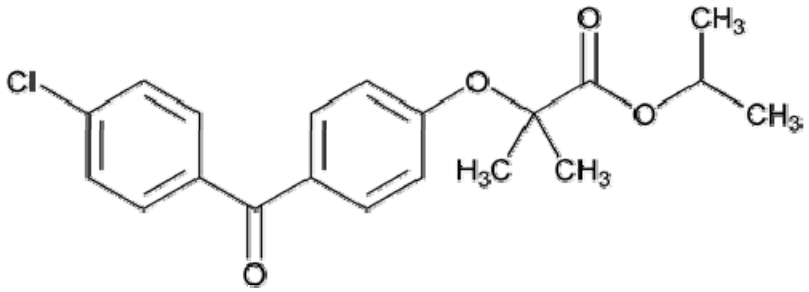
Fenofibrate

USP Method Fenofibrate RS
USP Method Fenofibrate Assay



Original Manufacturer:	Abbott Laboratories (patent expires 2012)
Original Brand Name:	Tricor and Trilipix
Generic Names:	Lipofen (Kowa Pharmaceuticals America Inc) Lofibra (Teva) Lipanthyl, Lipidil, and Supralip (Solvay Pharmaceutical) and as Fenocor-67, Fenogal, Antara, Golip

Fenofibrate is a drug of the fibrate class. Fenofibrate was developed by Groupe Fournier SA, before it was acquired in 2005 by Solvay Pharmaceutical. In 2009 Solvay Pharmaceutical was acquired by Abbott Laboratories.

Fenofibrate is mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. Fenofibrate reduces both low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels, as well as increasing high-density lipoprotein (HDL) levels and reducing triglycerides level.

Fenofibrate is used alone or in conjunction with statins in the treatment of hypercholesterolemia and hypertriglyceridemia.

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Fenofibrate

USP34 – NF29 S1

USP Columns:

LiChrospher RP-18e Assay and Related Compounds 4.0 mm x 25 cm, 5 µm, Merck KGaA

Equivalent Column:

Purospher®STAR RP-18 endcapped (5 µm) 250x4.0 mm (1.50037.0001)

Optional Scaled Column (narrower inner diameter):

Purospher®STAR RP-18 endcapped (5 µm) 250x3.0 mm (1.50620.0001)

Recommended Solvents and Reagents:

Acetonitrile isocratic grade for liquid chromatography LiChrosolv® (1.14291)

Water Water for chromatography LiChrosolv® (1.15333)
or freshly purified water from Milli-Q water purification system

Phosphoric Acid Use ACS reagent grade

USP Standards

Fenofibrate (200 mg)	USP Product Number:	1269447
Fenofibrate Related Compound A (25 mg)	USP Product Number:	1269607
Fenofibrate Related Compound B (25 mg)	USP Product Number:	1269618
Fenofibrate Related Compound C (25 mg)	USP Product Number:	1269629

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USP Method for Fenofibrate Assay

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.)*
Detector: UV 286 nm
Column: 4.0-mm × 25-cm; packing L1
Injection size: 5 µL
Flow rate: 1.0 mL/min

System suitability
Sample: Standard solution

Suitability requirements
Relative standard deviation: Not more than (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)

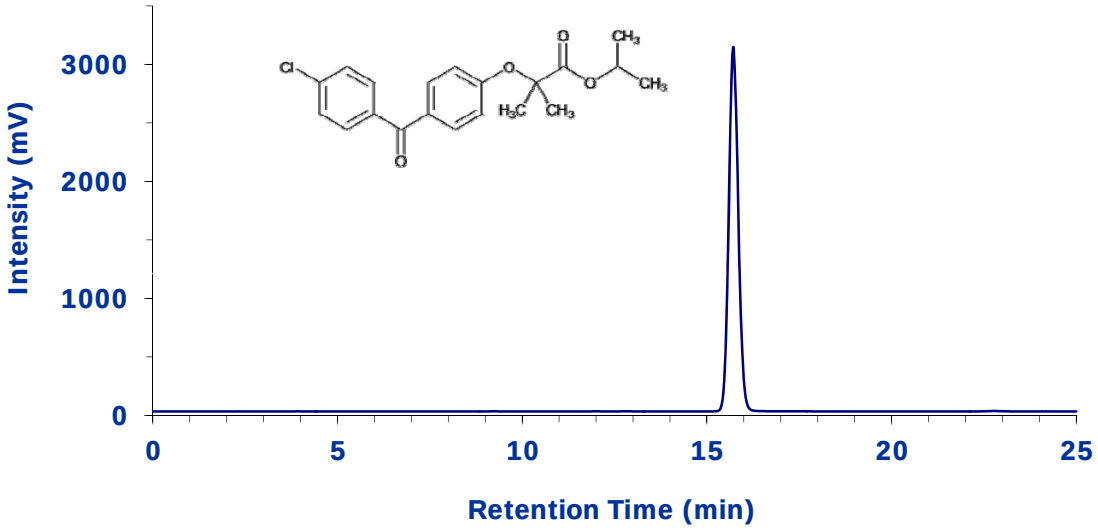
Acceptance criteria:
98.0%–102.0% on the dried basis

USP Method for Fenofibrate Assay

Purospher®STAR RP-18endcapped

Chromatographic Conditions

Column:	Purospher®STAR RP-18endcapped (5 µm) 250x4.0 mm	1.50037.0001
Injection:	5 µL	
Detection:	VWR-Hitachi LaChrom Elite, UV@286 nm	
Cell:	13 µL	
Flow Rate:	1.0 mL/min	
Mobile Phase (v/v):	Acetonitrile and water acidified with phosphoric acid to a pH of 2.5. Mix water and acetonitrile 30:70.	
Temperature:	Ambient	
Diluent	Mobile phase	
Sample:	1.0 mg/mL (1000 ppm) of Fenofibrate	
Pressure Drop:	225 Bar (3263 psi)	



Chromatographic Data

No.	Compound	Time (min)	Plates (N)	Asymmetry (T_{USP})
1	Fenofibrate	15.6	18023	1.07

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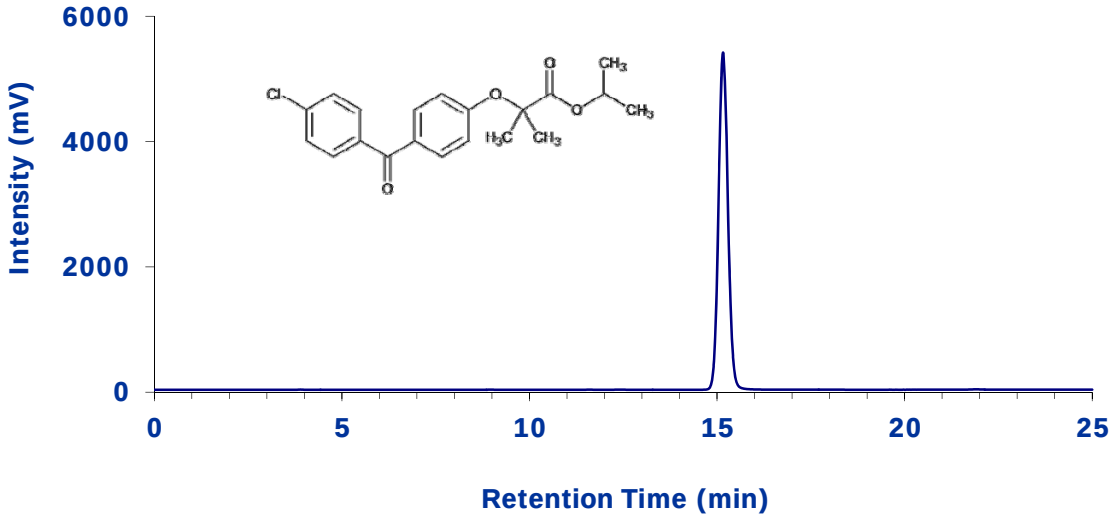
USP Method for Fenofibrate Assay

Purospher®STAR RP-18endcapped

Chromatographic Conditions

Column:	Purospher®STAR RP-18endcapped (5 µm) 250x3.0 mm	1.50620.0001
Injection:	5 µL	
Detection:	VWR-Hitachi LaChrom Elite, UV@286 nm	
Cell:	13 µL	
Flow Rate:	0.57 mL/min	
Mobile Phase (v/v):	Acetonitrile and water acidified with phosphoric acid to a pH of 2.5. Mix water and acetonitrile 30:70.	
Temperature:	Ambient	
Diluent	Mobile phase	
Sample:	1.0 mg/mL (1000 ppm) of Fenofibrate	
Pressure Drop:	225 Bar (3263 psi)	



Chromatographic Data

No.	Compound	Time (min)	Plates (N)	Asymmetry (T_{USP})
1	Fenofibrate	15.2	16368	1.10

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USP Method for Fenofibrate RS

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

Impurity standard solution
1 µg/mL (1 ppm) each of USP Fenofibrate RS, USP Fenofibrate Related Compound A RS, and USP Fenofibrate Related Compound B RS, and 2 µg/mL (2 ppm) 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.)*
Detector: UV 286 nm
Column: 4.0-mm × 25-cm; packing L1
Injection size: 20 µL
Flow rate: 1.0 mL/min

System suitability
Sample: Impurity standard solution

Suitability requirements
Resolution: Not less than (NLT) 1.5 between fenofibrate related compound A and fenofibrate RS 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 appropriate fenofibrate related compound in the Impurity standard solution (µg/mL)
C_U = concentration of Fenofibrate in the Sample solution (µg/mL)

Continued on next page

USP Method for Fenofibrate RS

Analysis

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

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. RRT means relative retention time.

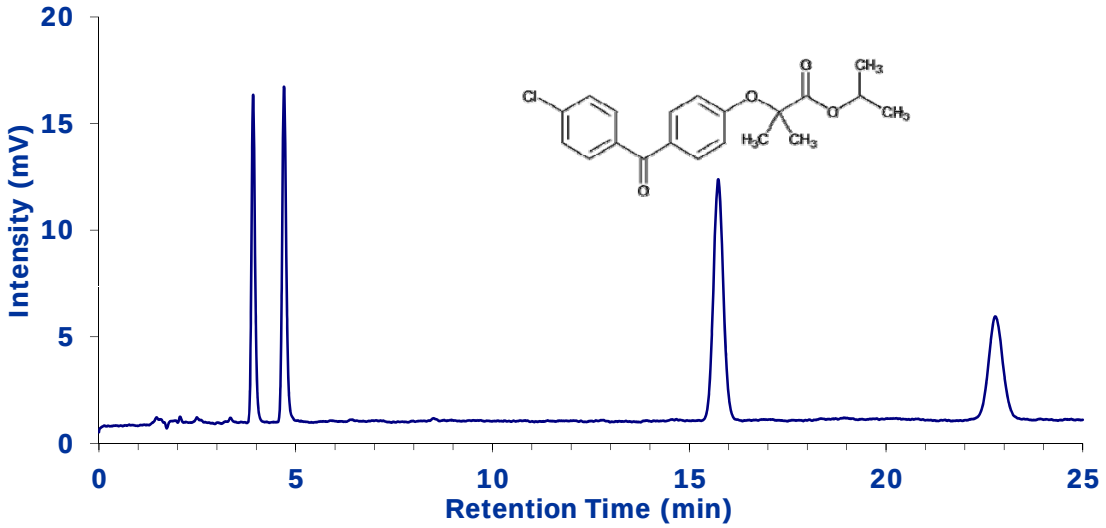
Name	(RRT)	Acceptance Criteria NMT (%)
Fenofibrate related compound A.	0.34	0.1
Fenofibrate related compound B.	0.36	0.1
(3RS)-3-[4-(4-Chlorobenzoyl)phenoxy]butan-2-one	0.50	0.1
Methyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoate	0.65	0.1
Ethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoate	0.80	0.1
(4-Chlorophenyl)[4-(1-methylethoxy)phenyl]methanone	0.85	0.1
Fenofibrate related compound C.	1.35	0.2
Any other impurity		0.1
Fenofibrate RS A = (4-Chlorophenyl)(4-hydroxyphenyl)methanone		
Fenofibrate RS B = 2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid (fenofibric acid)		
Fenofibrate RS C = 1-Methylethyl 2-[[2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoyl]oxy]-2-methylpropanoate		

USP Method for Fenofibrate RS

Purospher®STAR RP-18endcapped

Chromatographic Conditions

Column:	Purospher®STAR RP-18endcapped (5 µm) 250x4.0 mm	1.50037.0001
Injection:	20 µL	
Detection:	VWR-Hitachi LaChrom Elite, UV@286 nm	
Cell:	13 µL	
Flow Rate:	1.0 mL/min	
Mobile Phase (v/v):	Acetonitrile and water acidified with phosphoric acid to a pH of 2.5. Mix water and acetonitrile 30:70.	
Temperature:	Ambient	
Diluent	Mobile phase	
Sample:	1 ppm of Fenofibrate, Fenofibrate RS A and RS B, and 2ppm Fenofibrate RS C	
Pressure Drop:	225 Bar (3263 psi)	



Chromatographic Data

No.	Compound	Time (min)	Relative Retention Time (RRT)	Plates (N)	Resolution	Asymmetry (T_{USP})
1	Fenofibrate RS A	3.9	0.25	8919	-	1.2
2	Fenofibrate RS B	4.7	0.30	9719	4.4	1.2
3	**Fenofibrate**	15.7	1.00	17459	33.1	1.1
4	Fenofibrate RS C	22.7	1.45	17947	12.2	1.1

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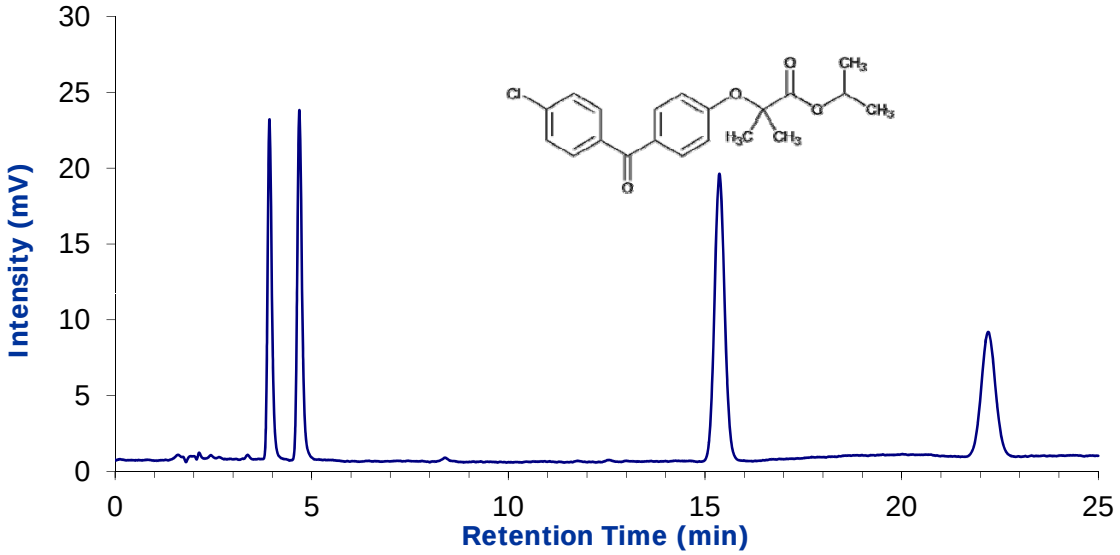
USP Method for Fenofibrate RS

Purospher®STAR RP-18endcapped

Chromatographic Conditions

Column:	Purospher®STAR RP-18endcapped (5 µm) 250x3.0 mm	1.50620.0001
Injection:	20 µL	
Detection:	VWR-Hitachi LaChrom Elite, UV@286 nm	
Cell:	13 µL	
Flow Rate:	0.57 mL/min	
Mobile Phase (v/v):	Acetonitrile and water acidified with phosphoric acid to a pH of 2.5. Mix water and acetonitrile 30:70.	
Temperature:	Ambient	
Diluent	Mobile phase	
Sample:	1 ppm of Fenofibrate, Fenofibrate RS A and RS B, and 2ppm Fenofibrate RS C	
Pressure Drop:	179 Bar (2596 psi)	



Chromatographic Data

No.	Compound	Time (min)	Relative Retention Time (RRT)	Plates (N)	Resolution	Asymmetry (T_{USP})
1	Fenofibrate RS A	3.9	0.26	6277	-	1.3
2	Fenofibrate RS B	4.7	0.30	7291	3.6	1.3
3	**Fenofibrate**	15.4	1.00	15826	30.2	1.1
4	Fenofibrate RS C	22.2	1.45	16858	11.7	1.1

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Analysis protocol for Fenofibrate

USP Method Repeatability (Purospher®STAR RP-18endcapped (5 µm) 250x4.0 mm)

No.	Compound	Mean Response (Arbitrary Area Units)	Relative Standard Deviation (%)	N
1	Fenofibrate	55472824	0.34	15

USP Method Repeatability (Purospher®STAR RP-18endcapped (5 µm) 250x3.0 mm)

No.	Compound	Mean Response (Arbitrary Area Units)	Relative Standard Deviation (%)	N
1	Fenofibrate	94554999	0.34	15

15 Replicate injections of standard solution (n=15) were analyzed to determine the USP method repeatability. Sample contained 1 mg/mL (1000 ppm) of Fenofibrate in Mobile phase

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

(Purospher®STAR RP-18endcapped (5 µm) 250x3.0 mm)

No.	Compound	LOD (ppm)	LOQ (ppm)	Curve Equation	Regression Coefficient (R^2)
1	Fenofibrate	17.1	51.8	y = 53940x + 815390	0.9998

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

(Purospher®STAR RP-18endcapped (5 µm) 250x3.0 mm)

No.	Compound	LOD (ppm)	LOQ (ppm)	Curve Equation	Regression Coefficient (R^2)
1	Fenofibrate	60.4	183	y = 86321x + 7E+06	0.9976

Injection of at least seven different conc. from LOQ level to 150 % of standard concentration 1 mg/mL (1000 ppm) to determine the linearity of the method.