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

• **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-Hydroxyhydromorphone[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′-Bishydromorphone 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] 2,2′-Bihydromorphone.

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*.

Change to read:

- **pH ⟨791⟩:** •3.5• (RB 1-Aug-2013)–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.

Change to read:

- **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• (RB 1-Aug-2013)