Caculate the percentage of ketoprofen dissolved at each time point:

$$\text{Result} = (D + \Sigma R) \times 100/L$$

D = [amount dissolved (mg)] = volume (mL) remaining before draw × concentration (mg/mL) of sample withdrawn at the sampling time point
R = [amount removed (mg)] = volume (mL) of sample withdrawn × concentration (mg/mL) of sample withdrawn at each time point
100 = conversion factor for percentage
L = Capsule label claim (mg)

Tolerances: The percentage of the labeled amount of ketoprofen released at the times specified conforms to *Acceptance Table 2.*

Time (h)	Amount Dissolved
1	10%–25%
4	55%–80%
8	NLT 80%

• **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements
Procedure for content uniformity: [NOTE—Protect the *Standard solution* and *Sample solution* from light.]
Mobile phase, Standard solution, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Sample solution: Transfer the contents of 10 Capsules, 1 Capsule each, to each of 10 250-mL volumetric flasks, add about 150 mL of *Mobile phase* to each flask, and stir for 2 h. Dilute with *Mobile phase* to volume, and mix. Centrifuge, and pipet a volume of clear supernatant that contains about 2.4 mg of ketoprofen into a 100-mL volumetric flask. Dilute with *Mobile phase* to volume.
System suitability
Samples: *Standard solution* and *System suitability solution*
Suitability requirements
Resolution: NLT 3.0 between ketoprofen and ketoprofen related compound A, *System suitability solution*
Tailing factor: NLT 1.5 for the ketoprofen peak, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_{16}H_{14}O_3$ in each Capsule:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Ketoprofen RS in the *Standard solution* (mg/mL)
C_U = concentration of ketoprofen in the *Sample solution* (mg/mL)

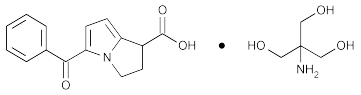
SPECIFIC TESTS

• **Water Determination,** *Method I* ⟨921⟩**:** NMT 3.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.
• **USP Reference Standards** ⟨11⟩
USP Ketoprofen RS
USP Ketoprofen Related Compound A RS
α-Methyl-3-(4-methylbenzoyl) benzeneacetic acid.

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].

» Ketorolac Tromethamine contains not less than 98.5 percent and not more than 101.5 percent of $C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$, calculated on the dried basis.

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

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩—
Solution: 10 µg per mL.
Medium: methanol.

C: *Tromethamine test*—Prepare a Standard solution of USP Ketorolac Tromethamine RS in a mixture of dichloromethane and methanol (2:1) containing 5 mg per mL. Similarly prepare a test solution of Ketorolac Tromethamine containing 5 mg per mL. Apply 40-µL volumes of the Standard solution and the test solution to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Place the plate in a chromatographic chamber previously equilibrated with a mixture of dichloromethane, acetone, and glacial acetic acid (95:5:2). Seal the chamber, and 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 a freshly prepared alcoholic solution containing 30 mg of ninhydrin per mL, and heat the plate at about 150° for 2 to 5 minutes. Yellow spots with pink to purple borders develop on the plate in the areas where the Standard solution and the test solution were applied.

pH ⟨791⟩**:** between 5.7 and 6.7, in a solution (1 in 100).

Loss on drying ⟨731⟩**—**Dry it in vacuum at 60° for 3 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Chromatographic purity—

Mobile phase, Solvent mixture, Standard preparation, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation.*

Procedure—Chromatograph the *Test solution* as directed for *Procedure* in the *Assay,* allowing the chromatography to extend to three times the retention time of ketorolac. Measure the responses of all the peaks. Calculate the percentage of each individual impurity in the portion of Ketorolac Tromethamine taken by the formula:

$$100 rf_i (r_i / r_s)$$

in which rf_i is the response factor of each individual impurity peak relative to that of ketorolac; r_i is the peak response for

each impurity; and r_s is the sum of all the peak responses of the impurity peaks and the major ketorolac peak. The rf_i values are 0.52 for the ketorolac 1-keto analog, 0.67 for the ketorolac 1-hydroxy analog, 2.2 for the impurity peak having a retention time of 0.54 relative to that of ketorolac, and 0.91 for the impurity peak at a relative retention time of 0.66. Not more than 0.1% of the ketorolac 1-keto analog or of the ketorolac 1-hydroxy analog is found; not more than 0.5% of any other impurity is found; and the sum of all impurities is not more than 1.0%.

Assay—

Mobile phase—Dissolve 5.75 g of monobasic ammonium phosphate in 1000 mL of water, and adjust with phosphoric acid to a pH of 3.0. Prepare a filtered and degassed mixture of this buffer solution and tetrahydrofuran (70:30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩) to achieve a retention time for ketorolac of about 8 to 12 minutes.

Solvent mixture—Prepare a mixture of water and tetrahydrofuran (70:30).

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Ketorolac Tromethamine RS in *Solvent mixture* to obtain a solution having a known concentration of about 0.4 mg per mL. [NOTE—Protect this solution from light.]

Assay preparation—Transfer about 20 mg of Ketorolac Tromethamine, accurately weighed, to a 50-mL volumetric flask, dilute with *Solvent mixture* to volume, and mix. [NOTE—Protect this solution from light.]

Resolution 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 to 15 minutes. 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 *Solvent mixture,* and swirl to dissolve. [NOTE—This solution may be stored under refrigeration and used as long as the chromatogram obtained as directed for *Procedure* 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.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 313-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7 and is maintained at a constant temperature of about 40°. The flow rate is about 1.5 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.63 for the ketorolac 1-hydroxy analog, 0.89 for the ketorolac 1-keto analog, and 1.0 for ketorolac; and the resolution, *R,* between the ketorolac 1-keto analog and ketorolac is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5500 theoretical plates; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$ in the portion of Ketorolac Tromethamine taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Ketorolac Tromethamine RS in the *Standard preparation;* and r_U and r_S are the ketorolac peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Ketorolac Tromethamine Injection

» Ketorolac Tromethamine Injection is a sterile solution of Ketorolac Tromethamine. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ketorolac tromethamine ($C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$).

Packaging and storage—Preserve in single-dose containers, preferably of Type I glass, at controlled room temperature, protected from light.

USP Reference standards ⟨11⟩**—**
USP Endotoxin RS
USP Ketorolac Tromethamine RS

Identification—Prepare a mixture of the *Standard preparation* and the *Assay preparation* (1:1), and chromatograph the mixture as directed in the *Assay*. The chromatogram thus obtained exhibits two main peaks corresponding to ketorolac and the internal standard.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 5.8 USP Endotoxin Units per mg of ketorolac tromethamine.

Sterility ⟨71⟩**—**It meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined*.

pH ⟨791⟩: between 6.9 and 7.9.

Particulate matter ⟨788⟩: meets the requirements for small-volume injections.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of methanol, water, and glacial acetic acid (55:44:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). Resolution may be increased by increasing the proportion of water in the *Mobile phase*.

Solvent mixture—Prepare a mixture of methanol and water (1:1).

Internal standard solution—Prepare a solution of naproxen in methanol containing about 0.3 mg per mL.

Standard stock solution—Dissolve an accurately weighed quantity of USP Ketorolac Tromethamine RS quantitatively in methanol to obtain a solution having a known concentration of about 0.24 mg per mL. [NOTE—Protect this solution from light.]

Standard preparation—Transfer 5.0 mL of the *Standard stock solution* and 5.0 mL of the *Internal standard solution* to a 50-mL volumetric flask, dilute with *Solvent mixture* to volume, and mix. [NOTE—Protect this solution from light.]

Assay preparation—Transfer an accurately measured volume of the Injection, equivalent to about 12 mg of ketorolac tromethamine, to a 50-mL volumetric flask, dilute with methanol to volume, and mix. Transfer 5.0 mL of this stock solution and 5.0 mL of *Internal standard solution* to a second 50-mL volumetric flask, dilute with *Solvent mixture* to volume, and mix. [NOTE—Protect both the stock solution and the *Assay preparation* from light.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.7 for ketorolac and 1.0 for naproxen, the resolution, *R,* between the ketorolac peak and the naproxen peak is not less than 5.4, the column efficiency determined from the ketorolac peak is not less than 2700 theoretical plates, the tailing factor is not more than 1.5, and the relative standard deviation for replicate injections is not more than 1.5%.