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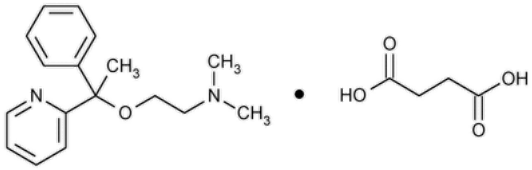
Doxylamine Succinate



$C_{17}H_{22}N_2O \cdot C_4H_6O_4$ 388.46

Ethanamine, *N*,*N*-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-, butanedioate (1:1);
2-[α-[2-(Dimethylamino)ethoxy]-α-methylbenzyl]pyridine succinate (1:1);
N,*N*-Dimethyl-2-[1-phenyl-1-(pyridin-2-yl)ethoxy]ethan-1-amine succinate CAS RN®: 562-10-7.

DEFINITION

Change to read:

Doxylamine Succinate contains NLT 98.0% and ▲NMT 102.0%▲ (USP 1-May-2019) of doxylamine succinate ($C_{17}H_{22}N_2O \cdot C_4H_6O_4$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: 197U**▲ (CN 1-May-2020)

Analytical wavelength: 262 nm

Sample solution: 20 µg/mL of Doxylamine Succinate in 0.1 N hydrochloric acid

Acceptance criteria: Absorptivities, calculated on the dried basis, do not differ by more than 3.0%

Delete the following:

▲• **B.** **Identification—Organic Nitrogenous Bases ⟨181⟩:** It meets the requirements.▲ (USP 1-May-2019)

Add the following:

▲• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2019)

• **C.**

Sample solution: Dissolve 500 mg of Doxylamine Succinate in 5 mL of water, and add a slight excess of 6 N ammonium hydroxide. Extract the liberated doxylamine with several portions of ether, discard the ether extracts, and evaporate the aqueous solution on a steam bath to dryness. Add 2 mL of 3 N hydrochloric acid, and again evaporate on the steam bath to dryness. Cool, add about 10 mL of ether, allow to stand for a few minutes, and decant the clear supernatant. Evaporate the ether solution to dryness, and dry the residue at 105° for 30 min.

Acceptance criteria: The succinic acid melts between 184° and 188°, as indicated for Class I under *Melting Range or Temperature ⟨741⟩, Procedures*.

ASSAY

Change to read:

• **Procedure**

▲**Solution A:** 50 mM ammonium acetate in water; adjusted with glacial acetic acid to a pH of 4.0

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10

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Time (min)	Solution A (%)	Solution B (%)
2	90	10
15	40	60
20	40	60
21	90	10
25	90	10

Diluent: *Solution A* and *Solution B* (90:10)

Standard solution: 0.1 mg/mL of USP Doxylamine Succinate RS in *Diluent*

Sample solution: 0.1 mg/mL of Doxylamine Succinate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 262 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of doxylamine succinate ($C_{17}H_{22}N_2O \cdot C_4H_6O_4$) in the portion of Doxylamine Succinate taken:

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

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

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

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

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

Acceptance criteria: 98.0%–102.0% on the dried basis▲ (USP 1-May-2019)

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

Delete the following:

▲• **Volatile Related Compounds**

Sample solution: Dissolve 650 mg in 20 mL of 0.1 N hydrochloric acid in a separator. Render the solution alkaline with 2.5 N sodium hydroxide, and immediately extract with four 25-mL portions of ether, filtering each extract through an ether-saturated pledget of cotton. Evaporate the combined ether extracts on a water bath with the aid of a current of air to dryness at a temperature not exceeding 50°, and dissolve the residue in 5 mL of alcohol.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 4-mm × 2-m glass column containing 5% packing G16 and 5% packing G12 on 60- to 80-mesh S1A

Temperatures

Column: 212°

Injection port: 250°

Detector block: 250°

Carrier gas: Dry helium

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Injection volume: 1 µL

Acceptance criteria: NMT 2.0%, the total relative area of all extraneous peaks (except that of the solvent peak); and NMT 1.0%, the relative area of any individual extraneous peak▲ (USP 1-May-2019)

Add the following:

▲• **Organic Impurities**

Solution A, Solution B, Mobile phase, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 0.001 mg/mL each of USP Doxylamine Succinate RS and USP Carbinoxamine Related Compound C RS in *Diluent*

Sample solution: 1.0 mg/mL of Doxylamine Succinate in *Diluent*

System suitability

Sample: *Standard solution*

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

Suitability requirements

Resolution: NLT 2 between doxylamine and carbinoxamine related compound C

Relative standard deviation: NMT 5.0% for the doxylamine and carbinoxamine related compound C peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of carbinoxamine related compound C in the portion of Doxylamine Succinate taken:

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

r_U = peak response of carbinoxamine related compound C from the *Sample solution*

r_S = peak response of carbinoxamine related compound C from the *Standard solution*

C_S = concentration of USP Carbinoxamine Related Compound C RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of each specified and any unspecified impurity in the portion of Doxylamine Succinate taken:

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

r_U = peak response of each specified and any unspecified impurity from the *Sample solution*

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

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

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

F = relative response factor of each specified and any unspecified impurity (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Doxylamine pyridinyl *N*-oxide[a]	0.64	2.1	0.10
Doxylamine dioxide[b]	0.70	1.8	0.10
Doxylamine pyridine-4-yl isomer[c]	0.81	1.0	0.15
Carbinoxamine related compound C	0.95	—	0.5
Doxylamine	1.0	—	—
Doxylamine ethylamine *N*-oxide[d]	1.06	1.0	0.10

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Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Doxylamine alcohol[e]	1.30	1.8	0.15
2-Benzoylpyridine[f]	1.44	5.8	0.15
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0▲ (USP 1-May-2019)

[a] 2-[1-(2-(Dimethylamino)ethoxy)-1-phenylethyl]pyridine 1-oxide.

[b] *N*,*N*-Dimethyl-2-(1-(1-oxidopyridin-2-yl)-1-phenylethoxy)ethan-1-amine oxide.

[c] *N*,*N*-Dimethyl-2-[1-phenyl-1-(pyridin-4-yl)ethoxy]ethan-1-amine.

[d] *N*,*N*-Dimethyl-2-[1-phenyl-1-(pyridin-2-yl)ethoxy]ethan-1-amine oxide.

[e] 1-Phenyl-1-(pyridin-2-yl)ethan-1-ol.

[f] Phenyl(pyridin-2-yl)methanone.

SPECIFIC TESTS

Delete the following:

▲• **Melting Range or Temperature, *Class I*⟨741⟩:** 103°–108°, the range between the beginning and end of melting does not exceed 3°.▲ (USP 1-May-2019)

• **Loss on Drying ⟨731⟩**

Analysis: Dry under vacuum over phosphorus pentoxide for 5 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

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

Change to read:

• **USP Reference Standards ⟨11⟩**

▲ USP Carbinoxamine Related Compound C RS

N,*N*-Dimethyl-2-[phenyl(pyridin-2-yl)methoxy]ethan-1-amine;
Desmethyl doxylamine.

$C_{16}H_{20}N_2O$ 256.35▲ (USP 1-May-2019)

USP Doxylamine Succinate RS

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

Topic/Question	Contact	Expert Committee
DOXYLAMINE SUCCINATE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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