Ibuprofen

C₁₃H₁₈O₂  206.28
Benzeneacetic acid, α-methyl-4-(2-methylpropyl) ((±)-(2)-p-isobutylhydrosopic 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 C₁₃H₁₈O₂, 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 254-nm detector and a 4.6 mm × 25-cm column containing 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 less than 2.5; and the relative standard deviation for replicate injections is not more 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:

\[
100C / R_i
\]

in which \( C \) is the response of an individual peak, other than the solvent peak and the main ibuprofen peak, and \( R_i \) 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 (C₁₃H₁₈O₂) in the portion of ibuprofen taken by the formula:

\[
10,000(C / W)(R_o / R_i)
\]

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 \( R_o \) and \( R_i \) 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 less 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 C₁₃H₁₈O₂ in the portion of ibuprofen taken by the formula:

\[
100C(R_o / R_i)
\]
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 °C 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—Quantitatively dissolve an accurately weighed quantity of USP Ibuprofen RS in Dissolution Medium to obtain a solution having a known concentration of about 0.011 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, $W_s$, 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:

\[
90,000(C/L)(D/W_s)(R_s / R_f)
\]

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; $W_s$ is the weight, in g, of the Oral Suspension added to the Dissolution Medium; and $R_s$ and $R_f$ 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 x 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 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 per centage of ibuprofen related