Duloxetine Delayed-Release Capsules

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Expert Committee: Chemical Medicines Monographs 4  
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Duloxetine Delayed-Release Capsules monograph. The purpose for the revision is to add two dissolution tests to accommodate drug products which have been approved by the FDA and to provide minor clarifications in the monograph.

The analysis within *Dissolution, Test 3* was validated using a Zorbax Eclipse XDB-C18 brand of L1 column. The typical retention time of duloxetine is about 4 min. The acid stage analysis within *Dissolution, Test 4* was validated using an Inertsil ODS-3 brand of L1 column. The typical retention time of duloxetine is about 5.7 min. Additionally, minor editorial changes have been made to update the monograph to current *USP* style.

The Duloxetine Delayed-Release Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *First Supplement to USP 41–NF 36*.

Should you have any questions, please contact Heather Joyce, Ph.D., Senior Scientific Liaison (301–881–0666 or hrj@usp.org).
Duloxetine Delayed-Release Capsules

**DEFINITION**
Duloxetine Delayed-Release Capsules contain an amount of Duloxetine Hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of duloxetine (C18H19NOS).

**IDENTIFICATION**

- **A. INFRARED ABSORPTION (197F):**
  - Change to read: Mr1 Duloxetine Delayed-Release Capsules
  - Change to read: Mr2 Duloxetine Hydrochloride RS in the Assay Standard solution, as CS3.4 g/L of monobasic potassium phosphate in water adjusted with 5 N sodium hydroxide to a pH of 7.5.
  - System suitability: Run time: 6.9 g/L of monobasic sodium phosphate in water adjusted with 5 N sodium hydroxide to a pH of 11.0. To 1 L of this solution add 15 mL of triethylamine, and adjust with phosphoric acid to a pH of 5.5.
  - Standard: 1 mg/mL of USP Duloxetine Hydrochloride RS in methylene chloride. Shake the contents, and sonicate for 1 min. Transfer 15 mL of filtrate into a separation funnel, and add 15 mL of Buffer. Collect the organic layer, and evaporate to dryness. Redissolve the residue with a few drops of methylene chloride, and transfer to a potassium bromide or sodium chloride plate. Allow it to dry. Sample: 1 mg/mL of duloxetine, from the contents of NLT 10 Capsules in methylene chloride. Proceed as directed in the Standard.
  - Acceptance criteria: Meet the requirements
  - **B.** The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

**ASSAY**

**Change to read:**

- **PROCEDURE**
  - Protect solutions of duloxetine from light.
  - **Buffer A:** 3.4 g/L of monobasic potassium phosphate in water. To 1 L of this solution add 15 mL of triethylamine, and adjust with phosphoric acid to a pH of 5.5.
  - **Buffer B:** 0.2 g/L of monobasic ammonium phosphate and 4.5 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 8.0.
  - **Mobile phase:** Methanol, tetrahydrofuran, and Buffer A (323:90:57).
  - **Diluent:** Methanol and Buffer B (50:50).
  - **System suitability solution:** 0.1 mg/mL of USP Duloxetine Hydrochloride RS, 0.05 mg/mL of α-naphthol, 0.01 mg/mL of USP Duloxetine Related Compound F RS, and 0.025 mg/mL of USP Duloxetine Related Compound H RS in Diluent. [NOTE—Add 1 mL of methanol before diluting to volume to assist with dissolving contents. Duloxetine related compound H is used for peak identification purposes in this solution.]
  - **Standard solution:** 0.1 mg/mL of USP Duloxetine Hydrochloride RS in Diluent.
  - **Sample solution:** Nominally 0.1 mg/mL of duloxetine from the contents of NLT 5 Capsules, in Diluent.
  - **Chromatographic system** (See Chromatography (621), System Suitability.) [NOTE—It is recommended to preheat the Mobile phase to 45°C.]

**Mode:** LC
**Detector:** UV 230 nm
**Column:** 4.6-mm x 7.5-cm; 3- or 3.5-µm packing L7
**Column temperature:** 45°C
**Flow rate:** 1.5 mL/min
**Injection volume:** 10 µL
**Run time:** 6 times the retention time of duloxetine

**System suitability**
**Samples:** System suitability solution
**[Note—See Table 2A (BB 1-Aug-2017) in Organic Impurities for relative retention times.]**
**Suitability requirements**
- **Resolution:** NLT 1.6 between duloxetine and duloxetine related compound F; NLT 2 between α-naphthol and duloxetine related compound H.
- **System suitability solution**
- **Relative standard deviation:** NMT 1.5%, Standard solution

**Analysis**
**Samples:** Standard solution and Sample solution
Calculate the percentage of the labeled amount of duloxetine (C18H19NOS) in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times (C_0/C_U) \times (M_1/M_2) \times 100
\]

- \(r_U\) = peak response from the Sample solution
- \(r_S\) = peak response from the Standard solution
- \(C_0\) = concentration of USP Duloxetine Hydrochloride RS in the Standard solution (mg/mL)
- \(C_U\) = nominal concentration of duloxetine in the Sample solution (mg/mL)
- \(M_1\) = molecular weight of duloxetine free base, 297.42
- \(M_2\) = molecular weight of duloxetine hydrochloride, 333.88
- **Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**
  - **Test 1**
    - **Acid stage**
      - **Acid stage medium:** 0.1 N hydrochloric acid VS;
      - **Apparatus 1:** 100 rpm
      - **Time:** 2 h
    - **Buffer stage**
      - **Buffer stage medium:** pH 6.8 phosphate buffer; 1000 mL
      - **Apparatus 1:** 100 rpm
      - **Time:** 60 min for Capsules containing 20% w/w pellets; 90 min for Capsules containing 32% w/w pellets
    - **Buffer A and Mobile phase:** Proceed as directed in the Assay.
  - **Standard stock solution:** 0.28 mg/mL of USP Duloxetine Hydrochloride RS, equivalent to 0.25 mg/mL of duloxetine, in Buffer stage medium. Use a small amount of methanol, not exceeding 2% of the final volume, to dissolve duloxetine.
  - **Acid stage standard solution:** 0.0023 mg/mL of USP Duloxetine Hydrochloride RS, equivalent to 0.002 mg/mL of duloxetine, in Buffer stage medium from the Standard stock solution diluted with Buffer stage medium.
Buffer stage standard solution: *0.023 mg/mL of USP Duloxetine Hydrochloride RS, equivalent to 0.02 mg/mL of duloxetine,* (RB 1-Aug-2017) from the Standard stock solution diluted with Buffer stage medium

Sample solution: After 2 h in the Acid stage medium, pass a portion of the solution under test through a suitable filter. Transfer the basket containing the pellets to the vessel containing the Buffer stage medium. After the appropriate time in the Buffer stage medium, pass a portion of the solution under test through a suitable filter.

Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 7.5-cm; 3- or 3.5-μm packing L7

Column temperature: 45°

Flow rate: 1.5 mL/min

Injection volume: 10 μL

System suitability
Sample: Acid stage standard solution

[Note—The relative retention times for duloxetine and α-naphthol are 1.0 and 1.4, respectively.]

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: Acid stage standard solution, Buffer stage standard solution, and Sample solution

Calculate the concentration of duloxetine in the Acid stage medium (C1):

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_1 \times \left( \frac{M_1}{M_2} \right)
\]

\( r_U \) = peak response of duloxetine from the Sample solution

\( r_S \) = peak response of duloxetine from the Acid stage standard solution

\( C_1 \) = concentration of USP Duloxetine Hydrochloride RS in the Acid stage standard solution (mg/mL)

\( M_1 \) = molecular weight of duloxetine free base, 297.42

\( M_2 \) = molecular weight of duloxetine hydrochloride, 333.88

Calculate the equivalent concentration of duloxetine from α-naphthol (RB 1-Aug-2017) in the Acid stage medium (C2):

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_2 \times \left( \frac{M_1}{M_2} \right) \times \left( \frac{M_1}{M_3} \right)
\]

\( r_U \) = peak response of α-naphthol (RB 1-Aug-2017) from the Sample solution

\( r_S \) = peak response of duloxetine from the Acid stage standard solution

\( C_2 \) = concentration of USP Duloxetine Hydrochloride RS in the Acid stage standard solution (mg/mL)

\( M_1 \) = molecular weight of duloxetine free base, 297.42

\( M_2 \) = molecular weight of duloxetine hydrochloride, 333.88

\( M_3 \) = molecular weight of α-naphthol, (RB 1-Aug-2017) 144.17

Calculate the percentage of the labeled amount of duloxetine dissolved (RB 1-Aug-2017) in the Acid stage medium (Qa):

\[
\text{Result} = \left( \frac{C_1 + C_2}{V} \right) \times \left( \frac{1}{L} \right) \times 100
\]

\( C_1 \) = concentration of duloxetine in the Acid stage medium (mg/mL)

\( C_2 \) = equivalent concentration of duloxetine from α-naphthol (RB 1-Aug-2017) in the Acid stage medium (mg/mL)

\( V \) = volume of Medium, 1000 mL

\( L \) = label claim of duloxetine (mg/Capsule)

Calculate the percentage of the labeled amount of duloxetine dissolved (RB 1-Aug-2017) in the Buffer stage medium:

\[
\text{Result} = \left[ \left( \frac{r_U}{r_S} \right) \times (C_1/L) \times V \times \left( \frac{M_1}{M_2} \right) \times 100 \right] + Q_a
\]

\( r_U \) = peak response of duloxetine from the Sample solution

\( r_S \) = peak response of duloxetine from the Buffer stage standard solution

\( C_1 \) = concentration of USP Duloxetine Hydrochloride RS in the Buffer stage standard solution (mg/mL)

\( L \) = label claim (mg/Capsule)

\( V \) = volume of Medium, 1000 mL

\( M_1 \) = molecular weight of duloxetine free base, 297.42

\( M_2 \) = molecular weight of duloxetine hydrochloride, 333.88

\( Q_a \) = percentage of the labeled amount of duloxetine dissolved (RB 1-Aug-2017) in the Acid stage medium

Tolerances

Acid stage: No individual unit releases more than 10% of the labeled amount of duloxetine in 2 h.

Buffer stage

For Capsules containing 20% w/w pellets: NLT 75% (Q) of the labeled amount of duloxetine is dissolved in 60 min.

For Capsules labeled to contain 32% w/w pellets: NLT 75% (Q) of the labeled amount of duloxetine is dissolved in 90 min.

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2. Protect solutions of duloxetine from light.

Acid stage

Acid stage medium: *0.1 N hydrochloric acid VS* (RB 1-Aug-2017) 750 mL

Apparatus 2: 100 rpm

Time: 2 h in Acid stage medium

Buffer stage

Buffer stage medium: pH 6.8 phosphate buffer (after 2 h, add 250 mL of 76 g/L of tribasic sodium phosphate, previously heated to 37 ± 0.5°, to the Acid stage medium), 1000 mL

Apparatus 2: 100 rpm

Time: 3 h in Buffer stage medium. The time in Buffer stage medium includes the time in Acid stage medium.

Solution A: A mixture of triethylamine and water prepared as follows. Add 15 mL of triethylamine to 1 L of water and adjust with phosphoric acid to a pH of 2.5 ± 0.05.

Mobile phase: Acetonitrile and Solution A (40:60)

Diluent: *0.1 N hydrochloric acid VS* (RB 1-Aug-2017) and 76 g/L of tribasic sodium phosphate (75:25)

Standard stock solution: 0.46 mg/mL of USP Duloxetine Hydrochloride RS, equivalent to 0.4 mg/mL of duloxetine, prepared as follows. Transfer a suitable amount of USP Duloxetine Hydrochloride RS to an appropriate volumetric flask and dissolve in 50% of the final flask volume of Mobile phase. Dilute with Mobile phase to volume.
Standard solution: 0.046 mg/mL of USP Duloxetine Hydrochloride RS, equivalent to 0.04 mg/mL of duloxetine, from the Standard stock solution in Diluent

Acid stage sample solution and Buffer stage sample solution: Pass a portion of the solution under test through a suitable filter, and use the filtrate. [Note—A cannula-style filter with a 20-µm pore size may be suitable.]

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 290 nm
Column: 4.6-mm × 15.0-cm; 3-µm packing L1
Column temperature: 40°C
Flow rate: 1.3 mL/min
Injection volume: 10 µL
System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 2.5
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution, Acid stage sample solution, and Buffer stage sample solution
Calculate the percentage of the labeled amount of duloxetine (C18H19NOS) dissolved in Acid stage medium:

\[
\text{Result} = \left( \frac{r_0}{r_1} \times C_s \times (M_1/M_2) \times V \times (1/L) \right) \times 100
\]

- \( r_0 \) = peak response of duloxetine from the Acid stage sample solution
- \( r_1 \) = peak response of duloxetine from the Standard solution
- \( C_s \) = concentration of USP Duloxetine Hydrochloride RS in the Standard solution (mg/mL)
- \( M_1 \) = molecular weight of duloxetine free base, 297.42
- \( M_2 \) = molecular weight of duloxetine hydrochloride, 333.88
- \( V \) = volume of Acid stage medium, 750 mL
- \( L \) = label claim of duloxetine (mg/Capsule)

Calculate the percentage of the labeled amount of duloxetine (C18H19NOS) dissolved in Buffer stage medium:

\[
\text{Result} = \left( \frac{r_0}{r_2} \times C_s \times (M_1/M_2) \times V \times (1/L) \right) \times 100
\]

- \( r_2 \) = peak response of duloxetine from the Buffer stage sample solution
- \( r_3 \) = peak response of duloxetine from the Standard solution
- \( C_s \) = concentration of USP Duloxetine Hydrochloride RS in the Standard solution (mg/mL)
- \( M_1 \) = molecular weight of duloxetine free base, 297.42
- \( M_2 \) = molecular weight of duloxetine hydrochloride, 333.88
- \( V \) = volume of Buffer stage medium, 1000 mL
- \( L \) = label claim of duloxetine (mg/Capsule)

Tolerances
Acid stage: For each individual value, NMT 10% of the labeled amount of duloxetine (C18H19NOS). The percentage of the labeled amount of duloxetine dissolved at the time specified conforms to Dissolution (711).

Buffer stage: NLT 80% (Q) of the labeled amount of duloxetine (C18H19NOS). The percentage of the la-
Official August 1, 2017

Duloxetine

Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 15.0-cm, 3.5-µm packing L1
Column temperature: 50°
Flow rate: 1.1 mL/min
Injection volume: 10 µL
Run time: NLT 2 times the retention time of duloxetine

System suitability

Samples: System suitability solution and Buffer stage standard solution

[NOTE—The relative retention times for duloxetine and α-naphthol are 1.0 and 1.7, respectively.]

Suitability requirements

Resolution: NLT 5 between duloxetine and α-naphthol, System suitability solution

Tailing factor: NMT 2.0, Buffer stage standard solution

Relative standard deviation: NMT 2.0%, Buffer stage standard solution

Analysis

Samples: Acid stage standard solution, Buffer stage standard solution, Acid stage sample solution, and Buffer stage sample solution

Calculate the concentration of duloxetine (C18H19NOS) dissolved in the Acid stage medium (C1):

Result = \( \frac{(r_1/r_0) \times C_i \times D \times (M_{i1}/M_{i2})}{F_1} \)

\( r_0 \) = peak response of duloxetine from the Acid stage sample solution
\( r_1 \) = peak response of duloxetine from the Acid stage standard solution
\( C_i \) = concentration of USP Duloxetine Hydrochloride RS in the Acid stage standard solution (mg/mL)
\( D \) = dilution factor of the Acid stage sample solution, 5
\( M_{i1} \) = molecular weight of duloxetine free base, 297.42
\( M_{i2} \) = molecular weight of duloxetine hydrochloride, 333.88

Calculate the equivalent concentration of duloxetine from α-naphthol in the Acid stage medium (C2):

Result = \( \frac{(r_1/r_3) \times C_i \times D \times (1/F_1) \times (M_{i1}/M_{i2})}{F_3} \)

\( r_3 \) = peak response of α-naphthol from the Acid stage sample solution
\( C_2 \) = concentration of USP Duloxetine Hydrochloride RS in the Acid stage standard solution (mg/mL)
\( F_3 \) = relative response factor of α-naphthol, 1.7

Calculate the equivalent concentration of duloxetine from all of the unspecified degradation products in the Acid stage medium (C3):

Result = \( \frac{(r_1/r_1) \times C_i \times D \times (M_{i1}/M_{i2})}{F_i} \)

\( r_i \) = sum of the peak responses from all of the unspecified degradation products in the Acid stage sample solution

Tolerances

Acid stage: For each individual value, NMT 10% of the labeled amount of duloxetine (C18H19NOS). The percentage of the labeled amount of duloxetine dissolved at the time specified conforms to Dissolution (711), Acceptance Table 3.

Buffer stage: NLT 75% (Q) of the labeled amount of duloxetine (C18H19NOS). The percentage of the labeled amount of duloxetine dissolved at the time specified conforms to Dissolution (711), Acceptance Table 4.

Test 4: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 4. Protect solutions of duloxetine from light.

Acid stage

Acid stage medium: 0.1 N hydrochloric acid VS; 1000 mL
Apparatus 1: 100 rpm
Time: 2 h in Acid stage medium

Buffer stage

Buffer stage medium: pH 6.8 phosphate buffer (6.8 g/L of monobasic potassium phosphate and 0.9 g/L of sodium hydroxide in water, adjusted with phosphoric acid or 1 N sodium hydroxide VS to a pH of 6.80); 1000 mL
Apparatus 1: 100 rpm
Time: 3 h in Buffer stage medium. The time in Buffer stage medium includes the time in Acid stage medium.

Procedure: After 2 h in the Acid stage medium, withdraw a sample from the solution under test and im-
mediately filter. Remove the Acid stage medium and
add the Buffer stage medium.
Solution A: Acetonitrile and water (20:80). To each
liter add 1.0 mL of phosphoric acid.
Solution B: Acetonitrile
Mobile phase: See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Acid stage standard stock solution: 0.011 mg/mL of
USP Duloxetine Hydrochloride RS, equivalent to
0.010 mg/mL of duloxetine, in methanol. Use this so-
lution within 10 h.
Acid stage standard solution: (L/20,000) mg/mL of
duloxetine from the Standard stock solution in solution
prepared as follows, where L is the label claim, in mg/
Capsule. Transfer a suitable volume of Acid stage stan-
dard stock solution to an appropriate volumetric flask,
Add 45% of the flask volume of 0.1 N hydrochloric
acid VS and dilute with 0.1 N sodium hydroxide VS
to volume. Use this solution within 10 h.
Buffer stage standard stock solution: 0.67 mg/mL of
USP Duloxetine Hydrochloride RS, equivalent to
0.6 mg/mL of duloxetine, in acetonitrile
Buffer stage standard solution: (L/1,000) mg/mL of
duloxetine from Buffer stage standard stock solution in
Buffer stage medium
Acid stage sample stock solution: Pass a portion of the
solution under test through a suitable filter, discard
NLT 1 mL, and use the filtrate. Use this solution
within 4 h.
Acid stage sample solution: Dilute 5.0 mL of the
Acid stage sample stock solution with 0.1 N sodium
hydroxide to 10.0 mL. Use this solution within 4 h.
Buffer stage sample stock solution: Pass a portion of the
solution under test through a suitable filter, discard
NLT 2 mL, and use the filtrate. Further dilute with
Buffer stage medium, if needed.
Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 10.0-cm; 5-mm packing L1
Flow rate: 1 mL/min
Injection volume: 10 µL
System suitability
Sample: Acid stage standard solution
[NOTE—The relative retention times for duloxetine
4-naphthyl isomer, duloxetine, and α-naphthol are
0.8, 1.0, and 1.5, respectively.]
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Instrumental conditions
(See Ultraviolet-Visible Spectroscopy (857),)

Mode: UV
Analytical wavelength: 291 nm
Blank: Buffer stage medium
System suitability
Sample: Buffer stage standard solution
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: Acid stage standard solution, Acid stage
standard solution, Acid stage sample solution, and
Buffer stage sample solution
Calculate the concentration of duloxetine
(C_{18}H_{19}NOS) dissolved in the Acid stage medium (C_{1}):
Calculate the percentage of the labeled amount of duloxetine dissolved in Acid stage medium (Q):

\[ \text{Result} = \sum (C_i \times V \times (1/L) \times 100) \]

\( C_i \) = concentration or equivalent concentration of duloxetine in the Acid stage medium (mg/mL) associated with duloxetine, \( \alpha \)-naphthol, and duloxetine 4-naphthyl isomer
\( V \) = volume of Acid stage medium, 1000 mL
\( L \) = label claim of duloxetine (mg/Capsule)

Calculate the percentage of the labeled amount of duloxetine dissolved in the Buffer stage medium:

\[ \text{Result} = (A_u/A_s) \times [C_i \times (M_1/M_2)] \times V \times D \times (1/L) \times 100 \]

\( A_u \) = absorbance of duloxetine from the Buffer stage sample solution
\( A_s \) = absorbance of duloxetine from the Buffer stage standard solution
\( C_i \) = concentration of USP Duloxetine Hydrochloride RS in the Buffer stage standard solution (mg/mL)
\( M_1 \) = molecular weight of duloxetine free base, 297.42
\( M_2 \) = molecular weight of duloxetine hydrochloride, 333.88
\( V \) = volume of Buffer stage medium, 1000 mL
\( D \) = dilution factor of the Buffer stage sample solution, if needed
\( L \) = label claim (mg/Capsule)

Tolerances:

- Acid stage: NMT 10% of the labeled amount of duloxetine (C\(_{18}\)H\(_{19}\)NOS). The percentage of the labeled amount of duloxetine dissolved at the time specified conforms to Dissolution (711), Acceptance Table 3.
- Buffer stage: NLT 75% (Q) of the labeled amount of duloxetine (C\(_{18}\)H\(_{19}\)NOS). The percentage of the labeled amount of duloxetine dissolved at the time specified conforms to Dissolution (711), Acceptance Table 4. (RB 1-Aug-2017)

**Unifor\(m\)ity of Dosage Units (905):** Meet the requirements

**Impurities**

**Organic impurities**

Protect solutions of duloxetine from light.

Buffer A, Buffer B, Mobile phase, Diluent, System suitability solution, Standard solution, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the Assay.

**Analysis**

Sample: Sample solution

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

\[ \text{Result} = \left( \frac{r_u}{r_T} \right) \times 100 \]

\( r_u \) = peak response for each impurity
\( r_T \) = sum of all the peak responses

Acceptance criteria: See **Table 2**.

**Table 2 (88 1-Aug-2017)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Duloxetine related compound F( ^{+} )</td>
<td>1.1</td>
<td>—</td>
</tr>
<tr>
<td>( \alpha )-Naphthol( ^{+} )</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Duloxetine related compound H( ^{+} )</td>
<td>2.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Any individual unspecified degradation</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>product</td>
<td>—</td>
<td>0.4</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*This is a process impurity that is included in Table 1 for identification purposes only. It is controlled in the drug substance and is not to be reported or included in total impurities.

**Additional requirements**

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **Labeling:** The labeling states with which Dissolution test the article complies, if other than Test 1.
- **USP Reference Standards (11)**
- USP Duloxetine Hydrochloride RS
- USP Duloxetine Related Compound F RS
- USP Duloxetine Related Compound H RS

**Change to read:**

- USP Duloxetine Related Compound F RS (S)-N-Methyl-3-(naphthalen-1-yl oxy)-3-(thiophen-3-yl)propan-1-amine hydrochloride.
- C\(_{18}\)H\(_{19}\)NOS - HCl 333.88
- USP Duloxetine Related Compound H RS (S)-4-[(Methyl)(3-(naphthalen-1-yl oxy)-3-(thiophen-2-yl)propyl]aminol]4-oxobutanoic acid.
- C\(_{22}\)H\(_{23}\)NO\(_4\)S 397.49