersion fluid, maintained at $37 \pm 2°$. At the end of the time limit specified ✦in the monograph,✦ lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated 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 are disintegrated.

✦**Plain-Coated Tablets**—Apply the test for *Uncoated Tablets,* operating the apparatus for the time specified in the individual monograph.

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 $37 \pm 2°$ 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 $37 \pm 2°$ 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 have disintegrated. 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 speci-

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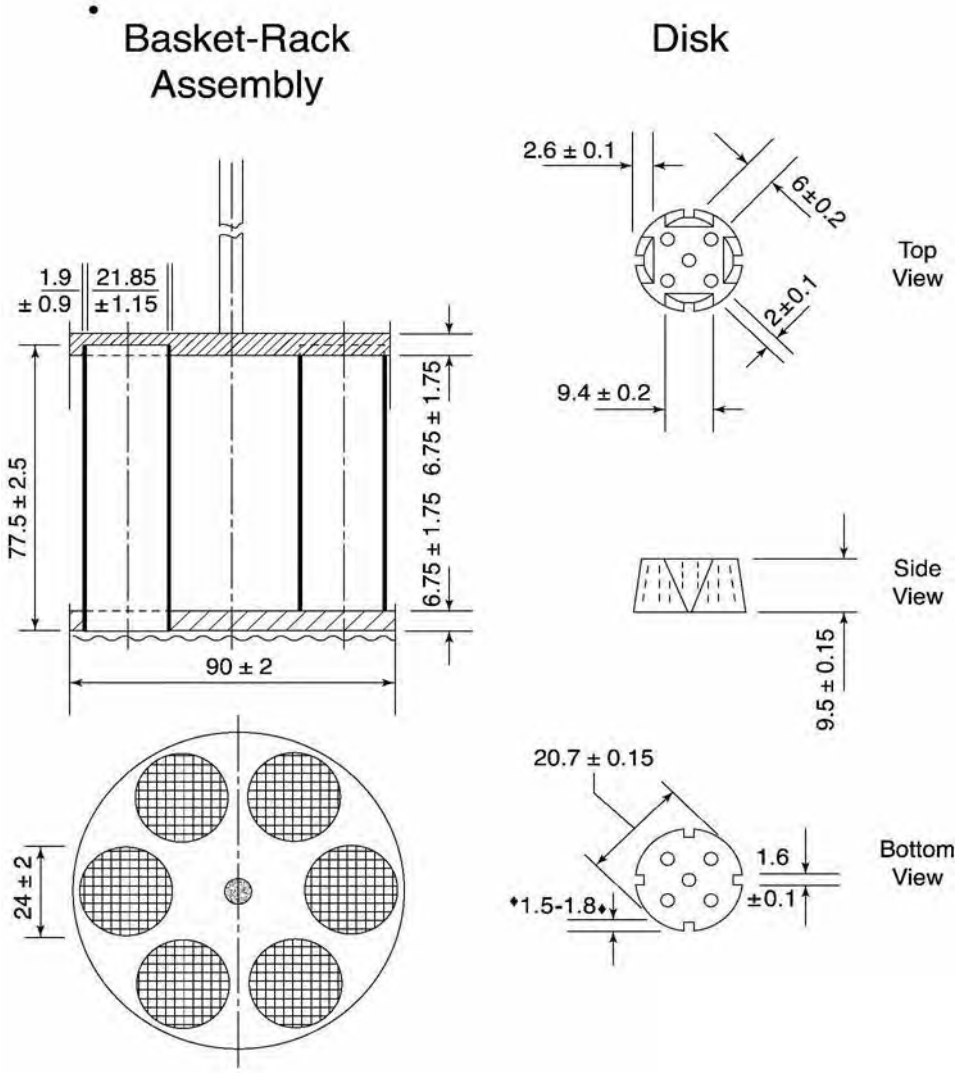

Figure 1. Disintegration apparatus. (All dimensions are expressed in mm.)•(RB 2008-08-01)

fied in the individual monograph: all of the tablets have disintegrated. 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 Gelatin Capsules—Apply the test for *Uncoated Tablets*. Attach a removable wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.60 to 0.655 mm, as described under *Basket-Rack Assembly,* to the surface of the upper plate of the basket-rack assembly. Observe the capsules within the time limit specified in the individual monograph: all of the capsules have disintegrated 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 Gelatin Capsules—Proceed as directed under *Hard Gelatin Capsules*.✦

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