Phenylephrine Hydrochloride Tablets

Type of Posting	Revision Bulletin
Posting Date	25–Mar–2016
Official Date	01–May–2016
Expert Committee	Chemical Medicines Monographs 6
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 6 Expert Committee has revised the Phenylephrine Hydrochloride Tablets monograph. The purpose for the revision is to postpone the *Organic Impurities* section of this monograph, because of comments received regarding the inclusion of limits for unspecified impurities, which is scheduled to become official on May 01, 2016.

The Phenylephrine Hydrochloride Tablets Revision Bulletin supersedes the currently official Phenylephrine Hydrochloride Tablets monograph. The Revision Bulletin will be incorporated in *USP 40–NF 35*.

Should you have any questions, please contact Clydewyn M. Anthony, Ph.D. (301–816–8139 or cma@usp.org)

Add the following:

▲Phenylephrine Hydrochloride Tablets

DEFINITION
Phenylephrine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$).

IDENTIFICATION
- **A.** The UV absorption spectra of the phenylephrine peak of the *Sample solution* and that of the *Standard solution* exhibit maxima and minima at the same wavelengths, as obtained in the *Assay*.
- **B.** The retention time of the phenylephrine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
- **PROCEDURE**

It is suggested to use plastic vials for analysis.
Buffer: 3.45 g/L of monobasic ammonium phosphate in water. Adjust with 10% phosphoric acid or 10% ammonium hydroxide solution to a pH of 4.5 ± 0.10, if necessary.
Solution A: Dilute 10 mL of glacial acetic acid with water to 1000 mL.
Mobile phase: Acetonitrile and *Buffer* (35:65)
Diluent: Methanol and *Solution A* (30:70)
Standard solution: 0.1 mg/mL of USP Phenylephrine Hydrochloride RS in *Diluent*
Sample solution: Nominally 0.1 mg/mL of phenylephrine hydrochloride prepared as follows. Transfer NLT 10 Tablets to a suitable volumetric flask, add 50% of the final volume of *Solution A*, and stir vigorously for NLT 30 min. Add 30% of the final volume of methanol and stir for NLT an additional 90 min. To ensure that particles do not collect above the solvent level, periodically rinse the particulate into the solution with *Solution A*. Allow the resulting solution to cool to room temperature and dilute with *Solution A* to volume. Pass a portion through a suitable filter of 0.45-µm pore size. Discard the first 2–3 mL of filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 214 nm. For *Identification A*, use a diode-array detector in the range of 200–350 nm.
Column: 4.6-mm × 10-cm; 5-µm packing L9
Flow rate: 2.0 mL/min
Injection volume: 25 µL
Run time: NLT 1.75 times the retention time of phenylephrine
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: 0.5–3.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$) in the portion of Tablets taken:

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

r_U = peak response of phenylephrine from the *Sample solution*
r_S = peak response of phenylephrine from the *Standard solution*
C_S = concentration of USP Phenylephrine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of phenylephrine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS
- **DISSOLUTION** ⟨711⟩

It is suggested to use plastic vials for analysis.
Medium: Simulated gastric fluid without pepsin; 900 mL
Apparatus 2: 50 rpm
Time: 45 min
Buffer, Mobile phase, and **System suitability:** Proceed as directed in the *Assay*.
Standard solution: (*L*/900) mg/mL of USP Phenylephrine Hydrochloride RS in *Medium*, where *L* is the label claim of phenylephrine hydrochloride in mg/Tablet
Sample solution: Pass a portion of the solution under test through a suitable filter of 10–20-µm pore size.
Chromatographic system: Proceed as directed in the *Assay*, except for the following.
Injection volume: 100 µL
Run time: NLT 1.5 times the retention time of phenylephrine
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$) dissolved:

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

r_U = peak response of phenylephrine from the *Sample solution*
r_S = peak response of phenylephrine from the *Standard solution*
C_S = concentration of USP Phenylephrine Hydrochloride RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

Tolerances: NLT 75% (*Q*) of the labeled amount of phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$) is dissolved.
- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

Solution A: Trifluoroacetic acid and water (1:1000)
Solution B: Trifluoroacetic acid and acetonitrile (1:1000)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	96.5	3.5
3	96.5	3.5
44	62.0	38.0

Table 1 *(Continued)*

Time (min)	Solution A (%)	Solution B (%)
45	96.5	3.5
50	96.5	3.5

Diluent: Phosphoric acid and water (0.5: 1000)
System suitability solution: 0.0002 mg/mL of USP Phenylephrine Related Compound F RS, 0.0002 mg/mL of USP Phenylephrine Related Compound G RS, and 0.2 mg/mL of USP Phenylephrine Hydrochloride RS in *Diluent*
Standard solution: 0.002 mg/mL of USP Phenylephrine Hydrochloride RS in *Diluent*
Sensitivity solution: 0.0002 mg/mL of USP Phenylephrine Hydrochloride RS in *Diluent* from the *Standard solution*
Sample solution: Nominally 0.2 mg/mL of phenylephrine hydrochloride prepared as follows. Transfer NLT 10 Tablets to a suitable volumetric flask, add about 50% of the final volume of *Diluent*, and shake for NLT 1 h. Dilute with *Diluent* to volume. Pass a portion through a suitable filter of 0.45-µm pore size. Discard the first 2 mL of filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 270 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L1
Column temperature: 35.0°
Flow rate: 1.2 mL/min
Injection volume: 50 µL
System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
Suitability requirements
Resolution: NLT 1.0 between phenylephrine related compound G and phenylephrine, *System suitability solution*
Relative standard deviation: NMT 6.0%, *Standard solution*
Signal-to-noise ratio: NLT 10, *Sensitivity solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of any individual degradation product in the portion of Tablets taken:

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

r_U = peak response of each individual degradation product from the *Sample solution*
r_S = peak response of phenylephrine from the *Standard solution*
C_S = concentration of USP Phenylephrine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of phenylephrine hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor of each individual degradation product (see *Table 2*)

Acceptance criteria: See *Table 2*. Disregard any peaks below 0.1%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Isoquinoline 4, 6-diol analog[a]	0.67	0.70	1.0
Phenylephrine related compound F[b]	0.88	1.0	0.3
Phenylephrine related compound G[c]	0.94	1.0	0.3
Phenylephrine	1.00	1.0	—
Phenylephrone (Phenylephrine related compound C)[d]	1.29	1.8	0.5
3-Hydroxybenzaldehyde	3.00	3.1	0.3
Phenylephrine isoquinolinone analog[e]	4.19	8.0	0.3
Any unspecified degradation product	—	1.0	0.3
Total degradation products	—	—	2.4

[a] 2-Methyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol.
[b] 2-Methyl-1,2,3,4-tetrahydroisoquinoline-4,8-diol.
[c] (*R*)-*N*-(2-Hydroxy-2-(3-hydroxyphenyl)ethyl)-*N*-methylglycine.
[d] 1-(3-Hydroxyphenyl)-2-(methylamino)ethan-1-one.
[e] 1-(3-Hydroxybenzoyl)-2-methylisoquinolin-6(2*H*)-one.

●(Postponed indefinitely)● (RB 1-May-2016)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at 20°–25°.

Change to read:

- **USP REFERENCE STANDARDS** ⟨11⟩
USP Phenylephrine Hydrochloride RS
USP Phenylephrine Related Compound F RS
2-Methyl-1,2,3,4-tetrahydroisoquinoline-4,8-diol.
$C_{10}H_{13}NO_2$ 179.22●(Postponed indefinitely)● (RB 1-May-2016)
USP Phenylephrine Related Compound G RS
(*R*)-*N*-(2-Hydroxy-2-(3-hydroxyphenyl)ethyl)-*N*-methylglycine.
$C_{11}H_{15}NO_4$ 225.24●(Postponed indefinitely)● (RB 1-May-2016)

▲*USP39*