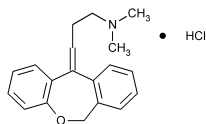


Doxepin Hydrochloride



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

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

N,N-Dimethyldibenz[*b,e*]oxepin- $\Delta^{11(6H),\gamma}$ -propylamine hydrochloride [1229-29-4; 4698-39-9 ((*E*)-isomer); 25127-31-5 ((*Z*)-isomer)].

» Doxepin Hydrochloride, an (*E*) and (*Z*) geometric isomer mixture, contains the equivalent of not less than 98.0 percent and not more than 102.0 percent of doxepin ($C_{19}H_{21}NO \cdot HCl$), calculated on the dried basis. It contains not less than 13.6 percent and not more than 18.1 percent of the (*Z*)-isomer, and not less than 81.4 percent and not more than 88.2 percent of the (*E*)-isomer.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards (11)—*USP Doxepin Hydrochloride RS*. *USP Doxepin Related Compound A RS*. *USP Doxepin Related Compound B RS*. *USP Doxepin Related Compound C RS*.

Identification—

A: *Infrared Absorption* (197K).

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

C: A solution (1 in 100) in a mixture of water and alcohol (1 : 1) meets the requirements of the test for *Chloride* (191) in amine hydrochlorides.

Loss on drying (731)—Dry it in vacuum at 60° for 3 hours; it loses not more than 0.5% of its weight.

Residue on ignition (281): not more than 0.2%.

Heavy metals, Method II (231): 0.002%.

Organic volatile impurities, Method I (467): meets the requirements.

(Official until July 1, 2008)

Related compounds—

Diluted phosphoric acid—Prepare a mixture of water and phosphoric acid (10 : 1), and mix well.

Buffer—Dissolve 1.42 g of dibasic sodium phosphate in 1 L of water, adjust with *Diluted phosphoric acid* to a pH of 7.7, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol, *Buffer*, and acetonitrile (50 : 30 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

Diluent—Prepare a mixture of *Mobile phase* and 2 N sodium hydroxide (1000 : 2).

Standard solution—Dissolve accurately weighed quantities of USP Doxepin Hydrochloride RS, USP Doxepin Related Compound A RS, USP Doxepin Related Compound B RS, and USP Doxepin Related Compound C RS in *Diluent* to obtain a solution having a known concentration of about 0.001 mg of doxepin related compound A and doxepin related compound B each per mL, and 0.002 mg per mL of doxepin related compound C. [NOTE—Sonication for about 1 minute may be used to aid the initial dissolution of the compounds.]

Test solution—Dissolve an accurately weighed quantity of Doxepin Hydrochloride in *Diluent* to obtain a final solution having a known concentration of about 1 mg per mL.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column that contains 5- μ m packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 30°. Chromatograph about 20 μ L of the *Standard solution*, and rec-

ord the peak areas as directed for *Procedure*: the resolution, *R*, between doxepin related compound A and doxepin related compound C is not less than 1.5; the resolution between doxepin related compound C and doxepin related compound B is not less than 1.5; and the signal-to-noise ratio for all the peaks is not less than 10. [NOTE—Use the approximate relative retention times given in *Table 1* for the purpose of peak identification. The doxepin related compound C peak will be the largest peak in the *Standard solution* chromatogram.]

Table 1

Name	Relative Retention Time (RRT)	Limit (%)
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 hydrochloride	1.0	—
Unknown impurity	—	0.10 each

Procedure—Inject a volume (about 20 μ L) of the *Test solution* into the chromatograph, record the chromatogram for up to 2.2 times the retention time of doxepin, and measure the peak responses. Calculate the percentage of each individual doxepin related compound in the portion of Doxepin Hydrochloride taken by the formula:

$$100(r_U / r_S)(C_S / C_T)$$

in which r_U is the individual peak response for each doxepin related compound obtained from the *Test solution*; r_S is the response of the corresponding peak in the *Standard solution*; C_S is the concentration, in mg per mL, of each doxepin related compound in the *Standard solution*; and C_T is the concentration, in mg per mL, of Doxepin Hydrochloride in the *Test solution*. The related substance limits are listed in *Table 1*. [NOTE—Discard any peak with a relative retention time less than 0.25. This method is not intended to resolve the *E*- and *Z*-isomers of doxepin hydrochloride. Minor variations in the 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 calculations.] Use the response of the doxepin peak obtained from the *Standard solution* and the concentration of doxepin hydrochloride in the *Standard solution* to calculate the percentage of unknown individual impurities.

Assay—

Mobile phase—Prepare a mixture of 0.2 M monobasic sodium phosphate buffer and methanol (7 : 3), adjust with 2 N phosphoric acid to a pH of 2.5, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

Standard preparation—Dissolve an accurately weighed quantity of USP Doxepin Hydrochloride RS in *Mobile phase*, and dilute quantitatively and stepwise with *Mobile phase* to obtain a solution having a known concentration of about 100 μ g per mL.

Assay preparation—Transfer about 50 mg of Doxepin Hydrochloride, accurately weighed, to a 100-mL volumetric flask. Add about 70 mL of *Mobile phase*, and sonicate to dissolve. Dilute with *Mobile phase* to volume, and mix. Pipet 10.0 mL of this solution into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system—The liquid chromatograph is equipped with a 254-nm detector and a 4-mm × 12.5-cm column, heated to 50°, that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure*: the resolution between the (*E*)- and (*Z*)-isomers is not less than 1.5, the tailing factor for each analyte peak is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 μ L) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the

major peaks. Calculate the quantity, in mg, of $C_{19}H_{21}NO \cdot HCl$ in the portion of Doxepin Hydrochloride taken by the formula:

$$0.5C[(r_{U(Z)} + r_{U(E)}) / (r_{S(Z)} + r_{S(E)})]$$

in which C is the concentration, in μg per mL, of USP Doxepin Hydrochloride RS in the *Standard preparation*, and $r_{U(Z)}$ and $r_{U(E)}$ are the respective peak responses of the (*Z*)- and (*E*)-isomers obtained from the *Assay preparation*, and $r_{S(Z)}$ and $r_{S(E)}$ are the respective peak responses of the (*Z*)- and (*E*)-isomers obtained from the *Standard preparation*. Calculate the percentage of the (*Z*)-isomer in the *Assay preparation* taken by the formula:

$$(r_{U(Z)} / r_{S(Z)})(W_S / W_T)(P_Z)$$

in which W_S is the weight, in mg, of USP Doxepin Hydrochloride RS in the *Standard preparation*, W_T is the weight, in mg, in the

portion of Doxepin Hydrochloride taken, and P_Z is the labeled percentage of (*Z*)-isomer in USP Doxepin Hydrochloride RS. Similarly calculate the percentage of (*E*)-isomer in the *Assay preparation* taken by the formula:

$$(r_{U(E)} / r_{S(E)})(W_S / W_T)(P_E)$$

in which P_E is the labeled percentage of (*E*)-isomer in USP Doxepin Hydrochloride RS.