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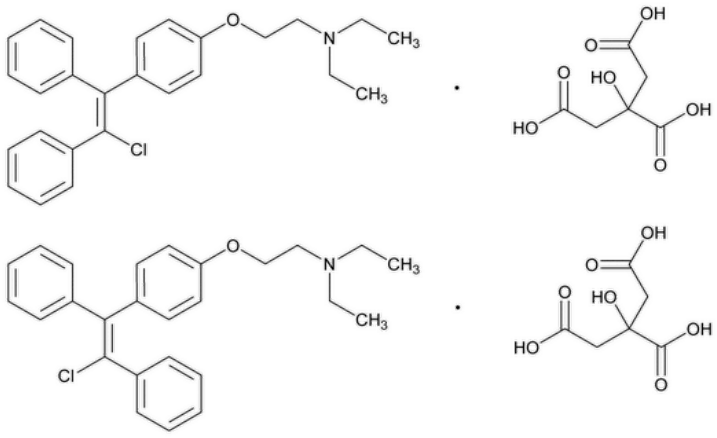
Clomiphene Citrate



$C_{26}H_{28}ClNO \cdot C_6H_8O_7$ 598.08

Ethanamine, 2-[4-(2-chloro-1,2-diphenylethenyl)phenoxy]-*N*,*N*-diethyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1);
2-[*p*-(2-Chloro-1,2-diphenylvinyl)phenoxy]triethylamine citrate (1:1) CAS RN®: 50-41-9; UNII: 1B8447E7YI.

DEFINITION

Clomiphene Citrate contains NLT 98.0% and NMT 102.0% of a mixture of the (*E*)- and (*Z*)-geometric isomers of clomiphene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$), calculated on the anhydrous basis. It contains NLT 30.0% and NMT 50.0% of the *Z*-isomer, [(*Z*)-2-[4-(2-chloro-1,2-diphenylethenyl)phenoxy]-*N*,*N*-diethylethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K

Change to read:

• **B. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet▲-Visible▲ (ERR-1-Oct-2020) Spectroscopy*:** 197U

Medium: 0.1 N hydrochloric acid

Sample solution: 20 µg/mL

Acceptance criteria: Meets the requirements

• **C. Identification Tests—General, *Citrate* ⟨191⟩**

ASSAY

• **Procedure**

Use low-actinic glassware for all solutions.

Mobile phase: Methanol, water, and triethylamine (55: 45: 0.3). Adjust with phosphoric acid to a pH of 2.5.

System suitability solution: 2 µg/mL of USP Clomiphene Related Compound A RS and 50 µg/mL of USP Clomiphene Citrate RS, in *Mobile phase*

Standard solution: 50 µg/mL of USP Clomiphene Citrate RS, in *Mobile phase*

Sample stock solution: 0.5 mg/mL of Clomiphene Citrate, in *Mobile phase*, filtered

Sample solution: 50 µg/mL of Clomiphene Citrate, in *Mobile phase*, from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 233 nm

Column: 4.6-mm × 25-cm; packing L26

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

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

[NOTE—The relative retention times for clomiphene related compound A, (*Z*)-isomer, and (*E*)-isomer are about 0.9, 1.0, and 1.2, respectively.]

Suitability requirements

Resolution: NLT 1.0 between clomiphene related compound A and (*Z*)-isomer; NLT 1.5 between (*Z*)-isomer and (*E*)-isomer, *System suitability solution*

Column efficiency: NLT 2000 theoretical plates for the (*E*)-isomer, *Standard solution*

Tailing factor: NMT 3.0 for the (*E*)-isomer, *Standard solution*

Relative standard deviation: NMT 2.0% for both (*E*)- and (*Z*)-isomers, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of clomiphene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$) in the portion of Clomiphene Citrate taken:

$$\text{Result} = [(r_{UE} + r_{UZ})/(r_{SE} + r_{SZ})] \times (C_S/C_U) \times 100$$

r_{UE} = peak response of the (*E*)-isomer from the *Sample solution*

r_{UZ} = peak response of the (*Z*)-isomer from the *Sample solution*

r_{SE} = peak response of the (*E*)-isomer from the *Standard solution*

r_{SZ} = peak response of the (*Z*)-isomer from the *Standard solution*

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

C_U = concentration of Clomiphene Citrate in the *Sample solution* (µg/mL)

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

OTHER COMPONENTS

• **CONTENT OF (*Z*)-ISOMER**

Mobile phase, 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 (*Z*)-isomer in the portion of Clomiphene Citrate taken:

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

r_Z = peak response of the (*Z*)-isomer from the *Sample solution*

r_T = sum of all the peak responses of the *Sample solution*

Acceptance criteria: 30.0%–50.0%

IMPURITIES

• **ORGANIC IMPURITIES**

Use low-actinic glassware for all solutions.

Buffer: Acetonitrile, diethylamine, and water (40: 0.8: 60). Adjust with phosphoric acid to a pH of 6.2.

Solution A: *Buffer* and water (90:10)

Solution B: *Buffer*

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
3.0	100	0
23.0	0	100
33.0	0	100
33.5	100	0
40.0	100	0

System suitability stock solution: 0.28 mg/mL of USP Clomiphene Related Compound A RS in *Buffer*

System suitability solution: 1.25 mg/mL of USP Clomiphene Citrate RS and 0.028 mg/mL of USP Clomiphene Related Compound A RS, prepared as follows. Transfer 12.5 mg of USP Clomiphene Citrate RS into a 10-mL volumetric flask, add 1.0 mL of *System suitability stock solution*, and dilute with *Buffer* to volume.

Standard solution: 0.025 mg/mL of USP Clomiphene Citrate RS in *Buffer*

Sample solution: 1.25 mg/mL of Clomiphene Citrate in *Buffer*

Chromatographic system

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

Mode: LC

Detector: UV 233 nm

Column: 4.6-mm × 10-cm; 2.6-µm packing L7

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

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

Suitability requirements

Relative standard deviation: NMT 5.0% from the sum of the peak areas of the (*E*)- and (*Z*)-isomers, *Standard solution*

Peak-to-valley ratio: The ratio of the height of the clomiphene related compound A peak to the height of the valley between clomiphene related compound A and clomiphene peaks is NLT 15, *System suitability solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Clomiphene Citrate taken:

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

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

r_S = sum of the peak responses of (*E*)- and (*Z*)-isomers of clomiphene from the *Standard solution*

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

C_U = concentration of Clomiphene Citrate in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. Disregard peaks less than 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Clomiphene benzophenone analog[a]	0.10	0.51	1.0
Clomiphene tritylphenone analog[b]	0.13	1.0	1.0
Clomiphene keto analog[c]	0.33	1.0	1.0
Clomiphene related compound A	0.92	1.0	2.0
Clomiphene *Z*-isomer	0.98	—	—
Clomiphene *E*-isomer	1.00	—	—
2-Chloroclomiphene[d]	1.57	1.0	1.0[e]
2-Chloroclomiphene[d]	1.63	1.0	
4-Chloroclomiphene[f]	1.70	1.0	1.0[e]
4-Chloroclomiphene[f]	1.77	1.0	
Deschloroclomiphene chlorophenyl analog[g]	2.36	0.77	1.0[e]
Deschloroclomiphene chlorophenyl analog[g]	2.48	0.77	
Benzyl clomiphene[h]	2.67	0.74	0.15
Benzyl clomiphene[h]	2.76	0.81	0.15
Any other unspecified impurity	—	1.0	0.10
Total impurities	—	—	2.5

[a] {4-[2-(Diethylamino)ethoxy]phenyl}(phenyl)methanone.

[b] 2,2-Bis{4-[2-(diethylamino)ethoxy]phenyl}-1,2-diphenylethanone.

[c] 2-{4-[2-(Diethylamino)ethoxy]phenyl}-1,2-diphenylethan-1-one.

[d] (*E*,*Z*)-2-[2-Chloro-4-(2-chloro-1,2-diphenylvinyl)phenoxy]-*N*,*N*-diethylethan-1-amine.

[e] The sum of these geometric isomers is NMT 1.0%.

[f] (*E*,*Z*)-2-{4-[2-Chloro-2-(4-chlorophenyl)-1-phenylvinyl]phenoxy}-*N*,*N*-diethylethan-1-amine.

[g] (*E*,*Z*)-2-{4-[1,2-Bis(4-chlorophenyl)vinyl]phenoxy}-*N*,*N*-diethylethan-1-amine.

[h] (*E*,*Z*)-2-{4-[1-(4-Benzylphenyl)-2-chloro-2-phenylvinyl]phenoxy}-*N*,*N*-diethylethan-1-amine.

SPECIFIC TESTS

• **Water Determination,** *Method I* ⟨921⟩**:** NMT 1.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.

• **USP Reference Standards** ⟨11⟩

USP Clomiphene Citrate RS

USP Clomiphene Related Compound A RS

(*E*,*Z*)-2-[4-(1,2-Diphenylvinyl)phenoxy]-*N*,*N*-diethylethanamine hydrochloride.

Also known as (*E*,*Z*)-2-[4-(1,2-Diphenylethenyl)phenoxy]-*N*,*N*-diethylethanamine hydrochloride.

$C_{26}H_{29}NO \cdot HCl$ 407.98

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

Topic/Question	Contact	Expert Committee
CLOMIPHENE CITRATE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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