Ampicillin Capsules

Type of Posting	Notice of Intent to Revise
Posting Date	24-Feb-2023
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 1

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 1 Expert Committee intends to revise the Ampicillin Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Ampicillin Capsules monograph to add *Dissolution Test 2*. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Yanyin Yang, Senior Scientist II (301-692-3623 or yanyin.yang@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Notice of Intent to Revise
Official: To Be Determined

Ampicillin Capsules

DEFINITION

Ampicillin Capsules contain an amount of ampicillin (anhydrous or as the trihydrate) equivalent to NLT 90.0% and NMT 120.0% of the labeled amount of ampicillin ($C_{16}H_{19}N_3O_4S$).

IDENTIFICATION

- **A. Thin-Layer Chromatography**

Diluent: Acetone and 0.1 N hydrochloric acid (4:1)

Standard solution: 5 mg/mL of USP Ampicillin RS in *Diluent*

Sample solution: 5 mg/mL of ampicillin in *Diluent* from the contents of Capsules

Chromatographic system

(See *Chromatography* ⟨621⟩*, Thin-Layer Chromatography*.)

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 2 µL

Developing solvent system: Acetone, toluene, glacial acetic acid, and water (650:100:25:100)

Spray reagent: 3 mg/mL of ninhydrin in alcohol

Analysis

Samples: *Standard solution* and *Sample solution*

Apply the *Standard solution* and the *Sample solution* to the plate, and develop the chromatogram using the *Developing solvent system*. When the solvent front has moved about three-fourths of the length of the plate, remove the plate from the chamber, mark the solvent front, and allow to air-dry. Locate the spots on the plate by spraying lightly with *Spray reagent*, and dry at 90° for 15 min.

Acceptance criteria: The R_F value of the principal spot of the *Sample solution* corresponds to that of the *Standard solution*.

ASSAY

- **Procedure**

Standard solution: Prepare as directed for *Standard Preparation* in *Iodometric Assay—Antibiotics* ⟨425⟩, using USP Ampicillin RS.

Sample solution: Nominally 1.25 mg/mL of ampicillin prepared as follows. Place NLT 5 Capsules in a high-speed glass blender jar containing a suitable volume of water, and blend for 4 ± 1 min. Dilute a suitable aliquot with water.

Analysis: Proceed as directed for *Procedure* in *Iodometric Assay—Antibiotics* ⟨425⟩.

Calculate the percentage of the labeled amount of ampicillin ($C_{16}H_{19}N_3O_4S$) in the portion of Capsules taken:

$$\text{Result} = (B - I) \times (F_1/2) \times (1/C_U) \times F_2 \times 100$$

B = volume of 0.01 N sodium thiosulfate consumed in the *Blank Determination* (mL)

I = volume of 0.01 N sodium thiosulfate consumed in the *Inactivation and Titration* of the *Sample solution* (mL)

F_1 = factor as calculated in *Iodometric Assay—Antibiotics* ⟨425⟩

C_U = nominal concentration of ampicillin in the *Sample solution* (mg/mL)

F_2 = conversion factor, 0.001 mg/µg

Acceptance criteria: 90.0%–120.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ▲~~(TBD)~~⟨711⟩

▲**Test 1:** See *Dissolution* ⟨711⟩*, Procedure for a Pooled Sample*.▲ (TBD)

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Standard solution: *L*/900 mg/mL of USP Ampicillin RS in water, where *L* is the labeled amount of ampicillin in mg/Capsule

Sample solution: Use a filtered portion of the solution under test.

Solution A: 1 in 1000 solution of polyoxyethylene (23) lauryl ether in water

Solution B: Dissolve 20 g of hydroxylamine hydrochloride in 5 mL of *Solution A*, and add water to make 1000 mL.

Buffer: 26 mg/mL of sodium hydroxide and 3.1 mg/mL of sodium acetate in water

Ferric nitrate solution: Suspend 233 g of ferric nitrate in about 600 mL of water, add 2.8 mL of sulfuric acid, stir until the ferric nitrate is dissolved, add 1 mL of polyoxyethylene (23) lauryl ether, dilute with water to 1000 mL, and mix.

Apparatus: Automatic analyzer consisting of (1) a liquid sampler, (2) a proportioning pump, (3) suitable spectrophotometers equipped with matched flow cells and analysis capability at 480 nm, (4) a means of recording spectrophotometric readings, and/or computer for data retrieval and calculation, and (5) a manifold consisting of the components illustrated in *Figure 1*.

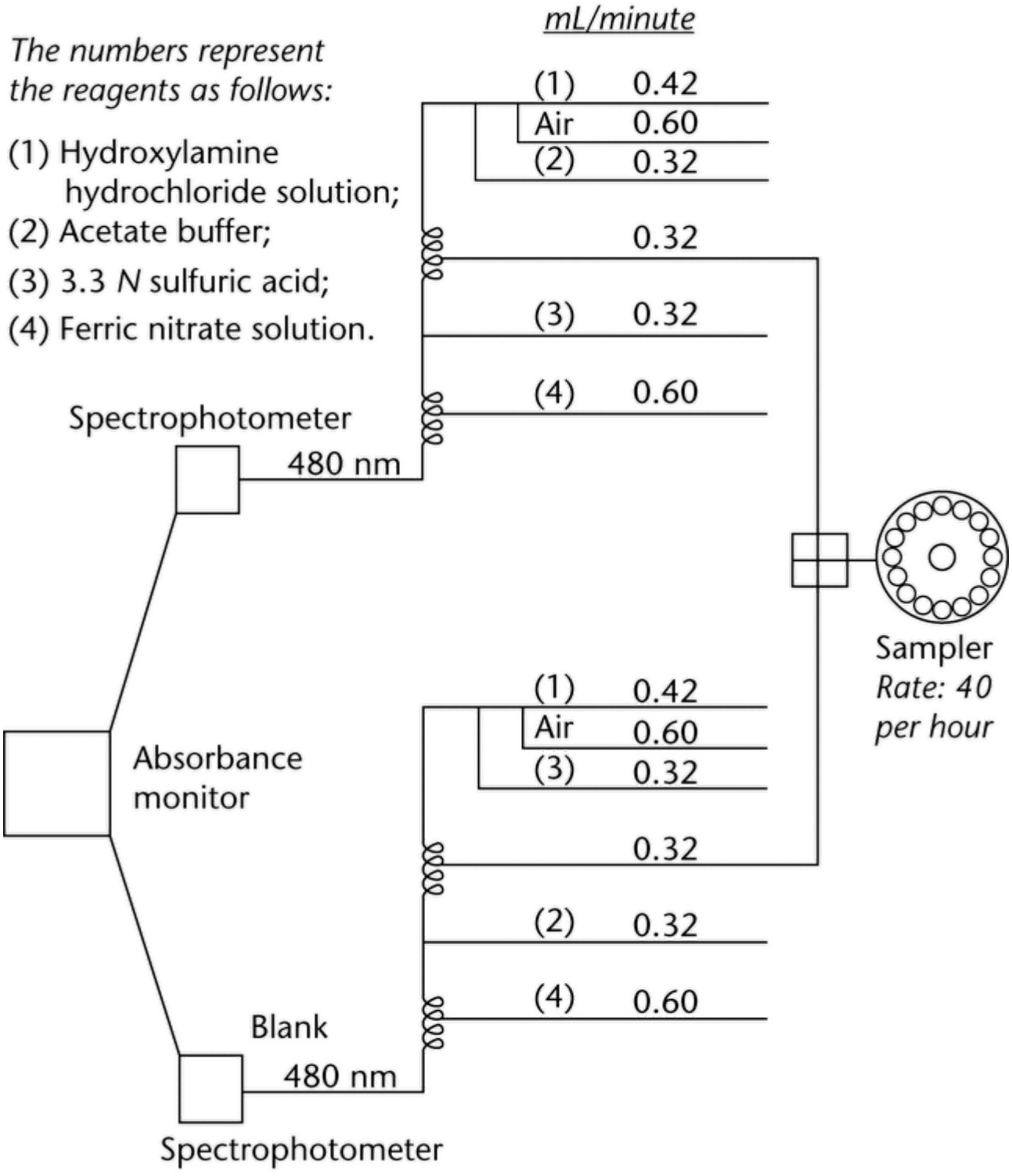

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Figure 1.

Analysis: With the sample line pumping water, the other lines pumping their respective reagents, and the spectrophotometer set at 480 nm, standardize the system until a steady absorbance baseline has been established. Transfer portions of the *Standard solution* and the *Sample solution* to sampler cups, and place in the sampler. Start the sampler, and conduct determinations of the *Standard solution* and the *Sample solution* typically at the rate of 40/h using a ratio of about 2:1 for sample and wash time.

Calculate the percentage of the labeled amount of ampicillin ($C_{16}H_{19}N_3O_4S$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times P \times F \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Ampicillin RS in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

P = potency of ampicillin in USP Ampicillin RS (µg/mg)

F = conversion factor, 0.001 mg/µg

L = label claim (mg/Capsule)

Tolerances: NLT 75% (Q) of the labeled amount of ampicillin ($C_{16}H_{19}N_3O_4S$) is dissolved.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 1: 100 rpm

Time: 20 min

Buffer: Dissolve 1.36 g of potassium phosphate, monobasic in 1000 mL of water. Add 0.6 mL of glacial acetic acid. Adjust with 1 N sodium hydroxide solution or 10% (v/v) phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile and *Buffer* (10:90)

Diluent: 87 g/L of potassium phosphate, dibasic in water

Standard stock solution: 1 mg/mL of USP Ampicillin RS in *Medium*. Sonicate to dissolve. Ensure the temperature of the water bath in the sonicator does not exceed 20°. Prepare the *Standard solution* as quickly as possible from the *Standard stock solution*.

Standard solution

For Capsules labeled to contain 250 mg: 0.417 mg/mL of USP Ampicillin RS in *Diluent* from the *Standard stock solution* prepared as follows. Immediately dilute 10 mL of the *Standard stock solution* with *Medium* to 20 mL. Immediately transfer 10 mL of the resulting solution into a stoppered glass tube containing 2 mL of *Diluent* and mix. Store this solution in the refrigerator.

For Capsules labeled to contain 500 mg: 0.833 mg/mL of USP Ampicillin RS in *Diluent* from the *Standard stock solution* prepared as follows. Immediately transfer 10 mL of the *Standard stock solution* into a stoppered glass tube containing 2 mL of *Diluent* and mix. Store this solution in the refrigerator.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of the filtrate. Immediately, transfer 5 mL of the filtered solution into a stoppered glass tube containing 1 mL of the *Diluent* and mix. Store this solution in the refrigerator.

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Temperatures

Autosampler: 6°

Column: 50°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: NLT 1.9 times the retention time of ampicillin

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ampicillin ($C_{16}H_{19}N_3O_4S$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times P \times F \times D \times (1/L) \times 100$$

r_U = peak response of ampicillin from the *Sample solution*

r_S = peak response of ampicillin from the *Standard solution*

C_S = concentration of USP Ampicillin RS in the *Standard solution* (mg/mL)

V = volume of *Medium*, 500 mL

P = potency of ampicillin in USP Ampicillin RS (µg/mg)

F = conversion factor, 0.001 mg/µg

D = dilution factor for the *Sample solution*

L = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of ampicillin ($C_{16}H_{19}N_3O_4S$) is dissolved. ▲ (TBD)

● **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

SPECIFIC TESTS

● **Water Determination** ⟨921⟩*, Method I*: NMT 4.0% where the Capsules contain anhydrous ampicillin, or between 10.0% and 15.0% where the Capsules contain ampicillin trihydrate

ADDITIONAL REQUIREMENTS

● **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.

Change to read:

● **Labeling:** Label the Capsules to indicate whether the ampicillin therein is in the anhydrous form or is the trihydrate. ▲When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used. ▲ (TBD)

● **USP Reference Standards** ⟨11⟩

USP Ampicillin RS

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Not Applicable

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