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Clozapine Tablets

DEFINITION

Clozapine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of clozapine ($C_{18}H_{19}ClN_4$).

IDENTIFICATION

Change to read:

• **A.** ▲The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2021)

• **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

Change to read:

• **Procedure**

Mobile phase: Methanol▲ ▲ (USP 1-May-2021) and water▲(80:20). To each liter add 0.75 mL of triethylamine.▲ (USP 1-May-2021)

System suitability stock solution: Transfer 10 mg of clozapine to a suitable container, add 5 mL of ▲0.1 N hydrochloric acid VS,▲ (USP 1-May-2021) and heat for 2 h at 90°. Transfer this solution to a 100-mL volumetric flask, add 15 mL of water, and dilute with methanol to volume.

Standard solution: 0.125 mg/mL of USP Clozapine RS prepared as follows. Transfer ▲a suitable portion of USP Clozapine RS to an appropriate volumetric flask.▲ (USP 1-May-2021) Dissolve in 80% of the flask volume of methanol. ▲Dilute with water to volume.▲ (USP 1-May-2021)

System suitability solution: *System suitability stock solution* and *Standard solution* ▲(50:50)▲ (USP 1-May-2021)

Sample solution: ▲Nominally 0.125 mg/mL of clozapine from Tablets prepared as follows. Finely powder NLT 20 Tablets and transfer a portion of powder equivalent to 125 mg of clozapine to a 1-L volumetric flask. Dissolve in 640 mL of methanol, sonicate for 10 min, and dilute with water to volume. Pass the resulting solution through an appropriate filter and use the filtrate.▲ (USP 1-May-2021)

Chromatographic system

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

Mode: LC

Detector: UV 257 nm. ▲For *Identification A*, use a diode array detector in the range of 210–400 nm.▲ (USP 1-May-2021)

Column: 4.0-mm × 25-cm; ▲10-µm▲ (USP 1-May-2021) packing L7

Flow rate: 1 mL/min

Injection ▲volume:▲ (USP 1-May-2021) 10 µL

▲Run time: NLT 3 times the retention time of clozapine▲ (USP 1-May-2021)

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between the clozapine peak and any other peak, *System suitability solution*

Column efficiency: NLT 1500 theoretical plates, *Standard solution*

Relative standard deviation: NMT ▲1.0%▲ (USP 1-May-2021) for replicate injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of clozapine ($C_{18}H_{19}ClN_4$) in the portion of Tablets taken:

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

r_U = peak response ▲of clozapine▲ (USP 1-May-2021) from the *Sample solution*

r_S = peak response ▲of clozapine▲ (USP 1-May-2021) from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Medium: pH 4.0 acetate buffer ▲▲ (USP 1-May-2021) (Dissolve 2 g of sodium hydroxide in 450 mL of water. Adjust with glacial acetic acid to a pH of 4.0. Dilute ▲with water▲ (USP 1-May-2021) to 1 L.); 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Standard solution: ▲(*L*/900) mg/mL of USP Clozapine RS in *Medium*, where *L* is the label claim, in mg/Tablet. Dilute with *Medium,* if necessary.▲ (USP 1-May-2021)

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Medium*, if necessary.

Instrumental conditions

Mode: UV

Analytical wavelength: 290 nm

Analysis

Samples: *Standard solution* and *Sample solution*

▲Calculate the percentage of the labeled amount of clozapine ($C_{18}H_{19}ClN_4$) dissolved:

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

A_U = absorbance of clozapine from the *Sample solution*

A_S = absorbance of clozapine from the *Standard solution*

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

V = volume of *Medium,* 900 mL

D = dilution factor, if needed

L = label claim (mg/Tablet)▲ (USP 1-May-2021)

Tolerances: NLT 85% (*Q*) of the labeled amount of clozapine ($C_{18}H_{19}ClN_4$) is dissolved.

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

IMPURITIES

Change to read:

• **Organic Impurities**

▲**Buffer:** 2.0 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.4–2.5.

Solution A: Acetonitrile, methanol, and *Buffer* (10:10:80)

Solution B: Acetonitrile, methanol, and *Buffer* (40:40:20)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
4	100	0
24	0	100
29	0	100
30	100	0
34	100	0

Diluent: Methanol and water (80:20)

System suitability stock solution: 100 µg/mL of clozapine *N*-oxide prepared as follows. Transfer a suitable quantity of clozapine *N*-oxide to an appropriate volumetric flask. Dissolve in 80% of the flask volume of methanol. Dilute with water to volume.

System suitability solution: 750 µg/mL USP Clozapine Resolution Mixture RS and 0.75 µg/mL of clozapine *N*-oxide from *System suitability stock solution* prepared as follows. Transfer a suitable quantity of USP Clozapine Resolution Mixture RS to an appropriate volumetric flask. Dissolve in 80% of the flask volume of methanol. Add a suitable portion of *System suitability stock solution.* Dilute with water to volume.

Standard solution: 0.75 µg/mL of USP Clozapine RS in *Diluent*

Sensitivity solution: 0.38 µg/mL of USP Clozapine RS from *Standard solution* in *Diluent*

Sample stock solution: Nominally 3000 µg/mL of clozapine from Tablets prepared as follows. Finely powder NLT 10 Tablets. Transfer a suitable quantity of the powder to an appropriate volumetric flask. Dissolve in 80% of the flask volume of methanol, and sonicate for 10 min. Dilute with water to volume.

Sample solution: Nominally 750 µg/mL of clozapine from *Sample stock solution* prepared as follows. Transfer a suitable volume of *Sample stock solution* to an appropriate volumetric flask. Dissolve in *Diluent*. Centrifuge the resulting solution and use the supernatant. [NOTE—A centrifuge speed of 10,000 rpm for 10 min may be suitable.]

Chromatographic system

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

Mode: LC

Detector: UV 257 nm

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

Column temperature: 35 ± 5°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—The relative retention time for didiazepinyl piperazine is 1.7. See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between benzoyl methylpiperazine analog and clozapine *N*-oxide; NLT 1.5 between chlorodibenzodiazepinone and didiazepinyl piperazine, *System suitability solution*

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

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each related compound and any unknown 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 any impurity from the *Sample solution*

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

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

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

F = relative response factor of the impurity (see Table 2)

Acceptance criteria: See Table 2. The reporting threshold is 0.1%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Demethyl clozapine[a]	0.9	1.0	0.3
Clozapine	1.0	—	—
Benzoyl methylpiperazine analog[b]	1.10	0.36	0.2
Clozapine *N*-oxide[c]	1.13	0.87	0.2
Chlorodibenzodiazepinone[d]	1.6	1.2	0.2
Individual unspecified impurity	—	1.0	0.2
Total impurities	—	—	2.0

[a] 8-Chloro-11-(piperazin-1-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine.

[b] 1-[2-[(2-Amino-4-chlorophenyl)amino]benzoyl]-4-methylpiperazine.

[c] 4-(8-Chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylpiperazine 1-oxide.

[d] 8-Chloro-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one.

▲ (USP 1-May-2021)

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** Preserve in well-closed containers. ▲Store at controlled room temperature.▲ (USP 1-May-2021)

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Clozapine RS

▲ USP Clozapine Resolution Mixture RS

Contains a mixture of the following 5 compounds:
Clozapine.
Chlorodibenzodiazepinone;
8-Chloro-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one.
$C_{13}H_9ClN_2O$ 244.68
Didiazepinyl piperazine;
1,4-Bis(8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)piperazine. $C_{30}H_{24}Cl_2N_6$ 539.46
Demethyl clozapine;
8-Chloro-11-(piperazin-1-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine. $C_{17}H_{17}ClN_4$ 312.80
Benzoyl methylpiperazine analog;
1-[2-[(2-Amino-4-chlorophenyl)amino]benzoyl]-4-methylpiperazine. $C_{18}H_{21}ClN_4O$ 344.84

[Note—The contents have previously been referred to as clozapine, Impurity A, Impurity B, Impurity C, and Impurity D, respectively.]▲ (USP 1-May-2021)

Topic/Question	Contact	Expert Committee
CLOZAPINE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4

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