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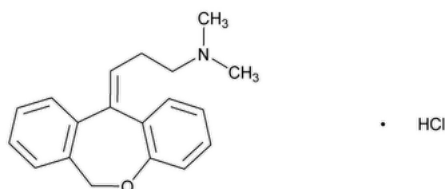
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Doxepin Hydrochloride


 $C_{19}H_{21}NO \cdot HCl$ 315.84
1-Propanamine, 3-dibenz[b,e]oxepin-11(6H)ylidene-*N,N*-dimethyl-, hydrochloride;*N,N*-Dimethyldibenz[b,e]oxepin- Δ^{11} -(6H)- 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- μ m ▲ (USP 1-May-2021) packing [L7](#)

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 20 μ L

▲**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