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Clomipramine Hydrochloride Capsules

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-clomipramine-hcl-caps-20240628.

DEFINITION

Clomipramine Hydrochloride Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** The UV spectrum 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**

Solution A: Add 2.5 mL of acetic acid to 1 L of water. Adjust with ▲ammonia water, stronger▲ (RB 1-Jul-2024) to a pH of 7.5.

Solution B: Acetonitrile, methanol, and ▲tetrahydrofuran, stabilizer-free▲ (RB 1-Jul-2024) (80:15:5)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0.0	65	35
2.0	65	35
5.0	50	50
11.0	20	80
14.0	20	80
14.1	65	35
18.0	65	35

Diluent: *Solution A* and acetonitrile (50:50)

System suitability solution: 0.2 mg/mL of USP Clomipramine Hydrochloride RS and 0.005 mg/mL of USP Clomipramine Related Compound A RS in *Diluent*

Standard solution: 0.2 mg/mL of USP Clomipramine Hydrochloride RS in *Diluent*

Sample solution: Nominally 0.2 mg/mL of clomipramine hydrochloride from Capsules in *Diluent* prepared as follows. Transfer a sufficient portion of the contents of Capsules (NLT 20) to a suitable volumetric flask. Add 60% of the final flask volume of *Diluent*. Shake by mechanical means for about 30 min. Dilute with *Diluent* to volume. Centrifuge to obtain a clear supernatant and use the clear supernatant. [Note—The use of a centrifuge speed of 3000 rpm for 10 min may be suitable.]

Chromatographic system

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

Mode: LC

Detector: UV 254 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 2.1-mm × 10-cm; 1.7-µm packing L1

Column temperature: 30°

Flow rate: 0.3 mL/min

Injection volume: 2 µL

System suitability

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

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between clomipramine and clomipramine related compound A, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) in the portion of Capsules taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

C_U = nominal concentration of clomipramine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION ⟨711⟩**

Test 1

Medium: ▲0.1 N hydrochloric acid▲ (RB 1-Jul-2024) ; 500 mL

Apparatus 2: 50 rpm. With suitable sinkers, if needed.

Time: 30 min

Standard solution: USP Clomipramine Hydrochloride RS in *Medium*

Sample solution: Pass the solution under test through a suitable filter and use the filtrate. Dilute with *Medium*, if necessary, to a concentration that is similar to the *Standard solution*.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

Mode: UV

Analytical wavelength: 252 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times D \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

D = dilution factor for the *Sample solution*

V = volume of *Medium*, 500 mL

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L = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) is dissolved.

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

Medium: ▲0.01 N hydrochloric acid▲ (RB 1-Jul-2024); 500 mL

Apparatus 2: 75 rpm with sinkers

Time: 15 min

Solution A: 55 g/L of sodium 1-heptanesulfonate in solution prepared as follows. Transfer a suitable amount of sodium 1-heptanesulfonate to an appropriate volumetric flask. Add 50% of the flask volume of water and dilute with glacial acetic acid to volume.

Solution B: To an appropriate volumetric flask, add 4% of the flask volume of *Solution A* and 0.4% of the flask volume of triethylamine. Dilute with water to volume.

Mobile phase: To an appropriate volumetric flask, add 50% of the flask volume of *Solution B*. Adjust the resulting solution with phosphoric acid to a pH of 3.2. Dilute with acetonitrile to volume.

Standard stock solution: 0.5 mg/mL of USP Clomipramine Hydrochloride RS in *Medium*. Sonication may be used to promote dissolution.

Standard solution: (L/500) mg/mL of USP Clomipramine Hydrochloride RS from the *Standard stock solution* in *Medium*, where L is the label claim in mg/Capsule

Sample solution: Pass a portion of the solution under test through a suitable filter and discard NLT the first 5 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

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

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: NLT 1.4 times the retention time of clomipramine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.8–2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

V = volume of the *Medium*, 500 mL

L = label claim of clomipramine hydrochloride (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) is dissolved.

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

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 2: 50 rpm

Time: 20 min

Standard solution: 0.025 mg/mL of USP Clomipramine Hydrochloride RS in *Medium*. Sonicate to dissolve, if necessary. [NOTE—The *Standard solution* may be stable for 17 h at room temperature.]

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained. Dilute the filtrate with *Medium* to a concentration similar to that of the *Standard solution*. [NOTE—The *Sample solution* may be stable for 17 h at room temperature.]

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Capsule shell solution: Transfer a suitable number of empty capsule shells separately into each of 500 mL of *Medium*. Start the dissolution test following the same conditions as the intact Capsules. At the specified time point, pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained. Dilute the filtrate with *Medium* in a manner consistent with the *Sample solution* preparation.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 252 nm

Blank: *Medium*

Analysis

Samples: *Standard solution*, *Sample solution*, and *Capsule shell solution*

Calculate the percentage of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) dissolved:

$$\text{Result} = \{[A_U - (A_{cs}/N)]/A_S\} \times C_S \times D \times V \times (1/L) \times 100$$

A_U = absorbance from the *Sample solution*

A_{cs} = absorbance from the *Capsule shell solution*

N = number of capsule shells used to prepare the *Capsule shell solution*

A_S = absorbance from the *Standard solution*

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

D = dilution factor for the *Sample solution*

V = volume of *Medium*, 500 mL

L = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) is dissolved.▲ (RB 1-Jul-2024)

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

Procedure for content uniformity

Standard solution: 30 µg/mL of USP Clomipramine Hydrochloride RS in methanol

Sample stock solution: Transfer the contents of 1 Capsule to a 100-mL volumetric flask with the aid of methanol. Add about 75 mL of methanol, shake by mechanical means for 1 h, and dilute with methanol to volume.

Sample solution: Nominally 30 µg/mL of clomipramine hydrochloride from the *Sample stock solution* in methanol

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 252 nm

Cell: 1 cm

Blank: Methanol

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) in the Capsule taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

C_U = nominal concentration of clomipramine hydrochloride in the *Sample solution* (µg/mL)

IMPURITIES

• **Organic Impurities**

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Solution A, Solution B, Mobile phase, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: 0.5 mg/mL of USP Clomipramine Hydrochloride RS and 0.0025 mg/mL of USP Clomipramine Related Compound A RS in *Diluent*

Standard solution: 0.0025 mg/mL each of USP Clomipramine Hydrochloride RS, USP Clomipramine Related Compound C RS, and USP Imipramine Hydrochloride RS in *Diluent*

Sample solution: Nominally 0.5 mg/mL of clomipramine hydrochloride from Capsules in *Diluent* prepared as follows. Transfer a sufficient portion of the contents of Capsules (NLT 20) to a suitable volumetric flask. Add 60% of the final flask volume of *Diluent*. Shake by mechanical means for about 30 min. Dilute with *Diluent* to volume. Centrifuge to obtain a clear supernatant and use the clear supernatant. [NOTE—The use of a centrifuge speed of 3000 rpm for 10 min may be suitable.]

System suitability

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

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between clomipramine and clomipramine related compound A, *System suitability solution*

Relative standard deviation: NMT 5.0% for all standard peaks, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

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

r_S = peak response of the corresponding USP Reference Standard from the *Standard solution*

C_S = concentration of the corresponding USP Reference Standard in the *Standard solution* (mg/mL)

C_U = nominal concentration of clomipramine hydrochloride in the *Sample solution* (mg/mL)

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

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

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

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

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

C_U = nominal concentration of clomipramine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.03%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Imipramine	0.77	1.0
Clomipramine related compound C	0.87	0.5
Clomipramine	1.00	—
Clomipramine related compound A[a]	1.1	—
Clomipramine related compound D[a,b]	1.2	—

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Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Clomipramine related compound F[a,c]	1.5	—
Any individual unspecified impurity	—	0.5
Total impurities	—	2.0

[a] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.

[b] 3-(3,7-Dichloro-10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

[c] 3-Chloro-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Protect from moisture. 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 Clomipramine Hydrochloride RS

USP Clomipramine Related Compound A RS

N^1-[3-(3-Chloro-10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)propyl]-N^1,N^3,N^3-trimethylpropane-1,3-diamine dihydrochloride.
$C_{23}H_{32}ClN_3 \cdot 2HCl$ 458.90

USP Clomipramine Related Compound C RS

3-(3-Chloro-5*H*-dibenzo[*b,f*]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride, monohydrate.
$C_{19}H_{21}ClN_2 \cdot HCl \cdot H_2O$ 367.31

USP Imipramine Hydrochloride RS

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

Topic/Question	Contact	Expert Committee
CLOMIPRAMINE HYDROCHLORIDE CAPSULES	Documentary Standards Support	SM42020 Small Molecules 4

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