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Clomiphene Citrate Tablets

DEFINITION
Clomiphene Citrate Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of clomiphene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$).

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
- **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: 0.002 mg/mL of USP Clomiphene Related Compound A RS and 0.05 mg/mL of USP Clomiphene Citrate RS in *Mobile phase*.

Standard solution: 0.05 mg/mL of USP Clomiphene Citrate RS in *Mobile phase*

Sample stock solution: Nominally 0.5 mg/mL of clomiphene citrate prepared in *Mobile phase* as follows. Transfer an equivalent of 50 mg of clomiphene citrate from finely powdered Tablets (NLT 20) to a 100-mL volumetric flask. Add about 50 mL of *Mobile phase*, and stir using a magnetic bar for 30 min. Remove the magnetic bar from the flask, dilute with *Mobile phase* to volume, and filter.

Sample solution: Nominally 0.05 mg/mL of clomiphene citrate prepared from the *Sample stock solution* in *Mobile phase*. Filter, and discard the first 10 mL.

Chromatographic system

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

Mode: LC

Detector: UV 233 nm. For *Identification B*, use a diode array detector in the range of 190–400 nm.

Column: 4.6-mm × 25-cm; 5-µm packing L26

Flow rate: 1.0 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 the labeled amount of clomiphene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$) in the portion of Tablets taken:

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

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

r_S = sum of the peak responses of the (*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 = nominal concentration of clomiphene citrate in the *Sample solution* (mg/mL)

Acceptance criteria: 93.0%–107.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Standard solution: USP Clomiphene Citrate RS in 0.1 N hydrochloric acid

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with 0.1 N hydrochloric acid to a concentration similar to the *Standard solution*.

Instrumental conditions

Mode: UV

Analytical wavelength: 232 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clomiphene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$) 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 the *Standard solution* (mg/mL)

D = dilution factor for the *Sample solution*

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of clomiphene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$) is dissolved.

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

IMPURITIES

Change to read:

• **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

Time (min)	Solution A (%)	Solution B (%)
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: 0.0125 mg/mL of USP Clomiphene Citrate RS in *Buffer*

Sample solution: Nominally 1.25 mg/mL of clomiphene citrate, prepared as follows. Transfer a suitable amount of clomiphene citrate from powdered Tablets (NLT 20) to a suitable volumetric flask. Add 50% of the flask volume of *Buffer* and shake for 30 min using a mechanical shaker. Dilute with *Buffer* to volume and pass through a suitable filter of 0.45-µm pore size, discarding the first 5 mL of filtrate.

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

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

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets 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 the (*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 = nominal concentration of clomiphene citrate in the *Sample solution* (mg/mL)

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Clomiphene benzophenone analog[a]	0.10	0.51	1.0
Clomiphene keto analog[b]	0.31	1.0	1.0

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Clomiphene related compound A	0.87	▲1.0▲ (ERR 1-Aug-2023)	2.0
Clomiphene *Z*-isomer	0.97	—	—
Clomiphene *E*-isomer	1.00	—	—
Any other individual impurity	—	1.0	1.0
Total impurities	—	—	2.5

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

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

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers, protected from light, heat, and excessive humidity. 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-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 TABLETS	Documentary Standards Support	SM52020 Small Molecules 5

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