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Imipramine Pamoate Capsules

DEFINITION

Imipramine Pamoate Capsules contain imipramine pamoate [$(C_{19}H_{24}N_2)_2 \cdot C_{23}H_{16}O_6$] equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$).

IDENTIFICATION

• **A.** The retention time of the imipramine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

• **B.** The UV spectrum of the imipramine peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the test for *Organic Impurities*.

ASSAY

Change to read:

• **Procedure**

Buffer: 5.2 g/L of dibasic potassium phosphate in water

Solution A: ▲Acetonitrile▲ (ERR 1-May-2019) and *Buffer* (15:85). Adjust with phosphoric acid to a pH of 8.0.

Solution B: ▲Acetonitrile▲ (ERR 1-May-2019) and *Buffer* (38:62). Adjust with phosphoric acid to a pH of 8.0.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
10	70	30
20	35	65
30	35	65
31	90	10
35	90	10

Diluent: ▲Acetonitrile▲ (ERR 1-May-2019) and water (75:25)

Standard stock solution: 0.75 mg/mL of USP Imipramine Pamoate RS in *Diluent*

Standard solution: 0.23 mg/mL of USP Imipramine Pamoate RS (equivalent to 0.15 mg/mL of imipramine hydrochloride) from the *Standard stock solution* in *Solution A*. Pass a portion through a suitable filter of 0.45-µm pore size. Use the filtrate.

Sample stock solution: Transfer the contents of Capsules (NLT 5) into a suitable volumetric flask, and add the corresponding Capsule shells. Add 10% of the final flask volume of acetonitrile, and sonicate for 10 min with intermittent shaking. Add 80% of the final flask volume of *Diluent*, and sonicate for 15 min with intermittent shaking. Allow to cool to room temperature, and dilute with *Diluent* to volume. Allow to stand for 5 min.

Sample solution: Nominally 0.23 mg/mL of imipramine pamoate (equivalent to 0.15 mg/mL of imipramine hydrochloride) from the *Sample stock solution* in *Solution A*. Pass a portion of the resulting solution through a suitable filter of 0.45-µm pore size. Use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 269 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Autosampler temperature: 10°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for pamoic acid and imipramine are 0.3 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between pamoic acid and imipramine

Tailing factor: NMT 2.0 for imipramine

Relative standard deviation: NMT 2.0% for imipramine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$) in the portion of Imipramine Pamoate Capsules taken:

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

r_U = peak area of imipramine from the *Sample solution*

r_S = peak area of imipramine from the *Standard solution*

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

C_U = equivalent concentration of imipramine hydrochloride in the *Sample solution* (mg/mL)

M = number of moles of imipramine hydrochloride equivalent to each mole of imipramine pamoate, 2

M_{r1} = molecular weight of imipramine hydrochloride, 316.87

M_{r2} = molecular weight of imipramine pamoate, 949.18

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **DISSOLUTION ⟨711⟩**

Test 1

Tier 1

Medium 1: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Times: 30 and 90 min

Tier 2

Medium 2: 0.1 N hydrochloric acid with 0.3% purified pepsin; 900 mL

Apparatus 1: 100 rpm

Times: 30 and 90 min

Buffer: 4.4 g/L of dibasic potassium phosphate in water

Mobile phase: Acetonitrile, triethylamine, and *Buffer* (400:5:600). Adjust with phosphoric acid to a pH of 8.0.

Diluent A: Acetonitrile and water (75:25)

Diluent B: 20.4 g/L of monobasic potassium phosphate and 3 g/L of sodium hydroxide. Adjust with 1 N sodium hydroxide or 1 N phosphoric acid to a pH of 7.4.

Standard stock solution: 0.63 mg/mL of USP Imipramine Pamoate RS in *Diluent A*

Standard solution: 0.038 mg/mL of USP Imipramine Pamoate RS from the *Standard stock solution* prepared as follows. Transfer a suitable volume of the *Standard stock solution* to an appropriate flask that already contains 60% of the final flask volume of *Diluent B* and 30% of the final flask volume of *Medium*. Dilute with *Diluent B* to volume.

Sample stock solution: Centrifuge a portion of the solution under test. Use the supernatant. Replace the portion of solution removed from the vessel with the same volume of fresh *Medium 1* or *Medium 2* at 37°. [NOTE—The use of a centrifuge speed of 5000 rpm for 10 min may

be suitable.]

Sample solution: Nominally equivalent to about 0.025 mg/mL of imipramine hydrochloride prepared from the *Sample stock solution* in *Diluent B* in a suitable volumetric flask

Dissolution procedure: Perform the test using the conditions under *Tier 1*. In the presence of cross-linking, repeat the test with a new set of Capsules using the conditions under *Tier 2*.

Chromatographic system

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

Mode: LC

Detector: UV 252 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Temperatures

Autosampler: 10°

Column: 30°

Flow rate: 1.2 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$) dissolved at each time point (*i*):

$$\text{Result}_i = (r_i/r_S) \times C_S \times [M \times (M_{r1}/M_{r2})] \times D \times V \times (1/L) \times 100$$

r_i = peak area of imipramine from the *Sample solution* at each time point

r_S = peak area of imipramine from the *Standard solution*

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

M = number of moles of imipramine hydrochloride equivalent to each mole of imipramine pamoate, 2

M_{r1} = molecular weight of imipramine hydrochloride, 316.87

M_{r2} = molecular weight of imipramine pamoate, 949.18

D = dilution factor of the *Sample solution*

V = volume of *Medium 1* or *Medium 2*, 900 mL

L = label claim (mg/Capsule)

Tolerances: See *Table 2*.

Table 2

Time Point (*i*)	Time (min)	Amount Dissolved NLT (%)
1	30	40
2	90	75

The percentage of imipramine pamoate dissolved equivalent to the labeled amount of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$) dissolved at the times specified conforms to *Dissolution ⟨711⟩, Acceptance Table 1*.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Times: 30 and 150 min

Standard solution: A solution containing USP Imipramine Pamoate RS at the concentrations listed in *Table 3* prepared as follows. Transfer a suitable quantity of USP Imipramine Pamoate RS to an appropriate volumetric flask. Add 5% of the final flask volume of methanol and sonicate for 5 min. Add 75% of the final flask volume of *Medium* that has been heated to NLT 60° and stir for 30 min. Allow to cool to room temperature. Dilute with *Medium* to volume and mix. Pass through a suitable filter and use the filtrate.

Table 3

Labeled Amount of Imipramine Hydrochloride (mg/Capsule)	Concentration of USP Imipramine Pamoate RS (mg/mL)	Equivalent Concentration of Imipramine Hydrochloride (mg/mL)
75	0.12	0.08
100	0.17	0.11
125	0.21	0.14
150	0.26	0.17

Sample solution: Pass a portion of the solution under test through a suitable filter. Use the filtrate.

Instrumental conditions

Mode: UV-Vis

Wavelength: 251 nm

Cell: 0.2 cm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$) dissolved at each time point (*i*):

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

A_i = absorbance of imipramine from the *Sample solution* at each time point

A_S = absorbance of imipramine from the *Standard solution*

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

M = number of moles of imipramine hydrochloride equivalent to each mole of imipramine pamoate, 2

M_{r1} = molecular weight of imipramine hydrochloride, 316.87

M_{r2} = molecular weight of imipramine pamoate, 949.18

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

Tolerances: See *Table 4*.

Table 4

Time Point (*i*)	Time (min)	Amount Dissolved NLT (%)
1	30	25
2	150	80

The percentage of imipramine pamoate dissolved equivalent to the labeled amount of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$) dissolved at the times specified conforms to *Dissolution ⟨711⟩*, *Acceptance Table 1*.

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

IMPURITIES

Change to read:

• **Organic Impurities**

Protect solutions containing imipramine from light.

Buffer: 5.2 g/L of dibasic potassium phosphate in water

Solution A: ▲Acetonitrile▲ (ERR 1-May-2019) and *Buffer* (3:100). Adjust with phosphoric acid to a pH of 7.2.

Solution B: Methanol and ▲acetonitrile▲ (ERR 1-May-2019) (70:30)

Mobile phase: See *Table 5*.

Table 5

Time (min)	Solution A (%)	Solution B (%)
0	62	38
12	62	38
25	50	50
65	20	80
70	20	80
75	62	38
95	62	38

System suitability solution: 1.5 mg/mL of USP Imipramine Pamoate RS (equivalent to 1 mg/mL of imipramine hydrochloride), and 0.001 mg/mL each of USP Desipramine Hydrochloride RS and USP Depramine RS in *Solution B*. Pass a portion through a suitable membrane filter of 0.2-µm pore size, and use the filtrate.

Standard solution: 0.015 mg/mL of USP Imipramine Pamoate RS (equivalent to 0.010 mg/mL of imipramine hydrochloride) in *Solution B*. Pass a portion through a suitable membrane filter of 0.2-µm pore size, and use the filtrate.

Sample solution: Nominally 1.5 mg/mL of imipramine pamoate (equivalent to 1.0 mg/mL of imipramine hydrochloride) from NLT 20 Capsules prepared as follows. Transfer a portion of the contents of the Capsules equivalent to 50 mg of imipramine hydrochloride to a 50-mL volumetric flask. Add 30 mL of *Solution B*, and sonicate for 10 min in a cool water bath with intermittent shaking. Dilute with *Solution B* to volume. Pass a portion through a suitable membrane filter of 0.2-µm pore size, and use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm. For *Identification* test *B*, a diode-array detector may be used in the wavelength range of 200–300 nm.

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Temperatures

Autosampler: 10°

Column: 45°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

[Note—See *Table 6* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between the desipramine and depramine peaks; NLT 2.0 between the depramine and imipramine peaks, *System suitability solution*

Tailing factor: NMT 1.5, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

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

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [M \times (M_{r1}/M_{r2})] \times (1/F) \times 100$$

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

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

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

C_U = equivalent concentration of imipramine hydrochloride in the *Sample solution* (mg/mL)

M = number of moles of imipramine hydrochloride equivalent to each mole of imipramine pamoate, 2

M_{r1} = molecular weight of imipramine hydrochloride, 316.87

M_{r2} = molecular weight of imipramine pamoate, 949.18

F = relative response factor (see *Table 6*)

Acceptance criteria: See *Table 6*. Disregard any degradation product peaks less than 0.02%.

Table 6

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%, w/w)
Pamoic acid[a]	0.1	—	—
Desipramine	0.40	1.0	0.2
Depramine	0.66	0.87	0.10
Imipramine	1.0	—	—
Iminodibenzyl[b]	1.3	1.5	0.2
Any individual unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	0.75

[a] Included for identification only. This peak is due to the pamoate counterion; hence it is not an impurity.

[b] 10,11-Dihydro-5*H*-dibenzo[*b,f*]azepine.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.
- **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

USP Depramine RS

3-(5*H*-Dibenzo[*b,f*]azepin-5-yl)-*N,N*-dimethylpropan-1-amine.

$C_{19}H_{22}N_2$ 278.39

USP Desipramine Hydrochloride RS

USP Imipramine Pamoate RS

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

Topic/Question	Contact	Expert Committee
IMIPRAMINE PAMOATE CAPSULES	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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