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Hydromorphone Hydrochloride Oral Solution

DEFINITION

Hydromorphone Hydrochloride Oral Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of hydromorphone hydrochloride ($C_{17}H_{19}NO_3 \cdot HCl$). It may contain suitable preservatives.

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*.

ASSAY

• **Procedure**

Diluent: Phosphoric acid and water (1:1000)

Solution A: 1.0 mg/mL of sodium 1-heptanesulfonate monohydrate in methanol and water (1:9). To each liter of this solution add 1.0 mL of triethylamine, and adjust with phosphoric acid to a pH of 2.5 ± 0.1.

Solution B: 1.0 mg/mL of sodium 1-heptanesulfonate monohydrate in methanol and water (1:1). To each liter of this solution add 1.0 mL of triethylamine, and adjust with phosphoric acid to a pH of 2.5 ± 0.1.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	85	15
24	5	95
25	85	15
30	85	15

The *Standard solution* and *Sample solution* should be kept in a cool place, protected from light.

Standard solution: 0.08 mg/mL of USP Hydromorphone Hydrochloride RS in *Diluent*

Sample solution: Nominally 0.08 mg/mL of hydromorphone hydrochloride obtained by diluting a suitable volume of Oral Solution in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 5-cm; 3.5-µm packing L1

Column temperature: 45°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5 for the hydromorphone peak

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of hydromorphone hydrochloride ($C_{17}H_{19}NO_3 \cdot HCl$) in the portion of Oral Solution 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 Hydromorphone Hydrochloride RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

IMPURITIES

Change to read:

• **Organic Impurities**

Diluent, Solution A, and **Solution B:** Prepare as directed in the *Assay*.

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	94	6
25	94	6
40	20	80
70	20	80
75	94	6
90	94	6

The *System suitability solution*, *Quantitation limit solution*, *Standard solution*, and *Sample solution* should be kept in a cool place, protected from light.

System suitability solution: 0.8 mg/mL of USP Hydromorphone Hydrochloride RS and 0.8 µg/mL of USP Hydromorphone Related Compound A RS in *Diluent*

Quantitation limit solution: 0.4 µg/mL of USP Hydromorphone Hydrochloride RS in *Diluent*

Standard solution: 4 µg/mL of USP Hydromorphone Hydrochloride RS in *Diluent*

Sample solution: Nominally 0.4 mg/mL of hydromorphone hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 3.9-mm × 15-cm; 5-µm packing L1

Column temperature: 45°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution*, *Quantitation limit solution*, and *Standard solution*

Suitability requirements

Resolution: NLT 1.0 between the hydromorphone related compound A and hydromorphone peaks, *System suitability solution*

Signal-to-noise ratio: NLT 10:1, *Quantitation limit solution*

Tailing factor: NMT 1.5 for the hydromorphone peak, *Standard solution*

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

Analysis

Samples: *Diluent*, *Standard solution*, and *Sample solution*

Calculate the percentage of any specified or unspecified degradation product in the portion of Oral Solution taken:

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

r_U = peak response for each degradation product found, including those in Table 3, from the *Sample solution*

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

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

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

F = relative response factor for the corresponding individual specified or unspecified impurity (see Table 3)

Calculate the total degradation products by summing the percentage of all individual specified and unspecified degradation products determined to be at a level of 0.1% or greater, excluding the known process impurities, as indicated in Table 3.

Acceptance criteria: See Table 3. Disregard peaks corresponding to those from the *Diluent,* peaks that elute before a relative retention time of about 0.50, except for any peak with a relative retention time of about 0.34, and peaks that elute at the relative retention times of the process-related substances designated in Table 3.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Specified and unidentified degradation product	0.34	1.0	0.2
8-Hydroxy-hydromorphone[a,b]	0.50	—	—
Dihydromorphine (DHM)[a,c]	0.61	—	—
Morphine[a,d]	0.65	—	—
Hydromorphone *N*-oxide[e,f]	0.79	0.87	0.2
Hydromorphone	1.0	—	—
2,2'-Bis hydromorphone dihydrochloride[e,g]	2.02	1.7	0.2
Individual unspecified degradation products	—	1.0	0.2
Total degradation products	—	—	1.0

[a] Process impurity.

[b] 4,5α-Epoxy-17-methylmorphinan-3,8-diol-6-one.

[c] 4,5α-Epoxy-17-methylmorphinan-3,6α-diol.

[d] 7,8-Didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol.

[e] Degradation product.

[f] 4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one *N*-oxide.

▲[g] (5α)-3-Hydroxy-2-[(5α)-3-hydroxy-17-methyl-6-oxo-4,5-epoxymorphinan-2-yl]-17-methyl-4,5-epoxymorphinan-6-one dihydrochloride.▲

(ERR 1-Feb-2021)

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count does not exceed 10^2 cfu/mL, and the total yeasts and molds count does not exceed 10 cfu/mL. It meets the requirements of the test for the absence of *Escherichia coli*.

• **pH ⟨791⟩:** 3.5–6.5

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, protected from light. Store at 25°, excursions permitted between 15° and 30°.

• **Labeling:** Identify in the product labeling any preservative used in the Oral Solution.

• **USP Reference Standards ⟨11⟩**

USP Hydromorphone Hydrochloride RS

USP Hydromorphone Related Compound A RS

7,8-Didehydro-4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride.

$C_{17}H_{17}NO_3$ 319.78

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

Topic/Question	Contact	Expert Committee
HYDROMORPHONE HYDROCHLORIDE ORAL SOLUTION	Documentary Standards Support	SM22020 Small Molecules 2

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