

the filtrate as the test solution as directed in §436.105. Repeat the test on five additional capsules.

(d) *Evaluation.* Use the interpretation described in the United States Pharmacopeia XX dissolution test.

[46 FR 16678, Mar. 13, 1981, as amended at 50 FR 47213, Nov. 15, 1985; 52 FR 35912, Sept. 24, 1987; 54 FR 41824, Oct. 12, 1989]

**§436.543 Acid resistance test for pellet-filled doxycycline hyclate capsules.**

(a) *Equipment.* Use Apparatus 1 as described in the United States Pharmacopeia XXI dissolution test.

(b) *Acid resistance medium.* Use 0.06*N* hydrochloric acid, pH 1.2. May be degassed by heating immediately prior to use.

(c) *Procedure.* Warm the acid resistance medium to a temperature of 37±2.0 ° C. Place the contents of one pellet-filled capsule into the basket. Lower the basket into a beaker containing 900 milliliters of acid resistance medium. Ensure that all air is displaced from the immersed basket and that the contents of the pellet-filled capsule remain in the basket.

Rotate the basket at the speed of 50 revolutions per minute for an accurately timed period of 20 minutes. Withdraw a 5-milliliter sample of the acid resistance medium from a point midway between the stirring shaft and the wall of the vessel and approximately midway in depth (this is the sample solution). Assay the sample solution for doxycycline as described in paragraph (d) of this section. Repeat the test on five additional pellet-filled capsules.

(d) *Doxycycline content*—(1) *Preparation of working standard solution.* Dissolve an accurately weighed portion of doxycycline hyclate working standard with 0.1*M* hydrochloric acid to obtain a concentration of 0.01 milligram per milliliter.

(2) *Preparation of sample solution.* Dilute the 5-milliliter sample portion to 25 milliliters with 0.1*M* hydrochloric acid.

(3) *Procedure.* Using a suitable spectrophotometer and 0.1*M* hydrochloric acid as the blank, determine the absorbance of each standard and sample solution at the absorbance peak at ap-

proximately 345 nanometers. Determine the exact position of the absorption peak for the particular instrument used.

(4) *Calculations.* Determine the total amount of doxycycline dissolved as follows:

$$\text{Milligrams of doxycycline dissolved} = \frac{A_u \times c \times d \times 900^*}{A_s}$$

where:

$A_u$ =Absorbance of sample;

$A_s$ =Absorbance of standard;

$c$ =Concentration of working standard in milligrams; and

$d$ =Dilution factor of sample withdrawn from beaker.

\*If more than 15 milliliters of dissolution medium is removed, correct for the volume removed.

(e) *Evaluation.* The pellet-filled capsule passes the test if no more than 50 percent of the drug is dissolved at 20 minutes. If one pellet-filled capsule fails to meet this requirement, repeat the test on six additional pellet-filled capsules. No more than 2 pellet-filled capsules in 12 may exceed 50 percent of the drug dissolved at 20 minutes.

[50 FR 41679, Oct. 15, 1985; 50 FR 45603, Nov. 1, 1985]

**§436.544 Dissolution test for pellet-filled doxycycline hyclate capsules.**

(a) *Equipment.* Use Apparatus 1 as described in the United States Pharmacopeia XXI dissolution test.

(b) *Dissolution medium.* Prepare the dissolution medium as follows: Dissolve 10.21 grams of potassium biphthalate and 1.4 grams of sodium hydroxide in approximately 950 milliliters of distilled water and adjust the pH to 5.5 using 1*M* sodium hydroxide solution. Dilute with distilled water to 1,000 milliliters.

(c) *Procedure.* Proceed as directed in the United States Pharmacopeia XXI dissolution test. Ensure that all air is displaced from the immersed basket and that the contents of the pellet-filled capsule remain in the basket. Rotate the basket at the speed of 50 revolutions per minute for an accurately timed period of 30 minutes. Withdraw a 5-milliliter sample of the dissolution medium from a point midway between the stirring shaft and the wall of the

vessel and approximately midway in depth (this is the sample solution). Assay the sample solution for doxycycline as described in paragraph (d) of this section. Repeat the test on five additional pellet-filled capsules.

(d) *Doxycycline content*—(1) *Preparation of working standard solution*. Dissolve an accurately weighed portion of doxycycline hyclate working standard with 0.1M hydrochloric acid to obtain a concentration of 0.01 milligram per milliliter.

(2) *Preparation of sample solution*. Dilute the 5-milliliter sample portion to 25 milliliters with 0.1M hydrochloric acid.

(3) *Procedure*. Using a suitable spectrophotometer and 0.1M hydrochloric acid as the blank, determine the absorbance of each standard and sample solution at the absorbance peak at approximately 345 nanometers. Determine the exact position of the absorption peak for the particular instrument used.

(4) *Calculations*. Determine the total amount of doxycycline dissolved as follows:

$$\frac{\text{Milligrams of doxycycline dissolved}}{A_s} = \frac{A_u \times c \times d \times 900^*}{A_s}$$

where:

- $A_u$ =Absorbance of sample;
- $A_s$ =Absorbance of standard;
- $c$ =Concentration of working standard in milligrams; and
- $d$ =Dilution factor of sample withdrawn from beaker.

\*If more than 15 milliliters of dissolution medium is removed, correct for the volume removed.

(e) *Evaluation*. Use the dissolution acceptance table and interpretation in the United States Pharmacopeia XXI.

[50 FR 41679, Oct. 15, 1985]

**§ 436.545 Acid resistance test for erythromycin particles in tablets.**

(a) *Equipment*. Use Apparatus 2 as described in the United States Pharmacopeia XXI dissolution test.

(b) *Acid resistance medium*. Use 0.1N hydrochloric acid, 500 milliliters.

(c) *Procedure*. Warm the immersion fluid to a temperature of 37±0.5 °C. Place one tablet into a vessel containing 500 milliliters of acid resistance

medium. Rotate the paddle at the speed of 50 revolutions per minute for an accurately timed period of 1 hour. Withdraw a 50-milliliter sample of the dissolution medium from a point midway between the stirring shaft and the wall of the vessel and approximately midway in depth. Filter the sample through a Whatman No. 1 filter paper or equivalent, discarding the first 5.0 milliliters. Assay for dissolved erythromycin as directed in paragraph (d) of this section using the filtrate as the sample solution. Repeat the test on five additional tablets.

(d) *Arsenomolybdate colorimetric assay for dissolved erythromycin*—(1) *Apparatus*. Automatic analyzer consisting of (i) a liquid sampler, (ii) a proportioning pump, (iii) suitable spectrophotometers equipped with matched flow cells and analysis capability at 660 nanometers, (iv) a means of recording spectrophotometric readings, and (v) a manifold consisting of the components illustrated in the diagram in paragraph (d)(4) of this section.

(2) *Reagents*—(i) *Arsenomolybdate solutions*—(a) *Stock solution*. Dissolve 100 grams of ammonium molybdate in approximately 1,700 milliliters of water contained in a 2-liter volumetric flask. Insert an inert plastic coated stirring bar into the flask, and begin mixing. While mixing, slowly add 84 milliliters of sulfuric acid (temperature of solution should not exceed 50 °C). Dissolve 12 grams of sodium arsenate in 100 milliliters of water, and add to the solution in the flask. Remove the stirring bar, dilute with water to volume, and mix. Store in an amber bottle for 24 hours before using. (This solution should not be allowed to come into contact with rubber.)

(b) *Working solution*. Dilute 1 part of stock solution with 2 parts of water, and mix. This solution is freshly prepared on the day of use.

(ii) *Acetate buffer, pH 4.8*. Dissolve 133 grams of ACS grade sodium acetate crystals in about 3.5 liters of water. Adjust the pH to 4.8±0.1 with glacial acetic acid. Dilute with water to 4,000 milliliters, and mix.

(iii) *9N Sulfuric acid*. Place a 2-liter volumetric flask containing an inert plastic coated magnetic stirring bar and about 1,500 milliliters of water in