Identification—Transfer a quantity of finely powdered Tablets, equivalent to about 50 mg of ketoconazole, to a suitable flask, add 50 mL of chloroform, shake for about 2 minutes, and filter. Apply separate 10-µL portions of this solution and of a Standard solution of USP Ketoconazole RS in chloroform containing 1 mg per mL to the starting line of a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in an unsaturated chamber with a solvent system consisting of a mixture of *n*-hexane, ethyl acetate, methanol, water, and glacial acetic acid (42:40:15:2:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, air-dry, and view under short-wavelength UV light: the R_F value of the principal spot obtained from the test solution corresponds to that obtained from the Standard solution.

Dissolution ⟨711⟩**—**

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Determine the amount of $C_{26}H_{28}Cl_2N_4O_4$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 270 nm on portions of the solution under test passed through a 0.45-µm filter and suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Ketoconazole RS in the same *Medium.*

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{26}H_{28}Cl_2N_4O_4$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Assay—

Methanol–methylene chloride—Mix equal volumes of methanol and methylene chloride.

Mobile phase—Prepare a suitable (7:3) mixture of a solution of diisopropylamine in methanol (1 in 500) and ammonium acetate solution (1 in 200).

Internal standard solution—Dissolve USP Terconazole RS in *Methanol–methylene chloride* to obtain a solution containing about 5 mg per mL.

Standard preparation—Transfer about 20 mg of USP Ketoconazole RS, accurately weighed, to a 50-mL volumetric flask, add 5.0 mL of *Internal standard solution,* dilute with *Methanol–methylene chloride* to volume, and mix.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg of ketoconazole, to a suitable screw-capped bottle, add 50.0 mL of *Methanol–methylene chloride,* shake by mechanical means for 30 minutes, and centrifuge. Transfer 5.0 mL of the clear supernatant so obtained to a 50-mL volumetric flask, add 5.0 mL of *Internal standard solution,* dilute with *Methanol–methylene chloride* to volume, and mix.

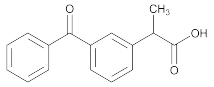
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.6 for ketoconazole and 1.0 for terconazole; the resolution, *R,* between ketoconazole and terconazole is not less than 2.0; and the relative standard deviation is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 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 ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$) in the portion of Tablets taken by the formula:

$$10W_S(R_U / R_S)$$

in which W_S is the weight, in mg, of USP Ketoconazole RS taken; and R_U and R_S are the ratios of the peak responses of ketoconazole to those of terconazole from the *Assay preparation* and the *Standard preparation,* respectively.

Ketoprofen



$C_{16}H_{14}O_3$ 254.28

Benzeneacetic acid, 3-benzoyl-α-methyl-, (±)-.

(±)-*m*-Benzoylhydratropic acid [22071-15-4].

» Ketoprofen contains not less than 98.5 percent and not more than 101.0 percent of $C_{16}H_{14}O_3$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩**—**

USP Ketoprofen RS

USP Ketoprofen Related Compound D RS

3-Acetylbenzophenone.

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 1 in 100,000.

Medium: a mixture of methanol and water (3:1).

Absorptivities at the wavelength of maximum absorbance at about 258 nm do not differ by more than 3.0%, calculated on the dried basis.

Melting range, *Class I* ⟨741⟩: between 92.0° and 97.0°.

Specific rotation ⟨781S⟩: between +1° and –1°.

Test solution: 10 mg per mL, in dehydrated alcohol.

Loss on drying ⟨731⟩**—**Dry it in vacuum at 60° for 4 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.2%.

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

Chromatographic purity—

pH 3.5 Buffer—Dissolve 68.0 g of monobasic potassium phosphate in 1000 mL of water, and adjust with phosphoric acid to a pH of 3.5 ± 0.05.

Mobile phase—Prepare a suitable filtered and degassed mixture of water, acetonitrile, and *pH 3.5 buffer* (55:43:2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Prepare a solution in *Mobile phase* containing about 5 µg per mL of USP Ketoprofen RS and 1.5 µg per mL of USP Ketoprofen Related Compound D RS. [NOTE—Protect this solution from light.]

Standard solution—Dissolve an accurately weighed quantity of USP Ketoprofen RS quantitatively in *Mobile phase* to obtain a solution having a known concentration of about 0.002 mg per mL. [NOTE—Protect this solution from light.]

Test solution—Transfer about 100 mg of Ketoprofen, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. [NOTE—Protect this solution from light.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 233-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.6 for ketoprofen related compound D (3-acetylbenzophenone) and 1.0 for ketoprofen; the resolution, *R,* between ketoprofen related compound D and ketoprofen is not less than 7.0; the

column efficiency, determined from the ketoprofen peak, is not less than 2250 theoretical plates; and the tailing factor for the ketoprofen peak is not more than 2.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, run the chromatograph for seven times the retention time for ketoprofen, record the chromatograms, and measure the areas for the peaks. Calculate the percentage of each impurity by the same formula:

$$10{,}000(C / W)(r_i / r_S)$$

in which C is the concentration, in mg per mL, of USP Ketoprofen RS in the *Standard solution; W* is the weight, in mg, of Ketoprofen taken to prepare the *Test solution;* r_i is the response of each individual peak, other than the main ketoprofen peak, obtained from the *Test solution;* and r_S is the response of the main ketoprofen peak obtained from the *Standard solution:* not more than 0.2% of any individual impurity is found, and the sum of all impurities found is not more than 1.0%.

Assay—Dissolve about 450 mg of Ketoprofen, accurately weighed, in 25 mL of alcohol. Add 25 mL of water and several drops of phenol red TS, and titrate with 0.1 N sodium hydroxide having been standardized by a similar titration of primary standard benzoic acid. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 25.43 mg of $C_{16}H_{14}O_3$.

Ketoprofen Extended-Release Capsules

DEFINITION

Ketoprofen Extended-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of ketoprofen ($C_{16}H_{14}O_3$).

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.*
- **B. ULTRAVIOLET ABSORPTION ⟨197⟩:** The UV spectrum from the *Sample solution* in the *Analysis* for the *Dissolution* section corresponds to the spectrum from the *Standard solution.*

ASSAY

- **PROCEDURE**

[NOTE—Protect the *Standard solution* and *Sample solution* from light.]

Mobile phase: Acetonitrile, water, and glacial acetic acid (90:110:1)

Standard stock solution: 0.24 mg/mL of USP Ketoprofen RS in *Mobile phase*

Standard solution: 0.024 mg/mL of USP Ketoprofen RS in *Mobile phase,* from the *Standard stock solution*

System suitability solution: 0.25 mg/mL of USP Ketoprofen RS and 0.5 mg/mL of USP Ketoprofen Related Compound A RS in *Mobile phase.* Pipet 4.0 mL of this solution into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Sample solution: Remove completely the contents of NLT 20 Capsules, and transfer a quantity of the beads, equal to 200 mg of ketoprofen, to a 250-mL volumetric flask. Add 150 mL of *Mobile phase* and mix; bring to volume. Centrifuge, and pipet 3.0 mL of clear supernatant that contains about 2.4 mg of ketoprofen into a 100-mL volumetric flask. Dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1.2 mL/min

Injection size: 20 µL

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 the portion of Capsules 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 Ketoprofen RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION ⟨711⟩**

Medium: pH 6.8 phosphate buffer; 1000 mL

Apparatus 2: 50 rpm

Time: 1, 4, and 8 h

Detector: UV 258 nm

Standard solution: About 0.1 mg/mL of USP Ketoprofen RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 10-µm pore size, then pass the filtrate through a suitable filter of 0.45-µm pore size.

Capsules labeled to contain 200 mg: In a test tube, dilute 5.0 mL of filtrate with 5.0 mL of *Medium.*

Capsules labeled to contain 150 mg: In a test tube, dilute 6.0 mL of filtrate with 3.0 mL of *Medium.*

Capsules labeled to contain 100 mg: No dilution is necessary.

Capsule blank: Place 10 empty, clean Capsules of the appropriate dosage into a 1000-mL volumetric flask. Add about 800 mL of *Medium* at 37°. Stir until Capsule shells are disintegrated. After equilibration to room temperature, dilute with *Medium* to volume. Transfer 100.0 mL to a 1000-mL volumetric flask, and dilute with *Medium* to volume. Pass through a suitable filter of 10-µm pore size, then pass the filtrate through a suitable filter of 0.45-µm pore size.

Capsules labeled to contain 200 mg: In a flask, dilute 25.0 mL with 25.0 mL of *Medium*.

Capsules labeled to contain 150 mg: In a flask, dilute 30.0 mL with 15.0 mL of *Medium*.

Capsules labeled to contain 100 mg: No dilution is necessary.

Analysis

Samples: *Standard solution*, *Sample solution*, and *Capsule blank*, using *Medium* as the blank

Calculate the concentration, in mg/mL, of ketoprofen in the sample withdrawn at each time point:

$$\text{Result} = (A_U - A_{CB}) \times (C_S/A_S)$$

A_U = absorbance of the *Sample solution*

A_{CB} = absorbance of the *Capsule blank*

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

A_S = absorbance of the *Standard solution*