silanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: Dissolve 1.34 g of potassium methanesulfonate in diluted phosphoric acid (1 in 1000) to make 1000 mL, and to 650 mL of this solution add 350 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of clofedanol is about 9 minutes.

Selection of column: Dissolve 0.01 g each of Clofedanol Hydrochloride and ethyl parahydroxybenzoate in methanol to make 100 mL. Proceed with 3 μL of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of clofedanol and ethyl parahydroxybenzoate in this order with the resolution of these peaks being not less than 4.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of clofedanol obtained from 3 μL of the standard solution composes between 20% and 50% of the full scale.

Time span of measurement: About three times as long as the retention time of clofedanol after the solvent peak.

Loss on drying Not more than 2.0% (1 g, in vacuum, silica gel, 80°C, 3 hours).

Residue on ignition Not more than 0.10% (1 g).

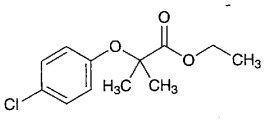
Assay Weigh accurately about 0.5 g of Clofedanol Hydrochloride, previously dried, dissolve in 15 mL of acetic acid (100), add 35 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 32.627 mg of $C_{17}H_{20}ClNO.HCl$

Containers and storage Containers—Tight containers.

Clofibrate

クロフィブラート



$C_{12}H_{15}ClO_3$: 242.70
Ethyl 2-(4-chlorophenoxy)-2-methylpropanoate
[*637-07-0*]

Clofibrate, calculated on the unhydrous basis, contains not less than 98.0% of $C_{12}H_{15}ClO_3$.

Description Clofibrate occurs as a colorless or light yellow, clear, oily liquid. It has a characteristic odor and taste, which is bitter at first, and subsequently sweet.

It is miscible with methanol, with ethanol (95), with ethanol (99.5), with diethyl ether and with hexane, and practically insoluble in water.

It is gradually decomposed by light.

Identification (1) Determine the absorption spectrum of a solution of Clofibrate in ethanol (99.5) (1 in 10,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum 1 or the spectrum of a solution of Clofibrate Reference Standard prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths. Separately, determine the absorption spectrum of a solution of Clofibrate in ethanol (99.5) (1 in 100,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum 2 or the spectrum of a solution of Clofibrate Reference Standard prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Clofibrate as directed in the liquid film method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of Clofibrate Reference Standard: both spectra exhibit similar intensities of absorption at the same wave numbers.

Refractive index n_D^{20}: 1.500 - 1.505

Specific gravity d_{20}^{20}: 1.137 - 1.144

Purity (1) Acid—Dissolve 2.0 g of Clofibrate in 100 mL of neutralized ethanol, and add 1 drop of phenolphthalein TS and 0.20 mL of 0.1 mol/L sodium hydroxide VS: the solution is red in color.

(2) Heavy metals—Proceed with 2.0 g of Clofibrate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(3) Arsenic—To 5.0 g of Clofibrate add 20 mL of nitric acid and 5 mL of sulfuric acid, and heat until white fumes are evolved. After cooling, if necessary, add further 5 mL of nitric acid, heat until white fumes are evolved, and repeat this procedure until the solution is colorless to light yellow. After cooling, add 15 mL of saturated ammonium oxalate solution, and heat again until white fumes are evolved. Cool, add water to make 25 mL, use 5 mL of this solution as the test solution, and perform the test using Apparatus B.

Standard stain: Prepare a solution according to the above procedure without using Clofibrate as the blank. Transfer 5 mL of the solution to a generator bottle, add 2.0 mL of Standard Arsenic Solution, and then proceed as directed in the test solution (not more than 20 ppm).

(4) *p*-Chlorophenol—To 1.0 g of Clofibrate add exactly 1 mL of the internal standard solution, then add the mobile phase to make 5 mL, and use this solution as the sample solution. Separately, dissolve 0.010 g of 4-chlorophenol in a mixture of hexane and 2-propanol (9:1) to make exactly 100 mL. Pipet 10 mL of this solution, and add a mixture of hexane and 2-propanol (9:1) to make exactly 50 mL. Pipet 6 mL of this solution, add exactly 4 mL of the internal standard solution, then add the mobile phase to make 20 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of 4-chlorophenol to that of the internal standard: Q_T is not greater than Q_S.

Internal standard solution—A solution of 4-ethoxyphenol in the mobile phase (1 in 30,000).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

Column: A stainless steel column about 4 mm in inside diameter and about 30 cm in length, packed with cyanopropylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: A mixture of hexane, 2-propanol and acetic acid (100) (1970:30:1).

Flow rate: Adjust the flow rate so that the retention time of clofibrate is about 2 minutes.

Selection of column: Dissolve 10.0 g of clofibrate, 6 mg of 4-chlorophenol and 6 mg of 4-ethoxyphenol in 1000 mL of hexane. Proceed with 20 μL of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of clofibrate, 4-chlorophenol and 4-ethoxyphenol in this order, with the resolution between the peaks of clofibrate and 4-chlorophenol is not less than 5, and with the resolution between the peaks of 4-chlorophenol and 4-ethoxyphenol is not less than 2.0.

Water Not more than 0.2% (1 g, direct titration).

Residue on ignition Not more than 0.10% (1 g).

Assay Weigh accurately about 0.5 g of Clofibrate, add exactly 50 mL of 0.1 mol/L potassium hydroxide-ethanol VS, and heat in a water bath under a reflux condenser with a carbon dioxide absorbing tube (soda-lime) for 2 hours with frequent shaking. Cool, and titrate immediately the excess potassium hydroxide with 0.1 mol/L hydrochloric acid VS (indicator: 3 drops of phenolphthalein TS). Perform a blank determination.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS
= 24.270 mg of $C_{12}H_{15}ClO_3$

Containers and storage Containers—Tight containers.
Storage—Light-resistant.

Clofibrate Capsules

クロフィブラートカプセル

Clofibrate Capsules contain not less than 93% and not more than 107% of the labeled amount of clofibrate ($C_{12}H_{15}ClO_3$: 242.70).

Method of preparation Prepare as directed under Capsules, with Clofibrate.

Identification Cut and open Clofibrate Capsules, and use the contents as the sample. Determine the absorption spectrum of a solution of the sample in ethanol (99.5) (1 in 10,000) as directed under the Ultraviolet-visible Spectrophotometry: it exhibits a maximum between 278 nm and 282 nm, and it exhibits a maximum between 224 nm and 228 nm after diluting this solution 10 times with ethanol (99.5)

Purity *p*-Chlorophenol—Cut and open not less than 20 Clofibrate Capsules, and proceed with 1.0 g of the well-mixed contents as directed in the Purity (4) under Clofibrate.

Assay Weigh accurately not less than 20 Clofibrate Capsules, cut and open the capsules, rinse the inside of the capsules with a small amount of diethyl ether after taking out the contents, evaporate the diethyl ether by allowing the capsules to stand at room temperature, and weigh the capsules accurately. Weigh accurately an amount of the contents, equivalent to about 0.1 g of clofibrate ($C_{12}H_{15}ClO_3$), dissolve in acetonitrile to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, and use this solution as the sample solution. Separately, weigh accurately about 0.1 g of Clofibrate Reference Standard, proceed in the same manner as directed for the sample solution, and use the solution so obtained as the standard solution. Perform the test with 10 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of clofibrate to that of the internal standard.

Amount (mg) of clofibrate ($C_{12}H_{15}ClO_3$)
= amount (mg) of Clofibrate Reference Standard, calculated on the anhydrous basis
$\times \frac{Q_T}{Q_S}$

Internal standard solution—A solution of ibuprofen in the mobile phase (1 in 100).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

Column: A stainless steel column about 4 mm in inside diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: A mixture of acetonitrile and diluted phosphoric acid (1 in 1000) (3:2).

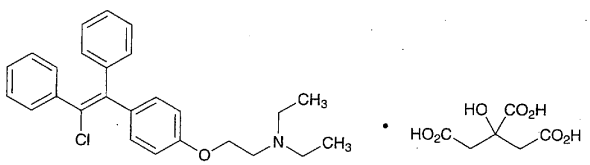
Flow rate: Adjust the flow rate so that the retention time of clofibrate is about 10 minutes.

Selection of column: Dissolve 0.05 g of clofibrate and 0.3 g of ibuprofen in 50 mL of acetonitrile. Proceed with 10 μL of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of ibuprofen and clofibrate in this order with the resolution between these peaks being not less than 6.

Containers and storage Containers—Well-closed containers.
Storage—Light-resistant.

Clomifene Citrate

クエン酸クロミフェン



$C_{26}H_{28}ClNO.C_6H_8O_7$: 598.08