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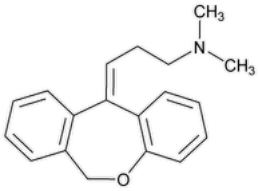
Doxepin Hydrochloride



• HCl

$C_{19}H_{21}NO \cdot HCl$ 315.84

1-Propanamine, 3-dibenz[*b*,*e*]oxepin-11(6*H*)ylidene-*N*,*N*- dimethyl-, hydrochloride;

N,*N*-Dimethyldibenz[*b*,*e*]oxepin-Δ^{11}-(6*H*)-γ-propylamine hydrochloride CAS RN®: 1229-29-4; UNII: 3U9A0FE9N5.

(*E*)-isomer CAS RN®: 4698-39-9; UNII: CU61C5RH24.

(*Z*)-isomer CAS RN®: 25127-31-5; UNII: XI27WMG8QK.

DEFINITION

Doxepin Hydrochloride, an (*E*) and (*Z*) geometric isomer mixture, contains the equivalent of NLT 98.0% and NMT 102.0% of doxepin hydrochloride ($C_{19}H_{21}NO \cdot HCl$), calculated on the dried basis. It contains NLT 13.6% and NMT 18.1% of the (*Z*)-isomer, and NLT 81.4% and NMT 88.2% of the (*E*)-isomer.

IDENTIFICATION

Change to read:

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

Change to read:

• **B.** The retention ▲times of the major peaks for the (*E*)- and (*Z*)-isomers of the *Sample solution* correspond to those▲ (USP 1-May-2021) of the *Standard solution*, as obtained in the *Assay*.

Change to read:

• **C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride***

Diluent: Alcohol and water (50:50)

Sample solution: 10 mg/mL of Doxepin Hydrochloride in *Diluent*

Acceptance criteria: Meets the requirements of ▲the test for amine hydrochlorides▲ (USP 1-May-2021)

ASSAY

Change to read:

• **Procedure**

▲**Solution A:** 27.6 g/L of monobasic sodium phosphate in water▲ (USP 1-May-2021)

Mobile phase: Methanol and ▲*Solution A* (30:70).▲ (USP 1-May-2021) Adjust with ▲diluted phosphoric acid▲ (USP 1-May-2021) to a pH of 2.5.

Standard solution: 0.1 mg/mL of USP Doxepin Hydrochloride RS in *Mobile phase*

Sample solution: 0.1 mg/mL of Doxepin Hydrochloride in *Mobile phase*. Sonication may be used to aid in dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4-mm × 12.5-cm; ▲5-µm▲ (USP 1-May-2021) packing L7

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 20 µL

▲**Run time:** NLT 2 times the retention time of the (*E*)-isomer▲ (USP 1-May-2021)

System suitability

Sample: *Standard solution*

▲[NOTE—The relative retention times for the (*E*)- and (*Z*)-isomers are 1.0 and 1.1, respectively.]▲ (USP 1-MAY-2021)

Suitability requirements

Resolution: NLT 1.5 between the (*E*)- and (*Z*)-isomers

Tailing factor: NMT 2.0 ▲each for▲ (USP 1-May-2021) the (*E*)- and (*Z*)-isomers

Relative standard deviation: NMT 2.0% ▲each for the (*E*)- and (*Z*)-isomers▲ (USP 1-May-2021)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of doxepin hydrochloride ($C_{19}H_{21}NO \cdot HCl$) in the portion of Doxepin Hydrochloride taken:

$$\text{Result} = [(r_{U(Z)} + r_{U(E)})/(r_{S(Z)} + r_{S(E)}] \times (C_S/C_U) \times 100$$

$r_{U(Z)}$ = peak response of the (*Z*)-isomer from the *Sample solution*

$r_{U(E)}$ = peak response of the (*E*)-isomer from the *Sample solution*

$r_{S(Z)}$ = peak response of the (*Z*)-isomer from the *Standard solution*

$r_{S(E)}$ = peak response of the (*E*)-isomer from the *Standard solution*

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

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

Calculate the percentage of the (*Z*)-isomer of doxepin hydrochloride ($C_{19}H_{21}NO \cdot HCl$) in the portion of Doxepin Hydrochloride taken:

$$\text{Result} = (r_{U(Z)}/r_{S(Z)}) \times (C_S/C_U) \times 100$$

$r_{U(Z)}$ = peak response of the (*Z*)-isomer from the *Sample solution*

$r_{S(Z)}$ = peak response of the (*Z*)-isomer from the *Standard solution*

C_S = concentration of the (*Z*)-isomer in the *Standard solution* (mg/mL) based on the labeled percentage of the (*Z*)-isomer in USP Doxepin Hydrochloride RS

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

Calculate the percentage of the (*E*)-isomer of doxepin hydrochloride ($C_{19}H_{21}NO \cdot HCl$) in the portion of Doxepin Hydrochloride taken:

$$\text{Result} = (r_{U(E)}/r_{S(E)}) \times (C_S/C_U) \times 100$$

$r_{U(E)}$ = peak response of the (*E*)-isomer from the *Sample solution*

$r_{S(E)}$ = peak response of the (*E*)-isomer from the *Standard solution*

C_S = concentration of the (*E*)-isomer in the *Standard solution* (mg/mL) based on the labeled percentage of the (*E*)-isomer in USP Doxepin Hydrochloride RS

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

Acceptance criteria

Doxepin hydrochloride: 98.0%–102.0% on the dried basis

(*Z*)-Isomer of doxepin hydrochloride: 13.6%–18.1%

(*E*)-Isomer of doxepin hydrochloride: 81.4%–88.2%

IMPURITIES

• **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.2%

Change to read:

• **ORGANIC IMPURITIES**

[NOTE—This procedure is not intended to resolve the (*E*)- and (*Z*)-isomers of doxepin hydrochloride. Minor variations in *Mobile phase* composition could result in a shoulder in the trailing edge of doxepin. In cases where there may be separation, both the (*E*)- and (*Z*)-isomers should be used in the appropriate calculation.]

Solution A: ▲Transfer 1 mL of phosphoric acid to a 10-mL volumetric flask containing about 5 mL of water. Cool and dilute with water to volume.▲ (USP 1-May-2021)

Buffer: 1.42 g/L of dibasic sodium phosphate, adjusted with *Solution A* to a pH of 7.7

Mobile phase: Methanol, acetonitrile, and *Buffer* (50:20:30)

Diluent: ▲To each liter of *Mobile phase* add 2 mL of 2 N sodium hydroxide TS.▲ (USP 1-May-2021)

Standard solution: 0.001 mg/mL each of USP Doxepin Hydrochloride RS, USP Doxepin Related Compound A RS, and USP Doxepin Related Compound B RS; and 0.002 mg/mL of USP Doxepin Related Compound C RS in *Diluent*. Sonication for about 1 min may be used to aid the initial dissolution of the compounds.

▲**Sensitivity solution:** 0.0005 mg/mL each of USP Doxepin Hydrochloride RS, USP Doxepin Related Compound A RS, and USP Doxepin Related Compound B RS; and 0.001 mg/mL of USP Doxepin Related Compound C RS from *Standard solution* in *Diluent*▲ (USP 1-May-2021)

Sample solution: 1 mg/mL of Doxepin Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: 2.2 times the retention time of doxepin

System suitability

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

[NOTE—See *Table 1* for relative retention times. The doxepin related compound C peak will be the largest peak in the *Standard solution* chromatogram.]

Suitability requirements

Resolution: NLT 1.5 between doxepin related compound A and doxepin related compound C; NLT 1.5 between doxepin related compound C and doxepin related compound B, ▲*Standard solution*

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

Signal-to-noise ratio: NLT 10 for ▲doxepin, doxepin related compound A, doxepin related compound B, and doxepin related compound C, *Sensitivity solution*▲ (USP 1-May-2021)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each doxepin related compound in the portion of Doxepin Hydrochloride taken:

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

r_U = peak response of doxepin related compound A, B, or C from the *Sample solution*

r_S = peak response of doxepin related compound A, B, or C from the *Standard solution*

C_S = concentration of USP Doxepin Related Compound A RS, USP Doxepin Related Compound B RS, or USP Doxepin Related Compound C RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of each unspecified impurity in the portion of Doxepin Hydrochloride taken:

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

r_U = peak response of each unspecified ▲impurity▲ (USP 1-May-2021) from the *Sample solution*

r_S = peak response of doxepin [sum of (*E*)- and (*Z*)-isomers] from the *Standard solution*

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

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

Acceptance criteria: See *Table 1*. Disregard any peak with a relative retention time less than 0.25. ▲The reporting threshold is 0.05%.▲ (USP 1-May-2021)

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Doxepin related compound A	0.48	0.10
Doxepin related compound C	0.55	0.20
Doxepin related compound B	0.63	0.10
Doxepin	1.0	—
Any individual, unspecified impurity	—	0.10
▲Total impurities	—	0.50▲ (USP 1-May-2021)

SPECIFIC TESTS

• **Loss on Drying** ⟨731⟩

Analysis: Dry under vacuum at 60° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

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

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Doxepin Hydrochloride RS

USP Doxepin Related Compound A RS

Dibenzo[*b*,*e*]oxepin-11(6*H*)-one.

$C_{14}H_{10}O_2$ 210.23

USP Doxepin Related Compound B RS

▲(11*RS*)▲ (USP 1-May-2021) -(3-(Dimethylamino)propyl)-6,11-dihydrodibenzo[*b*,*e*]oxepin-11-ol.

$C_{19}H_{23}NO_2$ 297.39

USP Doxepin Related Compound C RS

▲(*EZ*)▲ (USP 1-May-2021) -3-(Dibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)-*N*-methylpropan-1-amine hydrochloride.

$C_{18}H_{19}NO \cdot HCl$ 301.81

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

Topic/Question	Contact	Expert Committee
DOXEPIN HYDROCHLORIDE	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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