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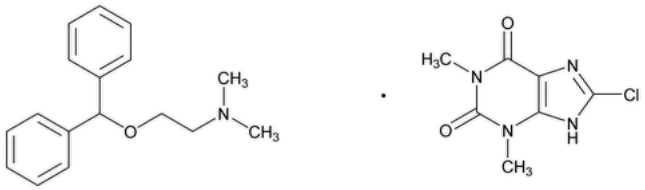
Dimenhydrinate



$C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$ 469.96

1*H*-Purine-2,6-dione, 8-chloro-3,7-dihydro-1,3-dimethyl-, compd. with 2-(diphenylmethoxy)-*N*,*N*-dimethylethanamine (1:1); 8-Chlorotheophylline, compound with 2-(diphenylmethoxy)-*N*,*N*-dimethylethylamine (1:1) CAS RN®: 523-87-5; UNII: JB937PER5C.

DEFINITION

Dimenhydrinate contains NLT 53.0% and NMT 55.5% of diphenhydramine ($C_{17}H_{21}NO$) and NLT 44.0% and NMT 47.0% of 8-chlorotheophylline ($C_7H_7ClN_4O_2$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K ▲or 197A▲ (USP 1-May-2021)

Add the following:

▲• **B.** The retention time of the diphenhydramine peak in the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay, Procedure 1: Diphenhydramine*.▲ (USP 1-May-2021)

Add the following:

▲• **C.** The retention time of the 8-chlorotheophylline peak in the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay, Procedure 2: 8-Chlorotheophylline*.▲ (USP 1-May-2021)

ASSAY

Change to read:

• ▲**Procedure 1:**▲ (USP 1-May-2021) **Diphenhydramine**

▲**Solution A:** 10.0 g/L (equivalent to 13.8 mL/L) of triethylamine in water; adjusted with phosphoric acid to a pH of 2.5

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)	Flow Rate (mL/min)
0	82	18	1.2
2	82	18	1.2
15	50	50	1.2
20	20	80	2.0
32	20	80	2.0

Return to original conditions, and re-equilibrate the system for NLT 10 min.

Diluent: Acetonitrile and water (18:82)

System suitability solution: 0.114 mg/mL of USP Diphenhydramine Hydrochloride RS and 0.1 mg/mL each of USP Diphenhydramine Related Compound A RS, USP Theophylline RS, and USP Dimenhydrinate Related Compound E RS in *Diluent*. Sonicate to dissolve, if necessary.

Standard solution: 0.05 mg/mL of USP Diphenhydramine Hydrochloride RS in *Diluent*

Sample solution: 0.1 mg/mL of Dimenhydrinate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

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

Column temperature: 30°

Flow rate: See *Table 1*.

Injection volume: 10 µL

System suitability

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

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between diphenhydramine related compound A and diphenhydramine, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of diphenhydramine ($C_{17}H_{21}NO$) in the portion of Dimenhydrinate taken:

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

r_U = peak response of diphenhydramine 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 = concentration of Dimenhydrinate in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of diphenhydramine, 255.36

M_{r2} = molecular weight of diphenhydramine hydrochloride, 291.82

▲ (USP 1-May-2021)

Acceptance criteria: 53.0%–55.5% on the dried basis

Change to read:

• **▲PROCEDURE 2:▲** (USP 1-MAY-2021) **8-CHLOROTHEOPHYLLINE**

▲Solution A, Solution B, Mobile phase, Diluent, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay, Procedure 1: Diphenhydramine*.

Standard solution: 0.05 mg/mL of USP 8-Chlorotheophylline RS in *Diluent*

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of 8-chlorotheophylline ($C_7H_7ClN_4O_2$) in the portion of Dimenhydrinate taken:

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

r_U = peak response of 8-chlorotheophylline from the *Sample solution*

r_S = peak response of 8-chlorotheophylline from the *Standard solution*

C_S = concentration of USP 8-Chlorotheophylline RS in the *Standard solution* (mg/mL)

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

▲ (USP 1-May-2021)

Acceptance criteria: 44.0%–47.0% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.3%

Change to read:

• **Organic Impurities**

▲**Solution A, Solution B, Mobile phase, Diluent, System suitability solution,** and **Chromatographic system:** Proceed as directed in the *Assay, Procedure 1: Diphenhydramine.*▲ (USP 1-May-2021)

Standard solution: 2.28 µg/mL of USP Diphenhydramine Hydrochloride RS in *Diluent*

Sensitivity solution: 0.57 µg/mL of USP Diphenhydramine Hydrochloride RS in *Diluent*, from the *Standard solution*

Sample solution: 1.0 mg/mL of Dimenhydrinate in *Diluent*

▲▲ (USP 1-May-2021)

System suitability

Samples: *System suitability solution*, ▲*Standard solution*,▲ (USP 1-May-2021) and *Sensitivity solution*

Suitability requirements

Resolution: NLT 1.5 between diphenhydramine related compound A and diphenhydramine, *System suitability solution*

▲**Relative standard deviation:** NMT 5.0%, *Standard solution*▲ (USP 1-May-2021)

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲each▲ (USP 1-May-2021) individual impurity in the portion of Dimenhydrinate taken:

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

r_U = peak response of each ▲individual▲ (USP 1-May-2021) impurity 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 = concentration of Dimenhydrinate in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of diphenhydramine, 255.36

M_{r2} = molecular weight of diphenhydramine hydrochloride, 291.82

Acceptance criteria: See *Table 2*. ▲The reporting threshold is▲ (USP 1-May-2021) 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Theophylline	0.3	0.2
8-Chlorotheophylline	0.47	—
Dimenhydrinate related compound E	0.7	0.15
Diphenhydramine related compound A	0.95	0.2
Diphenhydramine	1.0	—
Any other individual impurity	—	0.10
Total impurities	—	0.5

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry under vacuum over phosphorus pentoxide for 24 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

Change to read:

• **USP REFERENCE STANDARDS** ⟨11⟩

▲ USP 8-Chlorotheophylline RS

8-Chloro-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione.

$C_7H_7ClN_4O_2$ 214.61▲ (USP 1-May-2021)

USP Dimenhydrinate RS

USP Dimenhydrinate Related Compound E RS

8-Chlorocaffeine;

8-Chloro-3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione.

$C_8H_9ClN_4O_2$ 228.64

USP Diphenhydramine Hydrochloride RS

USP Diphenhydramine Related Compound A RS

2-(Diphenylmethoxy)-*N*-methylethanamine hydrochloride.

$C_{16}H_{19}NO \cdot HCl$ 277.79

USP Theophylline RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
DIMENHYDRINATE	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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