Signal-to-noise ratio: NLT 3, *Sensitivity solution*
Analysis
Sample: *Sample solution*
Calculate the percentage of duloxetine related compound A in the portion of Duloxetine Hydrochloride taken:

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

r_U = peak response for duloxetine related compound A from the *Sample solution*
r_T = sum of the responses of duloxetine and duloxetine related compound A peaks from the *Sample solution*

Acceptance criteria: NMT 0.5%

SPECIFIC TESTS
- **LOSS ON DRYING ⟨731⟩:** Dry at 105° for 3 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Protect from light. Store at room temperature.
- **USP REFERENCE STANDARDS ⟨11⟩:**
USP Duloxetine Hydrochloride RS
USP Duloxetine Related Compound A RS
(*R*)-*N*-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine hydrochloride.
$C_{18}H_{19}NOS \cdot HCl$ 333.88 ■2S (*USP35*)

Add the following:

▪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
- **A. INFRARED ABSORPTION ⟨197S⟩**
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 pH 7.5 phosphate buffer. Collect the organic layer, and evaporate to dryness. Redissolve the residue with a few drops of methylene chloride, and transfer to a KBr or NaCl plate. Allow it to dry.
Sample: 1 mg/mL of duloxetine, from the contents of NLT 10 Capsules in methylene chloride. Proceed as directed for the *Standard*.
- **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
- **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* (323:90:587)
Diluent: Methanol and *Buffer B* (50:50)
System suitability solution: 0.1 mg/mL USP Duloxetine Hydrochloride RS, 0.05 mg/mL of 1-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 size: 10 µL
Run time: 6 times the retention time of duloxetine
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—See *Table 1* under *Organic Impurities* for relative retention times.]
Suitability requirements
Resolution: NLT 1.6 between duloxetine and duloxetine related compound F; NLT 2 between 1-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
- **DISSOLUTION ⟨711⟩**
Acid stage medium: 0.1 N hydrochloric acid; 1000 mL
Time: 2 h
Buffer stage medium: pH 6.8 phosphate buffer; 1000 mL
Time: 60 min for Capsules containing 20% w/w pellets; 90 min for Capsules containing 32% w/w pellets
Apparatus 1: 100 rpm
Buffer A and **Mobile phase:** Proceed as directed in the *Assay*.
Standard stock solution: 0.28 mg/mL of USP Duloxetine Hydrochloride RS in *Buffer stage medium*. Use a small amount of methanol, not exceeding 2% of the final volume, to dissolve duloxetine.
Acid stage standard solution: 2.3 µg/mL of duloxetine hydrochloride, from the *Standard stock solution* diluted with *Buffer stage medium*
Buffer stage standard solution: 23 µg/mL of duloxetine hydrochloride, 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-µm packing L7
Column temperature: 45°
Flow rate: 1.5 mL/min
Injection size: 10 µL

System suitability
Sample: *Acid stage standard solution*
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 percentage of duloxetine released in the *Acid stage medium* (P_A):

$$P_A = \{(r_U/r_S) + [(r_{2U}/r_S) \times 1/F]\} \times C_S/L \times V \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of duloxetine from the *Sample solution*
r_S = peak response of duloxetine from the *Acid stage standard solution*
r_{2U} = peak response for 1-naphthol from the *Sample solution*
F = relative response factor for 1-naphthol, 0.49
C_S = concentration of duloxetine hydrochloride in the *Acid 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

Calculate the percentage of duloxetine released in the *Buffer stage medium*:

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

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 duloxetine hydrochloride 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
P_A = percentage of duloxetine released 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.

- **Uniformity 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:

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

r_U = peak response of each impurity from *Sample solution*
r_T = sum of the responses of all the peaks from *Sample solution*

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria NMT (%)
Duloxetine	1.0	—
Duloxetine related compound F[a,d]	1.1	—
1-Naphthol[b,d]	1.5	—
Duloxetine related compound H[c]	2.2	0.2
Any individual unspecified degradation product	—	0.2
Total impurities	—	0.4

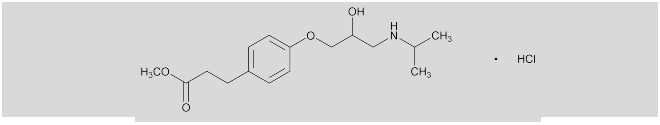
[a] (*S*)-*N*-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-3-yl)propan-1-amine hydrochloride.
[b] Napthalen-1-ol.
[c] (*S*)-4-{Methyl[3-(naphthalen-1-yloxy)-3-(thiophen-2-yl) propyl]amino}-4-oxobutanoic acid.
[d] For system suitability purposes only.

ADDITIONAL REQUIREMENTS

- **Packaging And Storage:** Preserve in tight containers. Store at controlled room temperature.
- **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 ■2S *(USP35)*

Add the following:

▪Esmolol Hydrochloride



$C_{16}H_{25}NO_4 \cdot HCl$ 331.83

Benzenepropanoic acid, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-, methyl ester, hydrochloride, (±);
(±)-Methyl *p*-[2-hydroxy-3-(isopropylamino)propoxy] hydrocinnamate hydrochloride [81161-17-3].

DEFINITION

Esmolol Hydrochloride contains NLT 98.0% and NMT 102.0% of $C_{16}H_{25}NO_4 \cdot HCl$, calculated on the anhydrous basis.

IDENTIFICATION

- **A. Infrared Absorption** ⟨197K⟩
- **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

- **Procedure**

Buffer: Dissolve 3.0 g of potassium dihydrogen phosphate in 650 mL of water.

Mobile phase: Acetonitrile, methanol, and *Buffer* (15:20:65)

System suitability stock solution: 1 mg/mL of esmolol hydrochloride prepared as follows. Transfer a suitable quantity of USP Esmolol Hydrochloride RS to a suitable volumetric flask, and dissolve in and dilute with 1 N hydrochloric acid to volume. Allow the contents to stand for at least 30 min. [Note—This results in the partial degradation of the esmolol resulting in the production of esmolol free acid (see *System suitability* for relative retention time).]

System suitability solution: 0.2 mg/mL in water from *System suitability stock solution*

Standard solution: 200 µg/mL of USP Esmolol Hydrochloride RS in water

Sample solution: 200 µg/mL of Esmolol Hydrochloride in water

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 222 nm
Column: 3.9-mm × 30-cm; 10-µm; L1 packing
Flow rate: 2 mL/min
Injection size: 20 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
[Note—The relative retention times for esmolol free acid and esmolol are 0.41 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 4.0 between esmolol free acid and esmolol, *System suitability solution*
Tailing factor: NMT 2.0 for the esmolol peak, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of esmolol hydrochloride ($C_{16}H_{25}NO_4 \cdot HCl$) in the portion of the sample taken:

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

r_U = peak response of esmolol from the *Sample solution*
r_S = peak response of esmolol from the *Standard solution*
C_S = concentration of USP Esmolol Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Esmolol Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **Heavy Metals** ⟨231⟩

Standard solution: Into a 50-mL color-comparison tube pipet 2 mL of *Standard Lead Solution* (20 µg of Pb), and dilute with water to 25 mL. Using a pH meter or short-range pH indicator paper as external indicator, adjust with 1 N acetic acid to a pH between 3.0 and 4.0, dilute with water to 40 mL, and mix.

Sample solution: Into a 50-mL color-comparison tube dissolve 1 g of the sample in water, and dilute with water to 25 mL. Using a pH meter or short-range pH indicator paper as external indicator, adjust with 1 N acetic acid to a pH between 3.0 and 4.0, dilute with water to 40 mL, and mix.

Analysis
Samples: *Standard solution* and *Sample solution*
To each of the tubes add 10 mL of hydrogen sulfide TS, and mix. Allow to stand for 2 min. View downward into the tube over a white background.

Acceptance criteria: The color of the *Sample solution* is not darker than the color of the *Standard solution* (NMT 20 ppm).

- **Residue on Ignition** ⟨281⟩**:** NMT 0.1%
- **Organic Impurities**

Buffer and **System suitability solution:** Prepare as directed in the *Assay*.

Solution A: Methanol

Solution B: Prepare as directed for *Mobile phase* in the *Assay*.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	0	100
20	0	100
25	25	75
35	25	75
36	0	100
40	0	100

Sample solution: 1 mg/mL of Esmolol Hydrochloride in water

Chromatographic system: Prepare as directed in the *Assay*.
Column temperature: 30°

System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 4.0 between esmolol free acid and esmolol
Tailing factor: NMT 2.0 for the esmolol peak

Analysis
Sample: *Sample solution*
Calculate the percentage of each individual impurity in the portion of Esmolol Hydrochloride taken:

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

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