

capsule (except fragments of the insoluble coating) remaining on the screen is a soft mass having no palpably firm core. The tablets, pastilles, or capsules pass the disintegration test if all of the units tested disintegrate completely under the conditions and time specified in the individual section for the antibiotic tablet, pastille, or capsule being tested. If one or two tablets, pastilles, or capsules fail to disintegrate completely, repeat the test on 12 additional tablets, pastilles, or capsules. The tablets, pastilles, or capsules pass the disintegration test if not less than 16 of the total 18 tested disintegrate completely. Enteric coated tablets fail the disintegration test if they show any distinct evidence of dissolution or disintegration after 1 hour immersion in simulated gastric fluid.

[39 FR 18944, May 30, 1974, as amended at 52 FR 4617, Feb. 13, 1987; 55 FR 19873, May 14, 1990]

§ 436.213 Nonaqueous titrations.

(a) *Equipment—(1) Apparatus.* Use a closed system consisting of a suitable titrimeter equipped with a potentiometer, an automatic burette, a chart recorder, and a glass calomel combination electrode (with saturated methanolic potassium chloride as the electrolyte).

(2) *Titration vessel.* Use a 100-milliliter tall form beaker without a spout.

(b) *Reagents—(1) Methyl alcohol,* reagent grade, anhydrous.

(2) Dimethylsulfoxide, A.C.S., reagent grade.

(3) Glacial acetic acid, A.C.S., reagent grade.

(4) Lithium methoxide reagent: 0.02*N* lithium methoxide in methyl alcohol, standardized against primary grade benzoic acid.

(5) Perchloric acid reagent: 0.02*N* perchloric acid in glacial acetic acid, standardized against primary grade potassium acid phthalate.

(c) *Preparation of sample solutions.* Select the weight of the sample and the solvent listed for each antibiotic. Transfer the accurately weighed sample to a titration vessel. Add the appropriate solvent, cover, and stir magnetically until the sample is dissolved. Proceed as directed in paragraph (e) of

this section, using the procedure or procedures specified in the individual section for each antibiotic.

Antibiotic	Weight in milligrams of sample	Solvent
Amoxicillin-acid titration	100	20 milliliters dimethylsulfoxide and 30 milliliters methyl alcohol.*
Amoxicillin-base titration.	100	50 milliliters glacial acetic acid.
Ampicillin-acid titration	100	20 milliliters dimethylsulfoxide and 30 milliliters methyl alcohol.*
Ampicillin-base titration	100	50 milliliters glacial acetic acid.
Ampicillin sodium-base titration.	50	Do.
Cephaloglycin-base titration.	50	Do.
Cephapirin sodium-base titration.	50	50 milliliters glacial acetic acid.
Cyclacillin-acid titration	100	20 milliliters dimethylsulfoxide and 30 milliliters methyl alcohol.*
Cyclacillin-base titration	100	50 milliliters glacial acetic acid.
Tobramycin-base titration.	30	50 ml glacial acetic acid.

*The methyl alcohol is added after the sample has dissolved in dimethylsulfoxide.

(d) *Blank determination.* Place the same volume of solvent used to prepare the sample solution into a titration vessel and proceed as directed in paragraph (e) of this section, using the procedure or procedures specified in the individual section for each antibiotic.

(e) *Titration procedures—(1) Acid titration.* Equilibrate the electrode by soaking it overnight in the solvent used for preparing the sample solution. Start the magnetic stirrer and titrate the sample solution with the lithium methoxide reagent. Record the change in potential of the solution with the addition of the titrant. Determine the number of milliliters of reagent consumed at neutralization (the inflection point of the titration curve). Calculate the antibiotic content as directed in the individual section.

(2) *Base titration.* Proceed as directed in paragraph (e)(1) of this section, except use the perchloric acid reagent as the titrant and calculate the antibiotic

content as directed in the individual section.

[39 FR 18944, May 30, 1974, as amended at 40 FR 22251, Apr. 22, 1975; 40 FR 23725, June 2, 1975; 40 FR 57797, Dec. 12, 1975; 46 FR 2981, Jan. 13, 1981]

§ 436.214 Heat stability.

Store an accurately weighed portion of the sample of approximately 30 milligrams in an unstoppered 50-milliliter Erlenmeyer flask for 4 days in an electric oven at 100° C±1° C. At the end of this period, remove the flask from the oven and allow to cool in a desiccator. Accurately weigh an unheated portion of the original sample of approximately 30 milligrams. Assay both the heated and unheated samples for potency as directed in §436.204 or §436.205 of this chapter. Determine the percent loss from the difference in potency between the unheated original sample and the heat-treated sample.

[42 FR 59856, Nov. 22, 1977]

§ 436.215 Dissolution test.

(a) *Equipment.* Use either Apparatus 1 or 2 as described in the United States Pharmacopeia XXI dissolution test.

(b) *Procedure.* For each dosage form listed in the table in this paragraph select the appropriate dissolution medium, rotation rate, sampling time, and apparatus, and proceed as set forth in either Apparatus 1 or 2 methodology of the United States Pharmacopeia XXI dissolution test. Determine the amount of drug substance dissolved by performing the assay described in paragraph (c) of this section. The amount of dissolution medium removed for sampling purposes may be disregarded if the amount removed is not more than 15 milliliters. If more than 15 milliliters is removed, then correct for the volume removed.

Dosage form	Dissolution medium	Rotation rate ¹	Sampling time(s)	Apparatus
Amoxicillin trihydrate and clavulanate potassium chewable tablets..	900 mL distilled water	75	30 min	2
Amoxicillin trihydrate and clavulanate potassium tablets.do	75do	2
Azithromycin capsules.	900 mL 0.10 M sodium phosphate buffer, pH 6.0, 0.1 mg/mL trypsin.	100	45 min	2
Bacampicillin hydrochloride tablets.do	75do	2
Cefadroxil hemihydrate capsules.	900 mL distilled water	100	45 min	1
Cefadroxil hemihydrate tablets.	900 mL distilled water	50	30 min	2
Cefixime tablets	900 mL 0.05 M potassium phosphate buffer, pH 7.2.	100	45 min	1
Cefpodoxime proxetil tablets	900 mL pH 3.0 glycine buffer	75	30 min	2
Cefprozil tablets.	900 mL purified water	100	45 min	1
Cefuroxime axetil for oral suspension	900 mL Sorenson's Modified Phosphate Buffer, pH 7.0.	50	30 min	2
Cefuroxime axetil tablets.	900 mL 0.07N hydrochloric acid ...	55	15 min. and 45 min	2
Cephalexin hydrochloride monohydrate tablets..	900 mL distilled water	150	45 min	1
Cephadrine dihydrate capsules.	900 mL 0.12N hydrochloric acid ...	75	60 min.	2
Clarithromycin tablets.	900 mL 0.10 M sodium acetate buffer, pH 5.0.	50	30 min.	2
Doxycycline hyclate tablets.	900 mL distilled water	75	60 min and 90 min	2
Doxycycline monohydrate hydrochloric acid capsules..	900 mL 0.1N hydrochloric acid.	75	60 min	2
Erythromycin particles in tablets	900 mL 0.05M potassium phosphate buffer, pH 6.8.	75	45 min.	2
Loracarbef capsules.	900 mL distilled water.	50	30 min	2
Oxytetracycline hydrochloride capsules..	900 mL distilled water	75	30 min and 60 min	2
Rifabutin capsules	900 mL 0.01 N hydrochloric acid	100	45 min	1
Tetracycline hydrochloride capsules (except 500-mg)..do	75do	2
Tetracycline hydrochloride capsules (500-mg)..do	75	30 min, 60 min, and 90 min	2
Tetracycline hydrochloride tablets.do	75	30 min and 60 min	2
Vancomycin hydrochloride capsules. ...	900 mL distilled water.	100	45 min	1

¹ Rotation rate of basket or paddle stirring element (revolutions per minute).