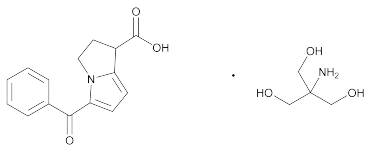
Ketorolac Tromethamine



$C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$ 376.40

1*H*-Pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, (±)-, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1);
(±)-5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) [74103-07-4].

DEFINITION

Ketorolac Tromethamine contains NLT 98.5% and NMT 101.5% of ketorolac tromethamine ($C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$), calculated on the dried basis.

IDENTIFICATION

• **A. Infrared Absorption** ⟨197K⟩

Delete the following:

•• **B. Ultraviolet Absorption** ⟨197U⟩
Sample solution: 10 µg/mL
Medium: Methanol
Acceptance criteria: Meets the requirements ● (IRA 1-May-2016)

Add the following:

•• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ● (IRA 1-May-2016)

• **C. Thin-Layer Chromatography,** *Tromethamine Test*
Diluent: Dichloromethane and methanol (2:1)
Standard solution: 5 mg/mL of USP Ketorolac Tromethamine RS in *Diluent*
Sample solution: 5 mg/mL of Ketorolac Tromethamine in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩*, Thin-Layer Chromatography*.)
Mode: TLC
Adsorbent: 0.25-mm layer of chromatographic silica gel mixture
Application volume: 40 µL
Developing solvent system: Dichloromethane, acetone, and glacial acetic acid (95:5:2)
Spray reagent: Freshly prepared alcoholic solution containing 30 mg/mL of ninhydrin
Analysis
Samples: *Standard solution* and *Sample solution*
Develop the chromatogram until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, and allow the solvent to evaporate. Spray the plate with *Spray reagent*, and heat the plate at about 150° for 2–5 min.
Acceptance criteria: Yellow spots with pink to purple borders develop on the plate in the areas where the *Standard solution* and the *Sample solution* were applied.

ASSAY

• **Procedure**
Protect all the solutions from light.
Buffer: 5.75 g/L of monobasic ammonium phosphate. Adjust with phosphoric acid to a pH of 3.0.
Mobile phase: Tetrahydrofuran and *Buffer* (30:70)
Diluent: Tetrahydrofuran and water (30:70)
System suitability solution: In a 250-mL separator, mix 100 mL of water, 100 mL of dichloromethane, 30 mg of USP Ketorolac Tromethamine RS, and 1 mL of 1 N hydrochloric acid. Insert the stopper, shake, and allow the layers to separate. Transfer the lower dichloromethane layer to a stoppered borosilicate glass flask, and discard the upper layer. Expose the dichloromethane solution to direct sunlight for 10–15 min. Transfer 1.0 mL of the solution to a vial, evaporate in a current of air or in a stream of nitrogen to dryness, add 1.0 mL of *Diluent*, and swirl to dissolve. [NOTE—This solution may be stored under refrigeration and used as long as the chromatogram obtained as directed for *Analysis* is suitable for identifying the peaks due to the ketorolac 1-keto analog and ketorolac 1-hydroxy analog, and for the measurement of the resolution between the ketorolac 1-keto analog and ketorolac.]
Standard solution: 0.4 mg/mL of USP Ketorolac Tromethamine RS in *Diluent*
Sample solution: 0.4 mg/mL of Ketorolac Tromethamine in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 313 nm
Column: 4.6-mm × 25-cm; 5-µm packing L7
Column temperature: 40°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for the ketorolac 1-hydroxy analog, the ketorolac 1-keto analog, and ketorolac are about 0.63, 0.89, and 1.0, respectively. Make adjustments, if necessary, to achieve a retention time for ketorolac of about 8–12 min.]
Suitability requirements
Resolution: NLT 1.5 between ketorolac 1-keto analog and ketorolac, *System suitability solution*
Column efficiency: NLT 5500 theoretical plates, *Standard solution*
Relative standard deviation: NMT 1.5%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of ketorolac tromethamine ($C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$) in the portion of Ketorolac Tromethamine taken:

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

r_U = peak area from the *Sample solution*
r_S = peak area from the *Standard solution*
C_S = concentration of USP Ketorolac Tromethamine RS in the *Standard solution* (mg/mL)
C_U = concentration of Ketorolac Tromethamine in the *Sample solution* (mg/mL)

Acceptance criteria: 98.5%–101.5% on the dried basis

IMPURITIES

• **Residue on Ignition** ⟨281⟩**:** NMT 0.1%

Delete the following:

•• **Heavy Metals,** *Method II* ⟨231⟩**:** NMT 20 ppm ● (Official 1-Jan-2018)

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Change to read:

- **ORGANIC IMPURITIES**

Mobile phase, Diluent, System suitability solution, Standard solution, and **Sample solution:** Proceed as directed in the *Assay*.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 313 nm
Column: 4.6-mm × 25-cm; 5-µm packing L7
Column temperature: 40°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
Run time: 3 times the retention time of ketorolac

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each individual impurity in the portion of Ketorolac Tromethamine taken:

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

r_U = peak response of each individual impurity from the *Sample solution*
r_T = sum of all the peak responses from the *Sample solution*
F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Impurity having a 0.54 relative retention time	0.54	2.2	0.5
Ketorolac 1-hydroxy analog	0.63	0.67	0.1
Impurity having a 0.66 relative retention time	0.66	0.91	0.5
Ketorolac 1-keto analog	0.89	0.52	0.1
● Individual unspecified impurity	—	1.0	0.5 ● (IRA 1-May-2016)
Ketorolac tromethamine	1.0	1.0	—
Total impurities	—	—	1.0

SPECIFIC TESTS

- **pH** ⟨**791**⟩
Sample solution: 10 mg/mL
Acceptance criteria: 5.7–6.7
- **LOSS ON DRYING** ⟨**731**⟩
Analysis: Dry under vacuum at 60° for 3 h.
Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Ketorolac Tromethamine RS

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