Diphenhydramine and Phenylephrine Hydrochlorides Tablets

Type of Posting	Revision Bulletin
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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 Diphenhydramine and Phenylephrine Hydrochlorides 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 Diphenhydramine and Phenylephrine Hydrochlorides Tablets Revision Bulletin supersedes the currently official Diphenhydramine and Phenylephrine Hydrochlorides 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:

▲Diphenhydramine and Phenylephrine Hydrochlorides Tablets

DEFINITION

Diphenhydramine and Phenylephrine Hydrochlorides Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) and phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$).

IDENTIFICATION

- **A.** The UV absorption spectra of the diphenhydramine and phenylephrine peaks of the *Sample solutions* and those of the *Standard solution* exhibit maxima and minima at the same wavelengths, as obtained in the *Assay*.
- **B.** The retention times of the diphenhydramine and phenylephrine peaks of the *Sample solution* correspond to those 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 phosphoric acid to a pH of 3.5 ± 0.05 if necessary.

Mobile phase: Acetonitrile and *Buffer* (25:75)

Solution A: Dilute 10 mL of glacial acetic acid with 1000 mL of water.

Diluent: Methanol and *Solution A* (30:70)

Standard solution: 0.25 mg/mL of USP Diphenhydramine Hydrochloride RS and 0.1 mg/mL of USP Phenylephrine Hydrochloride RS in *Diluent*

Sample solution: Nominally 0.25 mg/mL of diphenhydramine hydrochloride and 0.1 mg/mL of phenylephrine hydrochloride prepared as follows. Transfer NLT 10 Tablets to a suitable volumetric flask, add 50% final volume of *Solution A*, and stir for NLT 30 min. Add 30% final volume of methanol, and stir additionally for NLT 90 min. To ensure that particles do not collect above the solvent level, periodically rinse particulate into 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: 15 µL
Run time: NLT 3 times the retention time of phenylephrine

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: 0.5–3.0 for both phenylephrine and diphenhydramine
Relative standard deviation: NMT 2.0% for both phenylephrine and diphenhydramine

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amounts of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) and 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 diphenhydramine or phenylephrine from the *Sample solution*
r_S = peak response of diphenhydramine or phenylephrine from the *Standard solution*
C_S = concentration of USP Diphenhydramine Hydrochloride RS or USP Phenylephrine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of diphenhydramine hydrochloride or 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

Mobile phase: Proceed as directed in the *Assay*.

Standard solution: (L_1/900) mg/mL of USP Diphenhydramine Hydrochloride RS and (L_2/900) mg/mL of USP Phenylephrine Hydrochloride RS in *Medium*, where L_1 is the label claim of diphenhydramine hydrochloride in mg/Tablet; and L_2 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
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 214 nm
Column: 4.6-mm × 10-cm; 5-µm packing L9
Flow rate: 2.0 mL/min
Injection volume: 100 µL
Run time: NLT 3 times the retention time of phenylephrine

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: 0.5–3.0 for both phenylephrine and diphenhydramine
Relative standard deviation: NMT 2.0% for both phenylephrine and diphenhydramine

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amounts of phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$) and diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) dissolved:

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

r_U = peak response of diphehydramine or phenylephrine from the *Sample solution*
r_S = peak response of diphenhydramine or phenylephrine from the *Standard solution*
C_S = concentration of USP Diphenhydramine Hydrochloride RS or USP Phenylephrine Hydrochloride RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim of diphenhydramine hydrochloride (L_1) or phenylephrine hydrochloride (L_2) (mg/Tablet)

Tolerances: NLT 75% (*Q*) of the labeled amounts of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) and 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**

Protect solutions containing diphenhydramine and phenylephrine from light. Use glass pipettes and silanized vials for analysis.

Solution A: Transfer 6 mL of 70% perchloric acid solution to a 100-mL volumetric flask, and dilute with water to volume.

Solution B: Transfer 8.31 g of potassium perchlorate to a suitable container. Add 10 mL of *Solution A* and 990 mL of water.

Solution C: Transfer 6 mL of 70% perchloric acid solution to a 100-mL volumetric flask, and dilute with acetonitrile to volume.

Solution D: Mix 10 mL of *Solution C* with 990 mL of acetonitrile.

Solution E: *Solution B* and *Solution D* (45:55)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution B (%)	Solution E (%)
0.0	99	1
17.0	99	1
25.0	53	47
33.0	53	47
50.0	5	95
55.0	5	95
55.1	99	1
63.0	99	1

Diluent: 1.26 g/L of ammonium formate in water. Adjust with formic acid to a pH of 4.0 ± 0.1.

Sensitivity solution: 0.0005 mg/mL of USP Diphenhydramine Hydrochloride RS and 0.0002 mg/mL of USP Phenylephrine Hydrochloride RS in *Diluent*

System suitability solution: 0.0002 mg/mL of USP Phenylephrine Related Compound F RS, 0.0005 mg/mL of USP Diphenhydramine Related Compound A RS, 0.15 mg/mL of USP Diphenhydramine Hydrochloride RS, and 0.2 mg/mL of USP Phenylephrine Hydrochloride RS in *Diluent*

Standard solution: 0.005 mg/mL of USP Diphenhydramine Hydrochloride RS and 0.002 mg/mL of USP Phenylephrine Hydrochloride RS in *Diluent*

Sample solution: Nominally 0.5 mg/mL of diphenhydramine hydrochloride and 0.2 mg/mL of phenylephrine hydrochloride prepared as follows. Transfer NLT 10 Tablets to a suitable volumetric flask, using only PTFE stoppers. Add about 50% of final volume of *Diluent*, and shake on a flat bed shaker at low speed for NLT 1 h. Dilute with *Diluent* to volume. Centrifuge a portion until a clear supernatant is obtained, and use the supernatant.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L60

Column temperature: 43.0°

Flow rate: 1.0 mL/min

Injection volume: 35 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between phenylephrine related compound F and phenylephrine; NLT 2.0 between diphenhydramine related compound A and diphenhydramine, *System suitability solution*

Relative standard deviation: NMT 6.0% for phenylephrine and diphehydramine, *Standard solution*

Signal-to-noise ratio: NLT 10 for phenylephrine and diphenhydramine, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Identify the diphenhydramine degradation products using the relative retention times in *Table 2*.

Calculate the percentage of each diphenhydramine related 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 diphenhydramine related degradation product from the *Sample solution*

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

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

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

F = relative response factor of each individual impurity (see *Table 2*)

Identify the phenylephrine degradation products using the relative retention times in *Table 2*.

Calculate the percentage of each phenylephrine related degradation product and any other 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 phenylephrine related degradation product or any other 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 impurity (see *Table 2*)

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

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

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and store at 20°–25°.

Table 2

Name		Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Isoquinoline 4,6-diol analog[a,b]		0.72	1.2	1.0
Phenylephrine		1.00	1.0	—
3-Hydroxybenzaldehyde[c,b]		2.37	5.3	0.6
Diphenhydramine		3.55	1.0	—
Diphenhydramine *N*-oxide[d,e]		3.71	0.92	1.2
Benzhydrol[f,e]		3.92	1.6	0.5
Benzophenone[e]		4.37	0.86	0.66
Unspecified degradation products quantified relative to phenylephrine	Phenylephrine carboxy analog (phenylephrine related compound G)[g,b]	0.80	1.2	0.3
	Phenylephrine related compound F[h,b]	0.94	1.0	
	Phenylephrone (phenylephrine related compound C)[i,b]	1.35	2.9	
	Phenylephrine isoquinolinone analog[j,b]	2.83	3.5	
	Individual phenylephrine related degradation product and any unspecified degradation product[b]	—	1.0	
Unspecified degradation products quantified relative to diphenhydramine	Diphenhydramine quaternary salt[k,e]	3.47	0.80	0.2
	Diphenhydramine related compound A[l,e]	3.51	1.1	
	Individual diphenhydramine related degradation product[e]	—	1.0	
Total degradation products quantitated relative to phenylephrine		—	—	2.5
Total degradation products quantitated relative to diphenhydramine		—	—	3.0

[a] 2-Methyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol.
[b] Quantified relative to phenylephrine.
[c] 3-Hydroxybenzaldehyde.
[d] 2-(Benzhydryloxy)-*N*,*N*-dimethylethan-1-amine oxide.
[e] Quantified relative to diphenhydramine.
[f] Diphenylmethanol.
[g] (*R*)-*N*-[2-Hydroxy-2-(3-hydroxyphenyl)ethyl]-*N*-methylglycine.
[h] 2-Methyl-1,2,3,4-tetrahydroisoquinoline-4,8-diol.
[i] 1-(3-Hydroxyphenyl)-2-(methylamino)ethan-1-one.
[j] 1-(3-Hydroxybenzoyl)-2-methylisoquinolin-6(2*H*)-one.
[k] 2-{[2-(Benzhydryloxy)ethyl]dimethylammonio}acetate.
[l] 2-(Diphenylmethoxy)-*N*-methylethanamine.

Change to read:

- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Diphenhydramine Hydrochloride RS
  USP Diphenhydramine Related Compound A RS
  2-(Diphenylmethoxy)-*N*-methylethanamine hydrochloride.
  $C_{16}H_{19}NO$ 241.33●(Postponed indefinitely)● (RB 1-May-2016)
  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)

▲*USP39*