Fluphenazine Hydrochloride Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	24–Apr–2020
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 4

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 4 Expert Committee intends to revise the Fluphenazine Hydrochloride Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to the monograph.

- *Dissolution Test 2* was validated using a Zorbax SB C8 brand of L7 column. The typical retention time for Fluphenazine is about 2.3 min.

Labeling information has been incorporated to support the inclusion of *Dissolution Test 2*.

The proposed revision is contingent on FDA approval of the products that meet 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 Ren-Hwa Yeh, Senior Scientific Liaison to the Chemical Medicines Monographs 4 Expert Committee (301-998-6818 or rhy@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*.

Fluphenazine Hydrochloride Tablets

DEFINITION

Fluphenazine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of fluphenazine hydrochloride ($C_{22}H_{26}F_3N_3OS \cdot 2HCl$).

[NOTE—Throughout the following procedures, protect samples, the Reference Standard, and solutions containing them by conducting the procedures without delay, under subdued light, or using low-actinic glassware.]

IDENTIFICATION

• **A. THIN-LAYER CHROMATOGRAPHY**

Diluent: Methanol and water (80:20)

Standard solution: 20 mg/mL of USP Fluphenazine Hydrochloride RS in *Diluent* prepared as follows. Transfer 10 mg of USP Fluphenazine Hydrochloride RS to a separator. Add 5 mL of water and 20 mL of dilute hydrochloric acid (1 in 120) to the separator, shake for 10 min, and add 20 mL of chloroform-saturated sodium carbonate solution (1 in 10). Extract the resulting mixture with five 20-mL portions of chloroform, shaking gently to avoid emulsion formation, and pass the extract through a chloroform-washed cotton filter into a 150-mL beaker. Evaporate the extract on a steam bath to dryness, and dissolve the residue in 0.5 mL of *Diluent*.

Sample solution: Nominally 20 mg/mL of fluphenazine hydrochloride from Tablets in *Diluent* prepared as follows. Transfer a portion of finely powdered Tablets, equivalent to 10 mg of fluphenazine hydrochloride, to a separator. Add 5 mL of water and 20 mL of dilute hydrochloric acid (1 in 120) to the separator, shake for 10 min, and add 20 mL of chloroform-saturated sodium carbonate solution (1 in 10). Extract the resulting mixture with five 20-mL portions of chloroform, shaking gently to avoid emulsion formation, and pass the extract through a chloroform-washed cotton filter into a 150-mL beaker. Evaporate the extract on a steam bath to dryness, and dissolve the residue in 0.5 mL of *Diluent*.

Chromatographic system

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

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 10 µL

Developing solvent system: Acetone, cyclohexane, and diethylamine (40:15:1)

Spray reagent: Sulfuric acid in methanol (2 in 5)

Analysis

Samples: *Standard solution* and *Sample solution*

Allow the spots to dry, and develop the chromatogram in the *Developing solvent system* until the solvent front has moved three-fourths of the length of the plate. Locate the spots on the plate by lightly spraying it with *Spray reagent*.

Acceptance criteria: The R_F value and color of the principal spot of the *Sample solution* correspond to those of the *Standard solution*.

ASSAY

• **PROCEDURE**

Buffer: 0.05 M monobasic potassium phosphate adjusted with phosphoric acid to a pH of 2.5

Diluent: Acetonitrile, methanol, and *Buffer* (30:30:40)

Mobile phase: 0.2% triethylamine in *Diluent*

Standard solution: 0.06 mg/mL of USP Fluphenazine Hydrochloride RS in *Diluent*

Sample stock solution: Transfer 6 Tablets to a suitable volumetric flask, add *Diluent*, shake for 1 h, and sonicate for 10 min or until a fine suspension is obtained.

Sample solution: Nominally 0.06 mg/mL of fluphenazine hydrochloride from *Sample stock solution* in *Diluent*. Filter, and use the filtrate after discarding the first 5 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4-mm × 12.5-cm; packing L7

Flow rate: 1 mL/min

Injection volume: 25 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2000 theoretical plates

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 fluphenazine hydrochloride ($C_{22}H_{26}F_3N_3OS \cdot 2HCl$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

▲Test 1▲ (TBD)

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Buffer: 0.05 M monobasic potassium phosphate adjusted with phosphoric acid to a pH of 2.5

Diluent: Acetonitrile, methanol, and *Buffer* (30:30:40)

Mobile phase: 0.3% triethylamine in *Diluent*

Sample solution: Dilute a portion of the solution under test with an equal volume of *Mobile phase*.

Standard solution: USP Fluphenazine Hydrochloride RS at a concentration and composition similar to that of the *Sample solution*

Chromatographic system and **System suitability:** Proceed as directed in the *Assay*, except use a flow rate of 2 mL/min and an injection volume of 100 µL.

Analysis

Samples: *Sample solution* and *Standard solution*

Determine the amount of fluphenazine hydrochloride ($C_{22}H_{26}F_3N_3OS \cdot 2HCl$) dissolved.

Tolerances: NLT 75% (*Q*) of the labeled amount of fluphenazine hydrochloride ($C_{22}H_{26}F_3N_3OS \cdot 2HCl$) 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: 30 min
Diluted phosphoric acid solution: Transfer 10 mL of phosphoric acid to a 100-mL volumetric flask containing about 50 mL of water. Cool and dilute with water to volume.
Buffer: 6.8 g/L of monobasic potassium phosphate in water, adjusted with *Diluted phosphoric acid solution* to a pH of 2.5
Solution A: Acetonitrile, methanol, and *Buffer* (30:30:40)
Mobile phase: To each liter of *Solution A*, add 3.0 mL of triethylamine.
Diluent: *Medium* and *Mobile phase* (50:50)
Standard stock solution: 0.1 mg/mL of USP Fluphenazine Hydrochloride RS in *Diluent*. Sonicate to dissolve if needed.
Standard solution: (*L*/1000) mg/mL of USP Fluphenazine Hydrochloride RS from the *Standard stock solution* in *Diluent*, where *L* is the label claim in mg/Tablet
Sample stock solution: Pass a portion of the solution under test through an appropriate filter, and discard the first 2 mL of filtrate.
Sample solution: Transfer an equal volume of the *Sample stock solution* and the *Mobile phase* to a suitable container, and mix well.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 5-cm; 3.5-µm packing L7
Column temperature: 40°
Flow rate: 2 mL/min
Injection volume: 100 µL
Run time: NLT 2 times the retention time of fluphenazine
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 fluphenazine hydrochloride ($C_{22}H_{26}F_3N_3OS \cdot 2HCl$) dissolved:

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

r_U = peak response of fluphenazine from the *Sample solution*
r_S = peak response of fluphenazine from the *Standard solution*
C_S = concentration of USP Fluphenazine Hydrochloride RS in the *Standard solution* (mg/mL)
D = dilution factor for the *Sample solution*, 2
V = volume of *Medium*, 500 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of fluphenazine hydrochloride ($C_{22}H_{26}F_3N_3OS \cdot 2HCl$) is dissolved.▲ (TBD)

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

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers.

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)

- **USP Reference Standards** ⟨11⟩
USP Fluphenazine Hydrochloride RS