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 ($C_{18}H_{19}NOS$).

IDENTIFICATION

Change to read:

- **A. ▲SPECTROSCOPIC IDENTIFICATION TESTS** ⟨197⟩, *Infrared Spectroscopy*: **197F**▲ (CN 1-May-2020)

  Buffer: 6.9 g/L of *monobasic sodium phosphate* in *water* adjusted with *5 N sodium hydroxide* to a pH of 7.5

  Spectral range: 1650 cm^{-1} to 900 cm^{-1}

  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 separatory 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▲ (ERR 1-Jun-2019) 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▲ (ERR 1-Jun-2019) 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* (323:90:587)

  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°.]

  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

  Run time: 6 times the retention time of duloxetine

  System suitability

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

  [NOTE—See *Table 2* 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 ($C_{18}H_{19}NOS$) in the portion of Capsules taken:

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

  r_U = peak response from the *Sample solution*

  r_S = peak response from the *Standard solution*

  C_S = 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_{r1} = molecular weight of duloxetine free base, 297.42

  M_{r2} = 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; 1000 mL

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, 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, 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* (C_1):

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

r_U = peak response of duloxetine from the *Sample solution*
r_S = peak response of duloxetine from the *Acid stage standard solution*
C_S = concentration of USP Duloxetine Hydrochloride RS in the *Acid stage standard solution* (mg/mL)
M_{r1} = molecular weight of duloxetine free base, 297.42
M_{r2} = molecular weight of duloxetine hydrochloride, 333.88

Calculate the equivalent concentration of duloxetine from α-naphthol in the *Acid stage medium* (C_2):

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2}) \times (M_{r3}/M_{r3})$$

r_U = peak response of α-naphthol from the *Sample solution*
r_S = peak response of duloxetine from the *Acid stage standard solution*
C_S = concentration of USP Duloxetine Hydrochloride RS in the *Acid stage standard solution* (mg/mL)
M_{r1} = molecular weight of duloxetine free base, 297.42
M_{r2} = molecular weight of duloxetine hydrochloride, 333.88
M_{r3} = molecular weight of α-naphthol, 144.17

Calculate the percentage of the labeled amount of duloxetine dissolved in the *Acid stage medium* (Q_A):

$$\text{Result} = (C_1 + C_2) \times V \times (1/L) \times 100$$

C_1 = concentration of duloxetine in the *Acid stage medium* (mg/mL)
C_2 = equivalent concentration of duloxetine from α-naphthol 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 in the *Buffer stage medium*:

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

r_U = peak response of duloxetine from the *Sample solution*
r_S = peak response of duloxetine from the *Buffer stage standard solution*
C_S = 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_{r1} = molecular weight of duloxetine free base, 297.42
M_{r2} = molecular weight of duloxetine hydrochloride, 333.88
Q_A = percentage of the labeled amount of duloxetine dissolved 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; 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 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°