Penicillamine Capsules

Type of Posting	Notice of Intent to Revise
Posting Date	30-Jul-2021
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 Penicillamine Capsules monograph.

The purpose of this revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

- *Dissolution Test 2* was validated using the Atlantis dC18 brand of column with L1 packing (4.6-mm × 15-cm; 5 µm). The typical retention time for penicillamine is about 4.1 min.

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 Robyn Fales, Scientist IV (240-221-2047 or rnp@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

Penicillamine Capsules

DEFINITION
Penicillamine Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of penicillamine ($C_5H_{11}NO_2S$).

IDENTIFICATION

- **A. Thin-Layer Chromatography**

Standard solution: 100 mg of USP Penicillamine RS in 10 mL of methanol. Add 2 drops of 3 N hydrochloric acid and mix.

Sample solution: Transfer a portion of Capsule contents, containing nominally about 100 mg of penicillamine, to a 10-mL volumetric flask, and dilute with methanol to volume. Add 2 drops of 3 N hydrochloric acid, mix, and filter. Use the filtrate.

Chromatographic system

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

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture, heated at 105° for 30 min, and allowed to cool before use

Application volume: 10 µL

Developing solvent system: Butyl alcohol, glacial acetic acid, and water (8:2:2)

Spray reagent: 3-mg/mL solution of ninhydrin in dehydrated alcohol

Analysis

Samples: *Standard solution* and *Sample solution*

Separately apply the *Sample solution* and the *Standard solution* to the plate. Develop the chromatogram in the *Developing solvent system* until the solvent front has moved three-fourths the length of the plate. Remove the plate, mark the solvent front, allow the solvent to evaporate, and place the plate in an atmosphere of iodine vapors. After a few minutes, spray the plate with *Spray reagent*, heat it at 105° for 10 min, allow it to cool, and examine it.

Acceptance criteria: The R_F values, colors, and intensities of the principal spots from the *Sample solution* correspond to those from the *Standard solution*.

Change to read:

- **B.** ▲The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-Dec-2021)

ASSAY

Change to read:

- **Procedure**

Mobile phase: 6.9 g/L of monobasic sodium phosphate and 0.2 g/L of sodium 1-hexanesulfonate in water. Adjust with phosphoric acid to a pH of 3.0 ± 0.1.

Diluent: 1.0 g/L of edetate disodium in water

System suitability solution: 1 mg/mL of USP Penicillamine RS and 0.1 mg/mL of USP Penicillamine Disulfide RS in *Diluent*

Standard solution: 1.25 mg/mL of USP Penicillamine RS in *Diluent*

Sample solution: Nominally equivalent to 1.25 mg/mL of penicillamine in *Diluent* prepared as follows. Transfer the contents of Capsules (NLT 10) to a suitable volumetric flask. Add the empty Capsule shells to the flask, and add sufficient *Diluent* to the flask to fill it to three-fourths of its capacity. Shake for 1 min, and allow the mixture to stand for 90 min. Dilute with *Diluent* to volume. Pass a portion of this solution through a suitable filter of 1-µm or finer pore size, and use the clear filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm × 30-cm; ▲10-µm▲ (USP 1-Dec-2021) packing L1

Flow rate: 1.6 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for penicillamine and penicillamine disulfide are 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 3.0 between penicillamine and penicillamine disulfide, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of penicillamine ($C_5H_{11}NO_2S$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

▲Test 1▲ (TBD)

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Procedure for a pooled sample

Dilute hydrochloric acid: Dilute 37 mL of hydrochloric acid with water to 1 L.

Dilute sulfuric acid: Dilute 1 mL of sulfuric acid with water to 50 mL.

Ammonium sulfamate reagent: 2.5 mg/mL of ammonium sulfamate in *Dilute hydrochloric acid*

***N*-(1-Naphthyl)ethylenediamine dihydrochloride reagent:** 1 mg/mL of *N*-(1-naphthyl)ethylenediamine dihydrochloride in *Dilute hydrochloric acid*

Sulfanilamide–mercuric chloride reagent: 1 mg/mL of sulfanilamide and 1 mg/mL of mercuric chloride in *Dilute hydrochloric acid*

Sodium nitrite reagent: 2 mg/mL of sodium nitrite in *Dilute sulfuric acid*. Prepare fresh.

Standard solution: 250 µg/mL of USP Penicillamine RS in 0.1 N hydrochloric acid

Sample solution: Withdraw a portion of the solution under test, containing nominally about 278 µg of penicillamine, and pass through a suitable filter.

Blank: Volume of 0.1 N hydrochloric acid equivalent to a volume of the *Sample solution*

Instrumental conditions

Mode: UV-Vis

Analytical wavelength: 540 nm

Cell: 1 cm

Analysis: Pipet the *Sample solution* into a 100-mL volumetric flask. Into a similar flask, transfer the reagent *Blank*, and into a third 100-mL volumetric flask, pipet 1 mL of *Standard solution*. Treat each flask as follows. Add by pipet 3 mL of *Sodium nitrite reagent*, and mix by swirling occasionally. After 5 min, add 10 mL of *Ammonium sulfamate reagent*, swirl, and allow to stand for an additional 5 min. Add 5 mL of *Sulfanilamide–mercuric chloride reagent*, swirl, and immediately add 10 mL of *N-(1-Naphthyl)ethylenediamine dihydrochloride reagent*. Dilute with water to volume and mix. Determine the absorbances of both solutions against the *Blank*.

Calculate the percentage of the labeled amount of penicillamine ($C_5H_{11}NO_2S$) dissolved:

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

V = volume of the Medium, 900 mL

L = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of penicillamine ($C_5H_{11}NO_2S$) is dissolved.

Procedure for a unit sample

Buffer solution: 50 mM solution of monobasic potassium phosphate buffer at a pH of 3.0

Mobile phase: Methanol and *Buffer solution* (3:97)

Sample solution: Proceed as directed in *Dissolution* ⟨711⟩*, Procedure*. After 30 min, withdraw 10 mL of solution from each vessel, and immediately pass each aliquot through a polyvinylidene difluoride filter of 0.45-µm pore size. Discard the first 2 mL of filtered solution, and chromatograph the remaining filtrate.

System suitability solution: ▲USP Penicillamine RS at a concentration similar to the *Sample solution* and▲ (USP 1-Dec-2021) 0.002 mg/mL of USP Penicillamine Disulfide RS in 0.1 N hydrochloric acid

Standard solution: USP Penicillamine RS in 0.1 N hydrochloric acid at a concentration similar to the *Sample solution*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1.0 mL/min

Injection volume: 30 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between penicillamine and penicillamine disulfide, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of penicillamine ($C_5H_{11}NO_2S$) dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

V = volume of Medium, 900 mL

L = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of penicillamine ($C_5H_{11}NO_2S$) is dissolved.

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

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 1: 100 rpm

Time: 30 min

Buffer: pH 3.0 phosphate buffer (Dissolve 6.8 g of potassium phosphate monobasic in 1 L of water. Sonicate to dissolve. Adjust with 10% phosphoric acid TS to a pH of 3.0.)

Mobile phase: Methanol and *Buffer* (3:97)

System suitability solution: 0.5 mg/mL of USP Penicillamine RS and 0.002 mg/mL of USP Penicillamine Disulfide RS prepared as follows. Transfer suitable amounts of USP Penicillamine RS and USP Penicillamine Disulfide RS to an appropriate volumetric flask. Add about 70% of the flask volume of *Medium* and sonicate to dissolve. Dilute with *Medium* to volume.

Standard solution: 0.5 mg/mL of USP Penicillamine RS in *Medium*. Sonicate to dissolve, if necessary.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding NLT 5 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 15 µL

Run time: NLT 1.5 times the retention time of penicillamine

System suitability

[NOTE—The relative retention times for penicillamine and penicillamine disulfide are about 1.0 and 1.1, respectively.]

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between penicillamine and penicillamine disulfide, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of penicillamine ($C_5H_{11}NO_2S$) dissolved:

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

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

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

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

V = volume of *Medium*, 500 mL

L = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of penicillamine ($C_5H_{11}NO_2S$) is dissolved. ▲ (TBD)

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

IMPURITIES

- **LIMIT OF PENICILLAMINE DISULFIDE**

Mobile phase, Diluent, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 0.025 mg/mL of USP Penicillamine Disulfide RS in *Diluent*

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for penicillamine and penicillamine disulfide are 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 3.0 between penicillamine and penicillamine disulfide, *System suitability solution*

Relative standard deviation: NMT 2.0% for penicillamine disulfide, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of penicillamine disulfide ($C_{10}H_{20}N_2O_4S_2$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area of penicillamine disulfide from the *Sample solution*

r_S = peak area of penicillamine disulfide from the *Standard solution*

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

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

Acceptance criteria: NMT 2.0%

ADDITIONAL REQUIREMENTS

Change to read:

- **Packaging and Storage:** Preserve in tight containers. ▲Store at controlled room temperature.▲ (USP 1-Dec-2021)

Add the following:

▲- **Labeling:** When more than one dissolution test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (TBD)

Change to read:

- **USP Reference Standards** ⟨11⟩

USP Penicillamine RS

USP Penicillamine Disulfide RS

▲3,3′-Dithiodi-D-valine.▲ (USP 1-Dec-2021)

$C_{10}H_{20}N_2O_4S_2$ ▲296.40▲ (USP 1-Dec-2021)

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