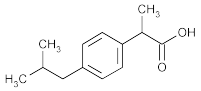
Ibuprofen



$C_{13}H_{18}O_2$ 206.28
Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-.
(±)-*p*-Isobutylhydratropic acid.
(±)-2-(*p*-Isobutylphenyl)propionic acid [15687-27-1].
(±) Mixture [58560-75-1].

» Ibuprofen contains not less than 97.0 per cent and not more than 103.0 per cent of $C_{13}H_{18}O_2$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩**—**
USP Ibuprofen RS
USP Ibuprofen Related Compound C RS

Identification—

A: *Infrared Absorption* ⟨197M⟩—Do not dry specimens.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 250 µg per mL.

Medium: 0.1 N sodium hydroxide.

Respective absorptivities at 264 nm and 273 nm, calculated on the anhydrous basis, do not differ by more than 3.0%.

C: The chromatogram of the *Assay preparation* obtained as directed in the *Assay* exhibits a major peak for ibuprofen, the retention time of which, relative to that of the internal standard, corresponds to that exhibited in the chromatogram of the *Standard preparation,* obtained as directed in the *Assay*.

Water, *Method I* ⟨921⟩: not more than 1.0%.

Residue on ignition ⟨281⟩: not more than 0.5%.

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

Chromatographic purity—

Mobile phase—Prepare a suitable filtered mixture of water, previously adjusted with phosphoric acid to a pH of 2.5 and acetonitrile (1340:680). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Test preparation—Prepare a solution of Ibuprofen in acetonitrile containing about 5 mg per mL.

Resolution solution—Prepare a solution in acetonitrile containing in each mL about 5 mg of Ibuprofen and 5 mg of valerophenone.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4-mm × 15-cm column that contains 5- µm packing L1 and is maintained at 30 ±0.5°. The flow rate is about 2 mL per minute. Chromatograph a series of 5- µL injections of the *Test preparation* to condition the column. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for valerophenone and 1.0 for ibuprofen, and the resolution, *R,* between the valerophenone peak and the ibuprofen peak is not less than 2.0.

Procedure—[NOTE—Use peak areas where peak responses are indicated.] Inject about 5 µL of the *Test preparation* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity taken by the formula:

$$100 r_i / r_t$$

in which r_i is the response of an individual peak, other than the solvent peak and the main ibuprofen peak, and r_t is the sum of the responses of all the peaks, excluding that of the solvent peak: not more than 0.3% of any individual impurity is found, and the sum of all the individual impurities found does not exceed 1.0%.

Limit of ibuprofen related compound C—Using the chromatograms of the *Assay preparation* and the *Ibuprofen related compound C standard solution,* obtained as directed in the *Assay,* calculate the percentage of ibuprofen related compound C ($C_{12}H_{16}O$) in the portion of Ibuprofen taken by the formula:

$$10{,}000(C / W)(R_U / R_S)$$

in which *C* is the concentration, in mg per mL, of USP Ibuprofen Related Compound C RS in the *Ibuprofen related compound C standard solution; W* is the weight, in mg, of Ibuprofen taken to prepare the *Assay preparation;* and R_U and R_S are the peak response ratios of ibuprofen related compound C to valerophenone obtained from the *Assay preparation* and the *Ibuprofen related compound C standard solution,* respectively: not more than 0.1% is found.

Assay—

Mobile phase—Dissolve 4.0 g of chloroacetic acid in 400 mL of water, and adjust with ammonium hydroxide to a pH of 3.0. Add 600 mL of acetonitrile, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Prepare a solution of valerophenone in *Mobile phase* having a concentration of about 0.35 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Ibuprofen RS in *Internal standard solution* to obtain a solution having a known concentration of about 12 mg per mL.

Ibuprofen related compound C standard solution—Quantitatively dissolve an accurately weighed quantity of USP Ibuprofen Related Compound C RS in acetonitrile to obtain a solution having a known concentration of about 0.6 mg per mL. Add 2.0 mL of this stock solution to 100.0 mL of *Internal standard solution,* and mix to obtain a solution having a known concentration of about 0.012 mg of ibuprofen related compound C per mL.

Assay preparation—Transfer about 1200 mg of Ibuprofen, accurately weighed, to a 100-mL volumetric flask, dilute with *Internal standard solution* to volume, and mix.

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 packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.4 for the internal standard and 1.0 for ibuprofen; the resolution, *R,* between ibuprofen and the internal standard is not less than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *Ibuprofen related compound C standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for valerophenone and 1.2 for ibuprofen related compound C; the resolution, *R,* between valerophenone and ibuprofen related compound C is not less than 2.5; the tailing factors for the individual peaks are not more than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation,* the *Assay preparation,* and the *Ibuprofen related compound C standard solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{13}H_{18}O_2$ in the portion of Ibuprofen taken by the formula:

$$100C(R_U / R_S)$$

in which *C* is the concentration, in mg per mL, of USP Ibuprofen RS in the *Standard preparation;* and R_U and R_S are the peak response ratios obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Ibuprofen Oral Suspension

» Ibuprofen Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{13}H_{18}O_2$.

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—
USP Ibuprofen RS
USP Ibuprofen Related Compound C RS

Identification—

A: Transfer a volume of Oral Suspension, equivalent to about 200 mg of ibuprofen, to a separator containing about 10 mL of chloroform, and shake for about 1 minute. Allow the layers to separate, and pass the lower chloroform layer through a filter containing about 2 g of anhydrous sodium sulfate. Use the filtrate as the test solution. [NOTE—Retain a portion of this test solution for use in *Identification* test *B*.] Separately apply 10-µL portions of the test solution and of a Standard solution containing 20 mg per mL of USP Ibuprofen RS in chloroform to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel and previously activated by heating at 105 ° for 30 minutes. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of *n*-hexane, butyl acetate, and glacial acetic acid (17:3:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and dry in a current of cool air. Examine the chromatograms 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.

B: *Infrared Absorption* ⟨197K⟩—Prepare the test specimen and the standard as follows. Evaporate about 20 drops of the test solution and the Standard solution retained from *Identification* test *A* to dryness in a current of air without heating.

Dissolution ⟨711⟩—

Medium: pH 7.2 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 900 mL.

Apparatus 2: 50 rpm.

Time: 60 minutes.

Determine the percentage of the labeled amount of $C_{13}H_{18}O_2$ dissolved by the following procedure:

Mobile phase and *Chromatographic system*—Proceed as directed in the *Assay.*

Internal standard solution—Prepare a solution of benzophenone in acetonitrile containing about 0.3 mg per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Ibuprofen RS in *Dissolution Medium* to obtain a solution having a known concentration of about 0.011 *J* mg per mL, *J* being the labeled quantity, in mg, of ibuprofen in each mL of the Oral Suspension. Mix 10.0 mL of this solution and 10.0 mL of the *Internal standard solution,* pass the mixture through a filter having a 0.5-µm or finer porosity, and use the filtrate as the *Standard solution.*

Test solution—Filter a portion of the solution under test. Mix 10.0 mL of the filtrate and 10.0 mL of the *Internal standard solution,* pass the mixture through a filter having a 0.5-µm or finer porosity, and use the filtrate as the *Test solution.*

Procedure—Using an accurately tared syringe, draw about 10 mL of well-mixed Oral Suspension into the syringe, which is connected to tubing, and accurately weigh. [NOTE—The tubing of the syringe is placed into a zone that is between the surface of the *Dissolution Medium* and the top of the rotating blade.] Express the Oral Suspension into the *Dissolution Medium.* Promptly reweigh the syringe, and determine the weight, W_U, in g, of the Oral Suspension added to the *Dissolution Medium.* Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of the labeled amount of $C_{13}H_{18}O_2$ dissolved by the formula:

$$90{,}000(C/L)(D/W_U)(R_U / R_S)$$

in which C is the concentration, in mg per mL, of USP Ibuprofen RS in the *Standard solution; L* is the labeled quantity, in mg per mL, of ibuprofen in the Oral Suspension; D is the density, in g per mL, of the Oral Suspension, determined as directed for *Density* in the *Assay; W_U* is the weight, in g, of the Oral Suspension added to the *Dissolution Medium;* and R_U and R_S are the ratios of the ibuprofen peak areas to the benzophenone peak areas obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{13}H_{18}O_2$ is dissolved in 60 minutes.

Uniformity of dosage units ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.

Deliverable volume ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.

pH ⟨791⟩**:** between 3.6 and 4.6.

Deliverable volume ⟨698⟩**:** meets the requirements.

Limit of ibuprofen related compound C—

Mobile phase and *Diluent*—Proceed as directed in the *Assay.*

Standard solution—Quantitatively dissolve an accurately weighed quantity of USP Ibuprofen Related Compound C RS in acetonitrile to obtain a stock solution having a known concentration of about 0.5 mg per mL. Transfer 3.0 mL of this stock solution to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix. Transfer 2.0 mL of this solution to a second 50-mL volumetric flask, add 18 mL of *Diluent,* dilute with acetonitrile to volume, mix, and pass through a filter having a porosity of 0.22-µm. This *Standard solution* contains about 0.0012 mg of ibuprofen related compound C per mL.

Test solution—Transfer 20.0 mL of the portion of the stock solution retained from the *Assay preparation* in the *Assay* into a 50-mL volumetric flask, dilute with acetonitrile to volume, mix, and pass through a filter having a porosity of 0.22-µm.

System suitability solution—Transfer 1.5 mL of the stock solution of USP Ibuprofen Related Compound C RS prepared as directed for *Standard solution* and 9 mL of the stock solution of USP Ibuprofen RS prepared as directed for *Standard preparation* in the *Assay* to a 25-mL volumetric flask, dilute with acetonitrile to volume, mix, and pass through a filter having a porosity of 0.22-µm. This solution contains about 0.03 mg of ibuprofen related compound C and about 0.4 mg of ibuprofen per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 2 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.3 for ibuprofen related compound C and 1.0 for ibuprofen; the resolution, *R,* between ibuprofen and ibuprofen related compound C is not less than 1.5; and the tailing factor 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 2.0%.

Procedure—Separately inject equal volumes (about 35 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of ibuprofen related