Doxepin Hydrochloride Capsules

**Type of Posting**  |  Revision Bulletin  
**Posting Date**  |  18-Dec-2020  
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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).
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)
  Standard solution: 0.11 mg/mL of USP Doxepin Hydrochloride RS (equivalent to 0.1 mg/mL of doxepin) (USP 1-May-2021)
  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 \((\text{C}_{19}\text{H}_{21}\text{NO})\) in the portion of Capsules taken:

\[
\text{Result} = \left[\frac{r_U(Z) + r_U(E)}{r_S(Z) + r_S(E)}\right] \times \left(\frac{C_S}{C_U}\right) \times \left(\frac{M_{r1}}{M_{r2}}\right) \times 100
\]

- \(r_U(Z)\) = 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: 292 nm

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of doxepin \((\text{C}_{19}\text{H}_{21}\text{NO})\) in the portion of Capsules taken:

\[
\text{Result} = \left(\frac{A_U}{A_S}\right) \times C_S \times D \times \left(\frac{M_{r1}}{M_{r2}}\right) \times V \times (1/L) \times 100
\]

- \(A_U\) = 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) \(^\text{a} \) (USP 1-May-2021)  

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

\(^\text{a}\) 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 \( \times \) 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:
\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{M_{r_1}}{M_{r_2}} \right) \times (1/L) \times 100 \]

- \( r_U \) = 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
- \( M_{r_1} \) = molecular weight of doxepin, 279.38
- \( M_{r_2} \) = 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\textsubscript{19}H\textsubscript{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 \( 0.05 \text{ M monobasic sodium phosphate TS} \) ▲ (USP 1-May-2021) (50:50). Adjust with \( 2 \text{ N sodium hydroxide TS} \) ▲ (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**.

**IMPUSTERIES**

**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 x 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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_{r1}}{M_{r2}} \right) \times \left( \frac{1}{F} \right) \times 100
\]

- \( r_U \) = 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>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin related compound B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.73</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Doxepin related compound C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.88</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Doxepin</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Name</td>
<td>Relative Retention Time</td>
<td>Relative Response Factor</td>
<td>Acceptance Criteria, NMT (%)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------</td>
<td>--------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Doxepin related compound Ab</td>
<td>3.75</td>
<td>1.26</td>
<td>0.2</td>
</tr>
<tr>
<td>Any individual impurity</td>
<td>—</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>0.5 ▲ (USP 1-May-2021)</td>
</tr>
</tbody>
</table>

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[bc]oxepin-11(6H)-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
    - \( C_{19}H_{23}NO_2 \) 297.39
  - ▲ USP Doxepin Related Compound C RS
    - \( C_{18}H_{19}NO \cdot HCl \) 301.81 ▲ (USP 1-May-2021)

**Page Information:**

Not Applicable

**DocID:**

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