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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):

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

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°

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 ($C_{18}H_{19}NOS$) dissolved in *Acid stage medium*:

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

r_U = peak response of duloxetine from the *Acid stage sample solution*

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

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

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

M_{r2} = 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 ($C_{18}H_{19}NOS$) dissolved in *Buffer stage medium*:

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

r_U = peak response of duloxetine from the *Buffer stage sample solution*

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

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

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

M_{r2} = 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 ($C_{18}H_{19}NOS$). The percentage of the labeled amount of duloxetine dissolved at the time specified conforms to *Dissolution ⟨711⟩*, *Acceptance Table 3*.

Buffer stage: NLT 80% (*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*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Protect solutions of duloxetine from light.

Acid stage

Acid stage medium: 0.1 N hydrochloric acid VS with *pepsin* (mix 8.5 mL of hydrochloric acid and 3.2 g of *pepsin* in 1 L of *water*); 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 and immediately filter. Remove and rinse each basket with NMT 25 mL of ▲0.1 N hydrochloric acid VS.▲ (ERR 1-Jun-2019) Then transfer the baskets to the *Buffer stage medium*.

Solution A: 2.7 g/L of monobasic potassium phosphate in *water*. Add 2.0 mL of *triethylamine* per liter of solution and adjust with *phosphoric acid* to a pH of 6.0.

Mobile phase: *Acetonitrile* and *Solution A* (38:62)

Standard stock solution: 1.1 mg/mL of USP Duloxetine Hydrochloride RS, equivalent to 1.0 mg/mL of duloxetine, prepared as follows. Transfer a suitable amount of USP Duloxetine Hydrochloride RS to an appropriate volumetric flask and dissolve in 60% of the flask volume of *water*. Sonication may be used to promote dissolution. Dilute with *water* to volume.

System suitability stock solution: 0.011 mg/mL of USP Duloxetine Hydrochloride RS from the *Standard stock solution* in 0.1 N hydrochloric acid VS. Store this solution in a 37° water bath for 30 min.

System suitability solution: 0.002 mg/mL of USP Duloxetine Hydrochloride RS from the *System suitability stock solution* in *Mobile phase*. Pass the resulting solution through a suitable filter and use the filtrate.

Acid stage standard stock solution: 0.11 mg/mL of USP Duloxetine Hydrochloride RS, equivalent to 0.10 mg/mL of duloxetine, from the *Standard stock solution* in *water*

Acid stage standard solution: (*L*/50,000) mg/mL of duloxetine from the *Standard stock solution* in *Mobile phase,* where *L* is the label claim, in mg/Capsule

Buffer stage standard solution: (*L*/1,000) mg/mL of duloxetine from the *Standard stock solution* in *Buffer stage medium,* where *L* is the label claim, in mg/Capsule

Acid stage sample solution: Transfer 2 mL of the solution under test to a suitable container and dilute with *Mobile phase* to 10 mL. Pass a portion of the resulting solution through a suitable filter, discard NLT 3 mL, and use the filtrate.

Buffer stage sample solution: Pass a portion of the solution under test through a suitable filter, discard NLT 1 mL, and use the filtrate.

Chromatographic system

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

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 ($C_{18}H_{19}NOS$) dissolved in the *Acid stage medium* (C_1):

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

r_U = peak response of duloxetine from the *Acid stage 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)

D = dilution factor of the *Acid stage sample solution,* 5

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):

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

r_U = peak response of α-naphthol from the *Acid stage 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)

D = dilution factor of the *Acid stage sample solution,* 5

F = relative response factor of α-naphthol, 1.7

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 all of the unspecified degradation products in the *Acid stage medium* (C_3):

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

r_i = sum of the peak responses from all of the unspecified degradation products in the *Acid stage 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)

D = dilution factor of the *Acid stage sample solution,* 5

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

M_{r2} = molecular weight of duloxetine hydrochloride, 333.88

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

$$\text{Result} = (\Sigma C_i) \times V \times (1/L) \times 100$$

C_i = concentration or equivalent concentration of duloxetine in the *Acid stage medium* (mg/mL)

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 both the *Acid stage medium* and the *Buffer stage medium*:

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

r_U = peak response of duloxetine from the *Buffer stage 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)

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

M_{r2} = molecular weight of duloxetine hydrochloride, 333.88

V = volume of *Buffer stage medium*, 1000 mL

L = label claim (mg/Capsule)

Q_A = percentage of the labeled amount of duloxetine dissolved in the *Acid stage medium*

Tolerances

Acid stage: For each individual value, 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*.

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 immediately 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 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
10	35	65
11	100	0
15	100	0

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 solution 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 standard 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 VS to 10 mL. Use this solution within 4 h.

Buffer stage sample 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-µm 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*, *Buffer 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):

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

r_U = peak response of duloxetine from the *Acid stage 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)

D = dilution factor of the *Acid stage sample solution,* 2

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):

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

r_U = peak response of α-naphthol from the *Acid stage 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)

D = dilution factor of the *Acid stage sample solution,* 2

F = relative response factor of α-naphthol, 2.0

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

M_{r2} = molecular weight of α-naphthol, 144.17

Calculate the equivalent concentration of duloxetine from duloxetine 4-naphthyl isomer (4-[3-(Methylamino)-1-(thiophen-2-yl)propyl]naphthalen-1-ol) in the *Acid stage medium* (C_3):

$$\text{Result} = (r_U/r_S) \times C_2 \times D \times (1/F) \times (M_{r1}/M_{r2})$$

r_U = peak response of duloxetine 4-naphthyl isomer from the *Acid stage sample solution*

r_S = peak response of duloxetine from the *Acid stage standard solution*

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

D = dilution factor of the *Acid stage sample solution,* 2

F = relative response factor of duloxetine 4-naphthyl isomer, 0.70

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

M_{r2} = molecular weight of duloxetine 4-naphthyl isomer, 297.42

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

$$\text{Result} = \Sigma(C_i) \times V \times (1/L) \times 100$$

C_i = concentration or equivalent concentration of duloxetine in the *Acid stage medium* (mg/mL) associated with duloxetine, α-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*:

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

A_U = absorbance of duloxetine from the *Buffer stage sample solution*

A_S = absorbance of duloxetine from the *Buffer stage standard solution*

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

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

M_{r2} = 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*.

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

IMPURITIES

Change to read:

• **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:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for each impurity

r_T = sum of all the peak responses

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Duloxetine	1.0	—
Duloxetine related compound F[a]	1.1	—
α-Naphthol[b]	1.5	0.2
Duloxetine related compound H[c]	2.2	0.2
Any individual unspecified degradation product	—	0.2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Total impurities	—	0.4

[a] This is a process impurity that is included ▲▲ (ERR 1-Jun-2019) for identification purposes only. It is controlled in the drug substance and is not to be reported or included in total impurities.

[b] Naphthalen-1-ol.

[c] May not be present in all formulations.

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

(*S*)-*N*-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-3-yl)propan-1-amine hydrochloride.

$C_{18}H_{19}NOS \cdot HCl$ 333.88

USP Duloxetine Related Compound H RS

(*S*)-4-{Methyl[3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl]amino}-4-oxobutanoic acid.

$C_{22}H_{23}NO_4S$ 397.49

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
DULOXETINE DELAYED-RELEASE CAPSULES	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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