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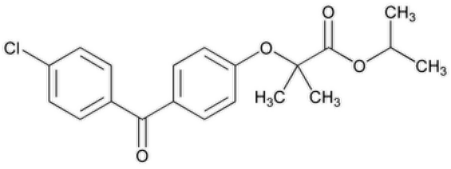
Fenofibrate



$C_{20}H_{21}ClO_4$ 360.83

Isopropyl 2-[*p*-(*p*-chlorobenzoyl)phenoxy]-2-methylpropanoate CAS RN®: 49562-28-9; UNII: U202363UOS.

DEFINITION

Fenofibrate contains NLT 98.0% and NMT 102.0% of $C_{20}H_{21}ClO_4$, calculated on the dried basis.

IDENTIFICATION

Change to read:

• ▲**Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: **197K**▲ (CN 1-May-2020)

ASSAY

• **Procedure**

Mobile phase: Acetonitrile and water acidified with phosphoric acid to a pH of 2.5 (7:3)

Standard solution: 1 mg/mL of USP Fenofibrate RS in *Mobile phase*

Sample solution: 1 mg/mL of Fenofibrate in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 286 nm

Column: 4.0-mm × 25-cm; packing L1

Flow rate: 1.0 mL/min

Injection size: 5 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 1.0% for six replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{20}H_{21}ClO_4$ in the portion of Fenofibrate 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 Fenofibrate RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

Inorganic Impurities

• **Residue on Ignition** ⟨281⟩**:** NMT 0.1%, determined on 1.0 g

• **Chloride and Sulfate,** *Chloride* ⟨221⟩

Sample solution: Add 25 mL of water to 5.0 g of Fenofibrate, and heat at 50° for 10 min. Cool, dilute with water to 50.0 mL, filter, and use the filtrate. [Note—Retain the remaining portion of the *Sample solution* for the test for *Chloride and Sulfate, Sulfate*.]

Analysis: Use 10 mL of the *Sample solution*.

Acceptance criteria: It shows no more chloride than corresponds to 0.15 mL of 0.020 N hydrochloric acid (0.01%).

- **Chloride and Sulfate,** *Sulfate*⟨221⟩

Sample: Use the *Sample solution* prepared in the test for *Chloride and Sulfate, Chloride*.

Analysis: Use 10 mL of the *Sample*.

Acceptance criteria: It shows no more sulfate than corresponds to 0.15 mL of 0.020 N sulfuric acid (0.01%).

Organic Impurities

- **Procedure**

Mobile phase: Acetonitrile and water acidified with phosphoric acid to a pH of 2.5 (7:3)

Impurity standard solution: 1 µg/mL each of USP Fenofibrate RS, USP Fenofibrate Related Compound A RS, and USP Fenofibrate Related Compound B RS, and 2 µg/mL of USP Fenofibrate Related Compound C RS in *Mobile phase*

Sample solution: 1 mg/mL of Fenofibrate in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 286 nm

Column: 4.0-mm × 25-cm; packing L1

Flow rate: 1.0 mL/min

Injection size: 20 µL

System suitability

Sample: *Impurity standard solution*

Suitability requirements

Resolution: NLT 1.5 between fenofibrate related compound A and fenofibrate related compound B

Analysis

Samples: *Impurity standard solution* and *Sample solution*

Identify the fenofibrate peak and the peaks due to the impurities and degradation products listed in *Impurity Table 1*.

Measure the responses for the major peaks, and calculate the percentage of each of fenofibrate related compound A, fenofibrate related compound B, and fenofibrate related compound C in the portion of Fenofibrate taken:

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

r_U = peak response of appropriate fenofibrate related compound from the *Sample solution*

r_S = peak response of appropriate fenofibrate related compound from the *Impurity standard solution*

C_S = concentration of the appropriate fenofibrate related compound in the *Impurity standard solution* (µg/mL)

C_U = concentration of Fenofibrate in the *Sample solution* (µg/mL)

Calculate the percentage of any other impurity in the portion of Fenofibrate taken:

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

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of fenofibrate from the *Impurity standard solution*

C_S = concentration of fenofibrate in the *Impurity standard solution* (µg/mL)

C_U = concentration of Fenofibrate in the *Sample solution* (µg/mL)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 0.5%

Impurity Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
(4-Chlorophenyl)(4-hydroxyphenyl) methanone[a]	0.34	0.1
2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid (fenofibric acid)[b]	0.36	0.1
(3*RS*)-3-[4-(4-Chlorobenzoyl) phenoxy]butan-2-one	0.50	0.1
Methyl 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoate	0.65	0.1
Ethyl 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoate	0.80	0.1
(4-Chlorophenyl)[4-(1-methylethoxy) phenyl]methanone	0.85	0.1
1-Methylethyl 2-[[2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoyl]oxy]-2-methylpropanoate[c]	1.35	0.2
Any other impurity	—	0.1

[a] Fenofibrate related compound A.

[b] Fenofibrate related compound B.

[c] Fenofibrate related compound C.

SPECIFIC TESTS

- **Melting Range or Temperature, *Class Ia*⟨741⟩:** 79°–82°
- **Acidity**

  Sample: 1.0 g

  Analysis: Dissolve the *Sample* in 50 mL of alcohol previously neutralized to phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS.

  Acceptance criteria: NMT 0.2 mL is required to change the color of the indicator to pink.
- **Loss on Drying ⟨731⟩**

  Analysis: Dry a sample in a vacuum over phosphorus pentoxide at 60° to constant weight.

  Acceptance criteria: NMT 0.5%
- **Color and Achromicity ⟨631⟩**

  Reference solution: Mix 5 mL of *Matching Fluid G* and 95 mL of dilute hydrochloric acid (1 in 40).

  Sample solution: 50 mg/mL of Fenofibrate in acetone

  Analysis: Proceed as directed in the chapter.

  Acceptance criteria: The *Sample solution* is not more intensely colored than the *Reference solution*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed, light-resistant containers. Store at room temperature.
- **USP Reference Standards ⟨11⟩**

  USP Fenofibrate RS

  USP Fenofibrate Related Compound A RS

  (4-Chlorophenyl)(4-hydroxyphenyl)methanone.

  USP Fenofibrate Related Compound B RS

  2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid, or fenofibric acid.

  USP Fenofibrate Related Compound C RS

  1-Methylethyl 2-[[2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoyl]oxy]-2-methylpropanoate.

Topic/Question	Contact	Expert Committee
FENOFIBRATE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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