Doxepin Hydrochloride Capsules

Type of Posting	Revision Bulletin
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Expert Committee	Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 4 Expert Committee has revised the Doxepin Hydrochloride Capsules monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

- *Dissolution Test 2* was validated using the Xterra RP18 brand of 150-mm × 4.6-mm, 3.5-µm column with L1 packing. The typical retention time for doxepin is about 4 min.

Additionally, minor editorial changes have been made to update the monograph to current *USP* style.

The Doxepin Hydrochloride Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Devarshi Narendra Thaker, Scientific Liaison (404-448-8945 or devarshinarendra.t@usp.org).

Revision Bulletin
Official: May 1, 2021

Doxepin Hydrochloride Capsules

Change to read:

DEFINITION

Doxepin Hydrochloride Capsules contain ▲an amount of Doxepin Hydrochloride equivalent to▲ (USP 1-May-2021) NLT 90.0% and NMT 110.0% of the labeled amount of doxepin ($C_{19}H_{21}NO$).

IDENTIFICATION

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

Add the following:

▲• **B.** The UV spectra of the major peaks for the (*E*)- and (*Z*)-isomers of doxepin in the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.▲ (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: ▲0.11 mg/mL of USP Doxepin Hydrochloride RS (equivalent to 0.1 mg/mL of doxepin)▲ (USP 1-May-2021) in *Mobile phase*

Sample stock solution: Nominally ▲0.57 mg/mL of doxepin hydrochloride (equivalent to 0.5 mg/mL of doxepin)▲ (USP 1-May-2021) from the contents of NLT 20 Capsules in *Mobile phase*, prepared as follows. Remove, as completely as possible, the contents of NLT 20 Capsules. Mix the combined contents, and transfer a suitable quantity of the powder, equivalent to 50 mg of doxepin, ▲▲ (USP 1-May-2021) to a 100-mL volumetric flask. Add 70 mL of *Mobile phase*, and shake by mechanical means for 30 min. Dilute with *Mobile phase* to volume, and filter. Use the filtrate.

Sample solution: Nominally 0.1 mg/mL of doxepin ▲▲ (USP 1-May-2021) from *Sample stock solution* in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm. ▲For *Identification B*, use a diode array detector in the range of 200–400 nm.▲ (USP 1-May-2021)

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 first peak of doxepin▲ (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.]

Suitability requirements

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

Tailing factor: NMT 2.0 each for 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 the labeled amount of doxepin ($C_{19}H_{21}NO$) in the portion of Capsules taken:

$$\text{Result} = [(r_{U(Z)} + r_{U(E)})/(r_{S(Z)} + r_{S(E)})] \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

$r_{U(Z)}$ = 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 doxepin hydrochloride in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of doxepin, 279.38

M_{r2} = molecular weight of doxepin hydrochloride, 315.84

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

▲**Test 1**▲ (RB 1-May-2021)

Medium: Water; 900 mL

Apparatus 1: 50 rpm

Time: 30 min

Standard solution: USP Doxepin Hydrochloride RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Medium*, if necessary, to the same concentration as the *Standard solution*.

Instrumental conditions

Mode: UV

Analytical wavelength: ▲▲ (USP 1-May-2021) 292 nm

Analysis

Samples: *Standard solution* and *Sample solution*

▲Calculate the percentage of the labeled amount of doxepin ($C_{19}H_{21}NO$) in the portion of Capsules taken:

$$\text{Result} = (A_U/A_S) \times C_S \times D \times (M_{r1}/M_{r2}) \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

D = dilution factor of the *Sample solution,* if necessary

M_{r1} = molecular weight of doxepin, 279.38

M_{r2} = molecular weight of doxepin hydrochloride, 315.84

V = volume of *Medium,* 900 mL

L = label claim of doxepin hydrochloride (mg/Capsule) ▲ (USP 1-May-2021)

Tolerances: NLT 80% (Q) of the labeled amount of doxepin ($C_{19}H_{21}NO$) is dissolved.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.15% w/v pepsin (1:10000 with albumin substrate) in water; 900 mL. [NOTE—The *Medium* may appear hazy.]

Apparatus 1: 50 rpm

Time: 30 min

Dilute phosphoric acid: Transfer 6.5 mL of phosphoric acid to a 100-mL volumetric flask and dilute with water to volume.

Buffer: 1.42 g/L of anhydrous dibasic sodium phosphate in water, adjust with dilute phosphoric acid to a pH of 7.7

Mobile phase: Acetonitrile and *Buffer* (60:40)

Standard stock solution: 0.63 mg/mL of USP Doxepin Hydrochloride RS (equivalent to 0.6 mg/mL of doxepin) prepared as follows. Transfer a suitable quantity of USP Doxepin Hydrochloride RS to an appropriate volumetric flask. Add 70% of the flask volume of *Medium*. Sonicate for about 5 min and dilute with *Medium* to volume.

Standard solution: (L/800) mg/mL of USP Doxepin Hydrochloride RS (equivalent to [L/900] mg/mL of doxepin) from *Standard stock solution*, where L is the label claim in mg/Capsule, prepared as follows. Transfer a portion of *Standard stock solution* to an appropriate volumetric flask and dilute with *Medium* to volume. Pass the resulting solution through a suitable filter discarding the first few milliliters.

Sample solution: Pass a portion of the solution under test through a suitable filter discarding the first few milliliters.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 10 µL

Run time: NLT 1.5 times the retention time of doxepin

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of doxepin ($C_{19}H_{21}NO$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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

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

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

V = volume of *Medium*, 900 mL

M_{r1} = molecular weight of doxepin, 279.38

M_{r2} = molecular weight of doxepin hydrochloride, 315.84

L = label claim for doxepin (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of doxepin ($C_{19}H_{21}NO$) is dissolved. ▲ (RB 1-May-2021)

Change to read:

● **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

The following procedure is used where the test for *Content Uniformity* is required.

Procedure for content uniformity

Diluent: Methanol and ▲0.05 M monobasic sodium phosphate TS▲ (USP 1-May-2021) (50:50). Adjust with ▲2 N sodium hydroxide TS▲ (USP 1-May-2021) to a pH of 6.7.

Standard solution: ▲0.11 mg/mL of USP Doxepin Hydrochloride RS (equivalent to 0.1 mg/mL of doxepin)▲ (USP 1-May-2021) in *Diluent*. Filter, and use the resulting filtrate.

Sample solutions: Nominally 0.1 mg/mL of doxepin ▲▲ (USP 1-May-2021) from 1 Capsule prepared as follows. Transfer the contents of 1 Capsule into an appropriate volumetric flask, add 80% of the final flask volume of *Diluent*, and shake the flask by mechanical means for about 30 min. Dilute with *Diluent* to volume. If necessary, transfer a suitable quantity of the resulting solution to another appropriate volumetric flask, and dilute with *Diluent* to volume. Prepare 10 *Sample solutions*.

Instrumental conditions

Mode: UV

Analytical wavelength: ▲▲ (USP 1-May-2021) 292 nm

Cell: 0.5 cm

Analysis

Samples: *Standard solution* and *Sample solutions*

Determine the amount of active ingredient in each unit of the *Sample solution* in comparison with the *Standard solution*.

IMPURITIES

Add the following:

▲● **Organic Impurities**

Solution A: 1.6 g/L of ammonium formate in water

Mobile phase: Acetonitrile and *Solution A* (45:55)

System suitability solution: 570 µg/mL of USP Doxepin Hydrochloride RS (equivalent to 500 µg/mL of doxepin), 0.5 µg/mL of USP Doxepin Related Compound B RS, and 1 µg/mL of USP Doxepin Related Compound C RS in *Mobile phase*

Standard solution: 5.7 µg/mL of USP Doxepin Hydrochloride RS (equivalent to 5 µg/mL of doxepin) in *Mobile phase*

Sensitivity solution: 0.28 µg/mL of USP Doxepin Hydrochloride RS (equivalent to 0.25 µg/mL of doxepin) from *Standard solution* in *Mobile phase*

Sample solution: Nominally 500 µg/mL of doxepin from Capsules prepared as follows. Combine the contents of NLT 20 Capsules. Transfer a portion of the contents, equivalent to 50 mg of doxepin, to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume and stir for 10 min. Pass the resulting solution through a suitable filter of 0.7-µm pore size and discard the first 5 mL.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Column temperature: 30°

Flow rate: 1.2 mL/min

Injection volume: 20 µL

Run time: NLT 6.3 times the retention time of doxepin

System suitability

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

[Note—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between doxepin related compound B and doxepin related compound C; NLT 1.5 between doxepin related compound C and doxepin, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

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

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

C_U = nominal concentration of doxepin in the *Sample solution* (µg/mL)

M_{r1} = molecular weight of doxepin, 279.38

M_{r2} = molecular weight of doxepin hydrochloride, 315.84

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*. The reporting threshold is 0.05%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Doxepin related compound B[a]	0.73	—	—
Doxepin related compound C[a]	0.88	—	—
Doxepin	1.0	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Doxepin related compound A[b]	3.75	1.26	0.2
Any individual impurity	—	1.0	0.2
Total impurities	—	—	0.5▲ (USP 1-May-2021)

[a] Process impurity included in the table for identification purposes only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.

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

SPECIFIC TESTS

- **WATER DETERMINATION ⟨921⟩, *Method I***

Sample: Contents of 1 Capsule

Acceptance criteria: NMT 9.0%

ADDITIONAL REQUIREMENTS

Change to read:

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. ▲Store at controlled room temperature.▲ (USP 1-May-2021)

Add the following:

▲- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (RB 1-May-2021)

Change to read:

- **USP REFERENCE STANDARDS ⟨11⟩**

USP Doxepin Hydrochloride RS

▲USP Doxepin Related Compound B RS

11(*RS*)-(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*)-3-(Dibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)-*N*-methylpropan-1-amine hydrochloride.

$C_{18}H_{19}NO \cdot HCl$ 301.81▲ (USP 1-May-2021)

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