Prochlorperazine Maleate Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	26-Aug-2022
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 3

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 3 Expert Committee intends to revise the Prochlorperazine Maleate Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to accommodate drug products with different dissolution conditions and/or tolerances than the existing dissolution test. *Labeling* information has been incorporated to support the inclusion of the dissolution test.

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, Senior Scientist I (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

Prochlorperazine Maleate Tablets

DEFINITION

Prochlorperazine Maleate Tablets contain an amount of Prochlorperazine Maleate equivalent to NLT 95.0% and NMT 105.0% of the labeled amount of prochlorperazine ($C_{20}H_{24}ClN_3S$).

[Note—Throughout the following procedures, protect the samples, Reference Standards, and solutions from light, and conduct the procedures without delay.]

IDENTIFICATION

● **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

● **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

● **Procedure**

Ion-pairing solution: Dissolve 4.33 g of sodium 1-octanesulfonate in 500 mL of water. Add 4.0 mL of glacial acetic acid, and dilute with water to 1 L.

Mobile phase: Acetonitrile, methanol, and *Ion-pairing solution* (40:15:45)

Standard solution: 0.2 mg/mL of USP Prochlorperazine Maleate RS in *Mobile phase*

Sample solution: Nominally equivalent to 0.12 mg/mL of prochlorperazine in *Mobile phase* prepared as follows. Transfer an equivalent to about 12 mg of prochlorperazine from finely powdered Tablets (NLT 20), to a 100-mL volumetric flask. Add 60 mL of *Mobile phase*, sonicate for 3 min, and shake by mechanical means for 30 min. Dilute with *Mobile phase* to volume, and filter, discarding the first 10 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm. For *Identification B*, use a diode array detector in the range of 210–400 nm.

Column: 3.9-mm × 30-cm; 10 µm packing L1

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of prochlorperazine ($C_{20}H_{24}ClN_3S$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

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

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

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

M_{r1} = molecular weight of prochlorperazine, 373.94

M_{r2} = molecular weight of prochlorperazine maleate, 606.09

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

▲**Test 1** ▲ (TBD)

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 2: 75 rpm

Time: 60 min

Standard solution: USP Prochlorperazine Maleate RS at a known concentration in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter, and dilute with *Medium*, if necessary, to a concentration that is similar to that of the *Standard solution*.

Instrumental conditions

Mode: UV

Analytical wavelength: 254 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of prochlorperazine ($C_{20}H_{24}ClN_3S$) dissolved:

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Prochlorperazine Maleate RS in the *Standard solution*

D = dilution factor for *Sample solution*, if needed

L = label claim (mg/Tablet)

V = volume of *Medium*, 500 mL

Tolerances: NLT 75% (Q) of the labeled amount of prochlorperazine ($C_{20}H_{24}ClN_3S$) 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 2: 50 rpm

Time: 30 min

Standard stock solution: 0.275 mg/mL of USP Prochlorperazine Maleate RS prepared as follows.

Transfer a suitable amount of USP Prochlorperazine Maleate RS to a suitable volumetric flask. Add

10% of the flask volume of acetonitrile and 60% of the flask volume of *Medium* and sonicate to dissolve. Dilute with *Medium* to volume.

Standard solution: (*L*/500) mg/mL of prochlorperazine prepared as follows, where *L* is the label claim in mg/Tablet. Dilute the *Standard stock solution* with *Medium* to obtain a solution with a final concentration of 0.0165 mg/mL of USP Prochlorperazine Maleate RS for Tablets labeled to contain 5 mg and 0.033 mg/mL of USP Prochlorperazine Maleate RS for Tablets labeled to contain 10 mg.

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

Instrumental conditions

Mode: UV

Analytical wavelength: 254 nm

Cell path length: 0.5 cm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of prochlorperazine ($C_{20}H_{24}ClN_3S$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

V = volume of *Medium*, 500 mL

M_{r1} = molecular weight of prochlorperazine, 373.94

M_{r2} = molecular weight of prochlorperazine maleate, 606.09

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of prochlorperazine ($C_{20}H_{24}ClN_3S$) is dissolved. ▲(TBD)

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

IMPURITIES

- **Organic Impurities**

Buffer solution: 1.36 g/L of sodium acetate trihydrate in water (0.01 M). Add 2.0 mL of triethylamine and 6.0 mL of glacial acetic acid per liter of solution.

Solution A: *Buffer solution*

Solution B: Acetonitrile

Mobile phase: See *Table 1*. Return to original conditions, and re-equilibrate the system for about 10 min.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25

Time (min)	Solution A (%)	Solution B (%)
20	65	35
25	65	35
55	35	65
65	35	65

Diluent: Acetonitrile and water (40:60)

Impurity stock solution: 0.16 mg/mL of USP Prochlorperazine Related Compound A RS in *Diluent*

Standard stock solution: 0.16 mg/mL of USP Prochlorperazine Maleate RS in *Diluent*

System suitability solution: 1.6 µg/mL of USP Prochlorperazine Maleate RS and 1.6 µg/mL of USP Prochlorperazine Related Compound A RS in *Diluent* from the *Standard stock solution* and the *Impurity stock solution*, respectively

Standard solution: 0.0064 mg/mL of USP Prochlorperazine Maleate RS in *Diluent* from the *Standard stock solution*

Sample solution: Nominally equivalent to 0.4 mg/mL of prochlorperazine in *Diluent*, prepared as follows. Transfer 20 Tablets to a suitable volumetric flask, using a 250-mL volumetric flask for 5-mg Tablets and a 500-mL volumetric flask for 10-mg Tablets. Add *Diluent* to about 80% of the final flask volume, sonicate with occasional swirling for 10 min or shake by mechanical means for 20 min, and dilute with *Diluent* to volume. Centrifuge a portion of the solution, and use the clear supernatant.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

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

Column temperature: 50 ± 5°

Flow rate: 2.0 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between prochlorperazine related compound A and prochlorperazine, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual specified or unspecified impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each corresponding impurity from the *Sample solution*

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

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

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

M_{r1} = molecular weight of prochlorperazine, 373.94

M_{r2} = molecular weight of prochlorperazine maleate, 606.09

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Maleic acid	0.07	—	—[a]
Prochlorperazinesulfoxide[b]	0.20	0.38	0.5
Perazine[c,d]	0.66	—	—
Prochlorperazine related compound A[d]	0.97	—	—
Prochlorperazine	1.00	—	—
4-Chlorophenothiazine[d,e]	2.01	—	—
2-Chlorophenothiazine[d,f]	2.08	—	—
Specified unknown 1[d]	2.64	—	—
Specified unknown 2[d]	2.79	—	—
Specified unknown 3[d]	2.88	—	—
Any individual unspecified impurity	—	1.0	0.5
Total impurities	—	—	2.0

[a] Disregard.

[b] 2-Chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-10*H*-phenothiazine sulfoxide.

[c] 10-[3-(4-Methylpiperazin-1-yl)propyl]-10*H*-phenothiazine.

[d] Process impurity controlled in the drug substance. It is included for identification purposes only. It should not be reported for the drug product, and should not be included in the total impurities.

[e] 4-Chloro-10*H*-phenothiazine.

[f] 2-Chloro-10*H*-phenothiazine.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, protected from light. Store at controlled room temperature.

Add the following:

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

- **USP Reference Standards** ⟨11⟩

  USP Prochlorperazine Maleate RS

  USP Prochlorperazine Related Compound A RS

  4-Chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-10*H*-phenothiazine dihydrochloride.

  $C_{20}H_{24}ClN_3S \cdot 2HCl$ 446.86

Page Information:

Not Applicable

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