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Determination Of Fenofibric Acid (Related Substance) In Marketed Formulations Of Fenofibrate By RP-HPLC

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Abstract
Fenofibrate is one of the most frequently prescribed drug in the treatment of hyperlipidemia either alone or in combination with other drugs. Fenofibrate is reported to undergo photodegradation to form perbenzoic acid derivative and also reported to undergo hydrolysis in alkaline medium to form fenofibric acid. Fenofibric acid is also a starting material for synthesis of fenofibrate. Fenofibric acid is considered a significant related substance as per USP. Various regulatory authorities like ICH, USFDA, Canadian Drug and Health Agency are emphasizing on the purity requirements and the identification of impurities in active pharmaceutical ingredient (API) as well as in pharmaceutical formulations. To this aim, various marketed formulations were assessed with special attention to identification and quantification of fenofibric acid using compendial reversed phase high performance liquid chromatography method. The use of a 250 × 4.6 mm, 5 µm, C_{18} column with 70:30 %, v/v acetonitrile and water (pH adjusted to 2.5 with orthophosphoric acid) as isocratic mobile phase at flow rate 1 ml/min enabled separation of the drug from its related substance. UV detection was performed at 286 nm. The method was verified for specificity, linearity, precision and accuracy. The related substance peak was well resolved from drug peak (R_s= 9.96). The linearity of the method was satisfactory over the range 60-140 ppm (correlation coefficient 0.9999). Recovery of fenofibric acid and fenofibrate ranged from 99.77- 100.39% and 99.48-100.18% respectively. The method was successfully applied to marketed formulations of fenofibrate for quantitative analysis of fenofibrate and fenofibric acid.

Key words:
Fenofibrate, Fenofibric acid, Related substance, RP-HPLC

INTRODUCTION

The determination of impurities in bulk drug substances and pharmaceutical formulations is one of the most important fields of activity in contemporary industrial analysis. Impurity is anything that is not the drug substance or an excipient in the drug product. According to ICH[1] (International Conference on Harmonisation) impurity profile of a drug material is "A description of the identified and unidentified impurities, present in a new drug substance." Impurity profiling is considered to be the common name of analytical activities, the aim of which is the detection, identification/structure elucidation and quantitative determination of organic and inorganic impurities as well as residual solvents in bulk drugs and pharmaceutical formulations.

The importance of drug impurity profiling is that it affords data which can directly contribute to the safety and efficacy of drug therapy by minimizing the impurity-related adverse effects of drug materials and the preparations made thereof. In recent years, the importance of assay methods for characterising the quality of bulk drug materials has decreased considerably. At the same time the importance of impurity profiling is continuously increasing. Various regulatory authorities like ICH, USFDA, Canadian Drug and Health Agency have emphasized on the purity requirements of drug substances and products.

Regulatory authorities have to ensure the quality of pharmaceutical formulations existing in the market. Here an analyst can play a key role in quality assurance of marketed formulations by providing information to drug law enforcement authorities through impurity determination studies.

In present research work, quality of marketed formulations of fenofibrate has been assessed by determining fenofibric acid (a significant related substance and degradation product of fenofibrate) content using compendial reversed phase high performance liquid chromatography method.

Fenofibrate is chemically isopropyl 2-[4-(4-chlorobenzoyl) phenoxy]-2-methylpropanoate. It is a prodrug, producing an active metabolite, fenofibric acid, which is responsible for the primary effects of the drug. Following oral administration, fenofibrate is well absorbed from gastrointestinal tract, and rapidly hydrolyzed by esterase to the active metabolite, fenofibric acid. Fenofibrate is prone to alkaline hydrolysis and converted to fenofibric acid.[2] Fenofibric acid is also a starting material for synthesis of fenofibrate. Although fenofibric acid is an active form of fenofibrate prodrug, it should not be present in API (< 0.1 % as per IP[3], BP[4], EP[5] and USP[6]) and marketed formulations (< 0.5 % as per USP[6]) above specified limit. IP, BP, EP and USP have included the test for related substances in fenofibrate and USP has included the test for related substances in fenofibrate dosage form. Different methods for analysis of fenofibrate have been reviewed. Fenofibrate is assayed by liquid chromatography in IP, BP, USP and EP. However, several chromatographic methods have been reported for the determination of fenofibrate, in pharmaceutical formulations and /or in biological fluids, including HPLC[7-10], stability indicating UPLC[11] and HPLC[12] method for simultaneous determination of fenofibrate with other drugs, LC-MS[13] and HPTLC[14, 15]. In addition, there are other methods reported for the determination of fenofibrate, including capillary electrophoresis[16], polarography[17], voltammetry[18] and derivative spectrophotometry[8, 12, 19]. Study for presence of

related substances in marketed formulations of fenofibrate is not reported. Therefore, various marketed formulations were analysed to determine fenofibric acid.

MATERIAL AND METHODS

Instrumentation:

The HPLC system (Shimadzu) consisting of an LC-10AT solvent delivery module, a Rheodyne sample injector and a UV-visible detector SPD-10A. Hamilton microliter syringe (25 µl capacity) was used. The chromatographic separation was accomplished on a Grace Smart C_{18} column (250 mm × 4.6 mm i.d.; 5 µ); protected by a guard column of the same phase.

Chemicals and reagents:

Fenofibrate (99.8 % w/w) was received as gift sample from Sun Pharma, Vadodara. Fenofibric acid was synthesized at lab scale. Acetonitrile (HPLC grade) and orthophosphoric acid (AR grade) were purchased from sd fine-chem Ltd. (Mumbai, India). Double distilled water was prepared in laboratory.

Chromatographic conditions:

The mobile phase consisted of acetonitrile: water (70: 30, % v/v), adjusted to pH 2.5 with 5 % orthophosphoric acid. Samples were analyzed using the following parameters: flow rate: 1 ml/min; injection volume: 20 µl; run time: 14 min; temperature: 25 ± 2ºC; detection wavelength: 286 nm.

Characterization of fenofibrate and fenofibric acid:

Fenofibrate and fenofibric acid were characterized by melting point, IR spectrophotometry, mass spectrometry, TLC and UV-visible spectrophotometry.

Preparation of standard solutions:

Stock solution of fenofibric acid

Accurately weighed quantity of fenofibric acid 25 mg was transferred into 100 ml volumetric flask, dissolved in and diluted to mark with mobile phase (250 ppm).

Working standard solution of fenofibric acid

Five ml aliquot of fenofibric acid stock solution was diluted to 25 ml with mobile phase (50 ppm).

Stock solution of fenofibrate

Accurately weighed quantity of fenofibrate 200 mg was transferred into 100 ml volumetric flask, dissolved in and diluted to mark with mobile phase (2000 ppm).

Working standard solutions of fenofibrate

Five ml aliquot of fenofibrate stock solution was diluted to 100 ml with mobile phase (100 ppm). Further, 5 ml was diluted to 10 ml with mobile phase (50 ppm).

Mixture solution for system suitability test

Five ml aliquot of fenofibrate stock solution and one ml aliquot of fenofibric acid working standard solution were transferred into a 10 ml volumetric flask and diluted to mark with mobile phase to give a mixture solution having strength 1000 ppm fenofibrate and 5 ppm fenofibric acid.

Calibration curve of fenofibrate

Aliquots (3 ml, 4 ml, 5 ml, 6 ml and 7 ml) of the stock solution of fenofibrate were diluted up to 100 ml with mobile phase to give solutions having strength 60 ppm, 80 ppm, 100 ppm, 120 ppm and 140 ppm respectively.

Mixture solution for repeatability

One ml aliquot of 50 ppm fenofibrate working standard solution and 1 ml aliquot of 50 ppm fenofibric acid working standard solution were transferred into a 10 ml volumetric flask and diluted to mark with mobile phase to give a mixture solution having strength 5 ppm each of fenofibrate and fenofibric acid.

Preparation of test solution of marketed formulations:

Determination of fenofibric acid in marketed formulations:

Twenty tablets were weighed accurately, finely powdered and mixed. Twenty apsules were emptied, content was weighed and mixed. Tablet/capsule powder equivalent to 100 mg of fenofibrate was accurately weighed and transferred to a 100 ml volumetric flask. The flask was filled to about 80 % with mobile phase, sonicated for 10 minutes, stirred for 15 minutes, diluted with mobile phase to mark, mixed well and filtered through Whatman filter paper (no. 42) (1000 ppm).

Assay of marketed formulations:

Twenty tablets were weighed accurately, finely powdered and mixed. Twenty apsules were emptied, content was weighed and mixed. Tablet/capsule powder equivalent to 100 mg of fenofibrate was accurately weighed and transferred to a 100 ml volumetric flask. The flask was filled to about 80 % with mobile phase, sonicated for 10 minutes, stirred for 15 minutes, diluted with mobile phase to mark, mixed well and filtered through Whatman filter paper (no. 42). Further, 1 ml of filtrate was diluted to 10 ml with mobile phase (100 ppm).

Syatem suitability:

The resolution, column efficiency and peak symmetry were calculated for the standard solution mixture and compared with USP specifications[6].

Solution stability:

Stability of sample solution was established by storage of fenofibrate and fenofibric acid sample solution at room temperature for 24 hours. Sample solution was re-analyzed after 24 hours and assay/impurities were determined, compared against freshly prepared sample and % variation was calculated.

Validation of the method:

Validation of the method was carried out in terms of specificity, linearity, precision, accuracy, limit of detection and limit of quantitation as per ICH guidelines[20]. The linear responses of fenofibrate in the range of 60-140 ppm were assessed in terms of slope, intercept and correlation coefficient values. The repeatability, intraday and interday precision were assessed in terms of %RSD. The accuracy was determined by standard addition method. To a fixed amount of pre-analyzed sample of fenofibrate, increasing amount of standard fenofibrate at three levels (i.e. 80 %, 100 % and 120 %) were added and analyzed. The recovery of fenofibric acid was also determined in the same manner.

Analysis of marketed formulations:

Determination of % fenofibric acid (test for related substance)

The sample solution of tablets or capsules (20 µl) was injected into the chromatographic column and mean peak area of fenofibric acid were noted. (n=3) The % fenofibric acid in the marketed formulations were estimated using following formula[6]:

$$\%\ \text{Fenofibric acid} = 100 * \frac{C_S}{C_T} * \frac{A_T}{A_S}$$

Where,

C_S = conc. of fenofibric acid in standard solution= 5 ppm

C_T = conc. of fenofibrate in test solution

A_T = peak area of fenofibric acid obtained from test solution

A_S = peak area of fenofibric acid obtained from standard solution

Determination of % fenofibrate (assay)

The sample solution of tablets or capsules (20 µl) was injected into the chromatographic column and mean peak area of fenofibrate was noted. (n=3) The % fenofibrate in the marketed formulations were estimated using following formula[6]:

$$\%\ \text{Fenofibrate} = 100 * \frac{C_S}{C_T} * \frac{A_T}{A_S}$$

Where,

C_S = conc. of fenofibrate in standard solution= 100 ppm

C_T = conc. of fenofibrate in assay preparation

A_T = peak area of fenofibrate obtained from assay preparation

A_S = peak area of fenofibrate obtained from standard solution

RESULTS

System suitability test:

Chromatogram for system suitability solution is shown in fig. 1. System suitability data is shown in table 1. System suitability data complied with USP specifications[6].

Solution stability study:

Results are shown in table 2. The results indicated that the retention time and peak area of fenofibrate and fenofibric acid did not show much variation. There was no significant degradation within the indicated period. Hence, it was concluded that both the solutions were stable for 24 hours at room temperature.

Validation of method:

Specificity

Chromatograms of blank, placebo, fenofibric acid standard (5 ppm) and fenofibrate standard (5 ppm) were recorded. Since there was no interference of impurities and excipients observed, the method can be considered specific.

Linearity (Calibration curve of fenofibrate)

The calibration curve was prepared by plotting peak areas against respective concentration. The peak areas of fenofibrate were linear with respect to concentrations over the range of 60-140 ppm. The overlain chromatogram is shown in fig. 2. Data is shown in table 3 and calibration graph is shown in fig. 3. The results show excellent correlation between peak area and concentrations. (R^2 = 0.9999)

Precision

Repeatability

Chromatogram of fenofibrate (100 ppm) and standard solution mixture are shown in fig. 4 and 5 respectively. Data is shown in table 4 and 5. Result is expressed in terms of % R.S.D. Repeatability data complied with USP specifications[6].

Intraday and Interday precision

Intraday and interday precision data is shown in table 6. From the data obtained, the method was found to be precise.

Accuracy

Percent recovery data for fenofibric acid and fenofibrate obtained by the method are shown in table 7 and 8 respectively. The % recovery in all cases were within the acceptable limit (98 -102 %).

LOD and LOQ

For fenofibric acid

Based on signal to noise ratio, the LOD and LOQ were eshtablished for fenofibric acid. Chromatograms are shown in fig. 6 and 7. Results are shown in table 9.

For fenofibrate

Based on the calibration curve, the LOD and LOQ were calculated for fenofibrate. Results are shown in table 10.

Validation summary

Validation summary is shown in table11.

Analysis of marketed formulations:

The method was successfully applied to marketed formulations of fenofibrate for the determination of fenofibric acid and fenofibrate. Results are shown in table 12.

Table No. 1: System suitability data

Parameters	Observed Values (n = 3)		USP 32 specifications [6]
	Fenofibric acid	Fenofibrate	
Resolution (Rs)	9.96		Not less than 3.0
Theoretical plates (N)	6174	4413	Not less than 3000 (for fenofibric acid)
Asymmetry factor (S)	1.26	0.56	Not more than 2.0

Table No. 2: Solution stability study data

Preparation	Mean area of peak (mV) Fresh solution (n=3)	Mean area of peak (mV) After 24 hours (n=3)	% variation
Fenofibrate Standard 100 ppm	2410.24	2383.72	1.11
Fenofibrate Standard 1000 ppm	15626.97	15682.56	0.35
FINATE 160 Test 100 ppm	2433.14	2486.71	2.20
FINATE 160 Test 1000 ppm	15575.43	15447.22	0.83

Table No. 3: Linearity data for fenofibrate

Concentration (ppm)	Area of peak (mV) Mean ± S.D. (n=5)	% R.S.D.
60	1410.11 ± 22.42	1.59
80	1904.55 ± 17.70	0.92
100	2395.19 ± 33.47	1.39
120	2900.61 ± 19.69	0.67
140	3408.13 ± 41.61	1.22

Table No. 4: Repeatability data for fenofibrate (100 ppm)

Replicate injections	Peak area (mV)
1	2391.64
2	2398.44
3	2397.13
4	2394.64
5	2400.16
6	2396.48
7	2399.81
Mean	2396.90
Standard Deviation	3.01
% R.S.D.	0.13 %
Acceptance limit[6]	Not more than 2.0 %

Table No. 5: Repeatability data for standard solution mixture

Replicate injections	Peak area (mV)	
	Fenofibric acid	Fenofibrate
1	124.36	126.96
2	124.71	126.16
3	125.04	128.31
4	124.19	127.69
5	125.49	128.16
6	124.02	128.54
7	125.64	127.30
Mean	124.77	127.58
Standard Deviation	0.63	0.84
% R.S.D.	0.51 %	0.66 %
Acceptance limit [6]	Not more than 2.0 %	Not more than 2.0 %

Table No. 6: Intraday and Interday precision data for fenofibrate

Concentration (ppm)	Intraday precision		Interday precision	
	Area of peak (mV) Mean ± S.D. (n=3)	% R.S.D.	Area of peak (mV) Mean ± S.D. (n=3)	% R.S.D.
80	1895.33 ± 13.23	0.69	1905.72 ± 24.78	1.30
100	2375.21 ± 22.78	0.96	2400.66 ± 45.01	1.87
120	2890.06 ± 03.09	0.11	2908.07 ± 23.64	0.81

Table No. 7: Recovery data for fenofibric acid

% Recovery level	Amount of Fenofibrate drug sample taken (mg)	Amount of standard Fenofibric acid spiked (mg)	Amount of Fenofibric acid recovered (mg)	% Recovery	Mean % recovery
80 %	50	40	39.41	98.53	100.31
	50	40	40.20	100.50	
	50	40	40.76	101.90	
100 %	50	50	49.68	99.36	100.39
	50	50	50.36	100.72	
	50	50	50.55	101.10	
120 %	50	60	59.33	98.88	99.77
	50	60	59.61	99.35	
	50	60	60.65	101.08	

Table No. 8: Recovery data for fenofibrate

% Recovery level	Amount of Fenofibrate drug sample taken (mg)	Amount of standard Fenofibrate spiked (mg)	Amount of Fenofibrate recovered (mg)	% Recovery	Mean % recovery
80 %	50	40	39.43	98.57	99.48
	50	40	40.20	100.50	
	50	40	39.74	99.37	
100 %	50	50	49.01	98.02	99.68
	50	50	50.79	101.58	
	50	50	49.72	99.44	
120 %	50	60	60.22	100.36	100.18
	50	60	61.13	101.88	
	50	60	58.98	98.30	

Table No. 9: LOD and LOQ data for fenofibric acid

Parameters	Observed values
LOD (ppm)	0.3
LOQ (ppm)	0.7

Table No. 10: LOD and LOQ data for fenofibrate

Parameters	Observed values
Standard deviation of the intercepts of the 5 calibration curves.	18.75
Mean slope of the 5 calibration curves.	24.96
LOD = 3.3 × (SD/Slope) (ppm)	2.47
LOQ = 10 × (SD/Slope) (ppm)	7.51

Table No. 11: Summary of validation results

Parameter	Results
	Fenofibrate
Specificity	Specific
Linearity Range (ppm) (n=5)	60 – 140
Straight Line Equation	y = 24.9605x - 92.3232
Correlation coefficient (R^2)	0.9999
Repeatability (% R.S.D.) (n=7)	0.13
Repeatability (standard solution mixture) (% R.S.D) (n=7)	0.84
Intraday precision (% R.S.D) (n=9)	0.11 – 0.96
Interday precision (% R.S.D) (n=9)	0.81 – 1.87
% Recovery (n=9)	99.48 - 100.18
LOD (ppm)	2.47
LOQ (ppm)	7.51

Table No. 12: Analysis of marketed formulations

	Strength		Fresh Batch	Middle Batch	Old Batch
			Mean of triplicate		
Formulation 1	200 mg Capsule	Batch no.	OCM045	OCM037	OCM027
		Mfg. date	12/2011	03/2011	02/2010
		Fenofibric acid (%)	**0.62**	**0.22**	**0.59**
		Assay (%)	**97.24**	**98.73**	**103.61**
Formulation 2	160 mg Tablet	Batch no.	M11028	M10038	M10017
		Mfg. date	09/2011	12/2010	06/2010
		Fenofibric acid (%)	**0.02**	**0.05**	**0.09**
		Assay (%)	**100.95**	**98.66**	**102.94**
Formulation 3	160 mg Tablet	Batch no.	28006165	28005162	28003161
		Mfg. date	11/2011	03/2011	05/2010
		Fenofibric acid (%)	**0.26**	**0.91**	**0.78**
		Assay (%)	**92.08**	**108.53**	**109.57**
Formulation 4	160 mg Tablet	Batch no.	VL0596	VK1013	VK0759
		Mfg. date	05/2010	10/2009	07/2009
		Fenofibric acid (%)	**0.14**	**0.19**	**0.09**
		Assay (%)	**101.54**	**102.84**	**99.78**
Formulation 5	145 mg Tablet	Batch no.	F18531	F18530	F18524
		Mfg. date	08/2011	06/2011	08/2010
		Fenofibric acid (%)	**0.07**	**0.11**	**0.03**
		Assay (%)	**98.11**	**103.92**	**102.69**
Formulation 6	145 mg Tablet	Batch no.	D12582	D10505	D09526
		Mfg. date	11/2011	02/2011	04/2010
		Fenofibric acid (%)	**0.18**	**0.75**	**0.58**
		Assay (%)	**98.23**	**96.89**	**99.90**
Formulation 7	145 mg Tablet	Batch no.	2300912	2272234	2148031
		Mfg. date	07/2011	04/2011	04/2010
		Fenofibric acid (%)	**0.02**	**0.07**	**0.10**
		Assay (%)	**98.31**	**100.27**	**101.53**

Values in Green color: Pass
Values in Red color: Fail

Table No. 13: Acceptance limit: USP 32 specifications[6]

Fenofibric acid	Not more than 0.5 %
Any other impurity	Not more than 0.2 %
Total impurities	Not more than 2.0 %
Assay	90 to 110 % of labelled claim

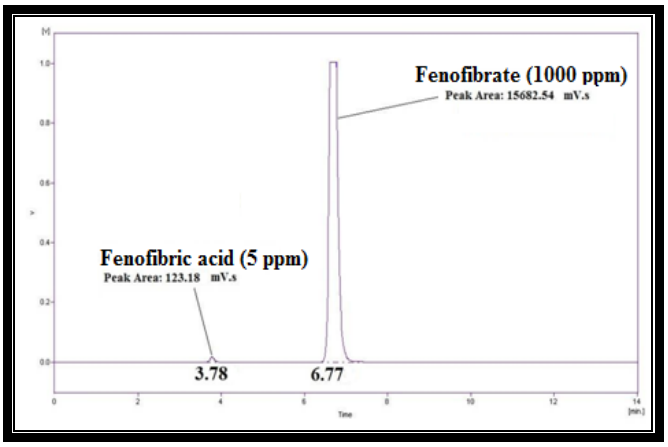

Fig. 1: Chromatogram of system suitability solution

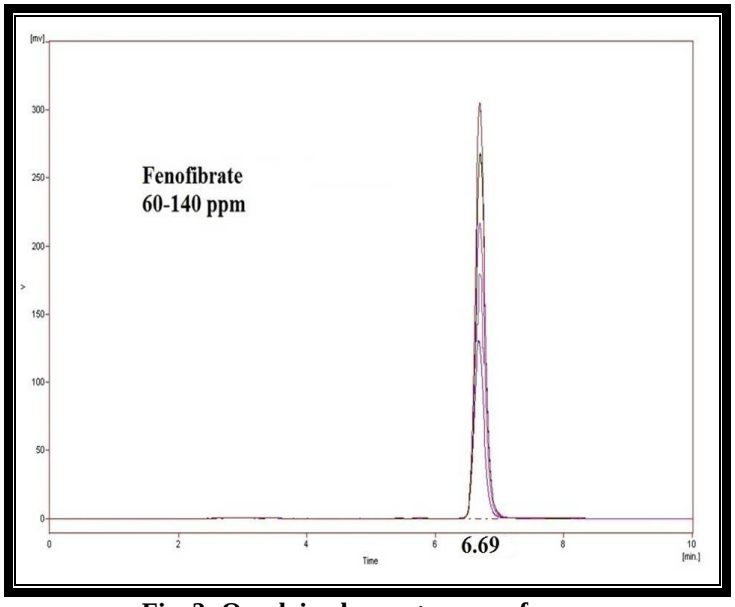

Fig. 2: Overlain chromatogram of fenofibrate (60-140 ppm)

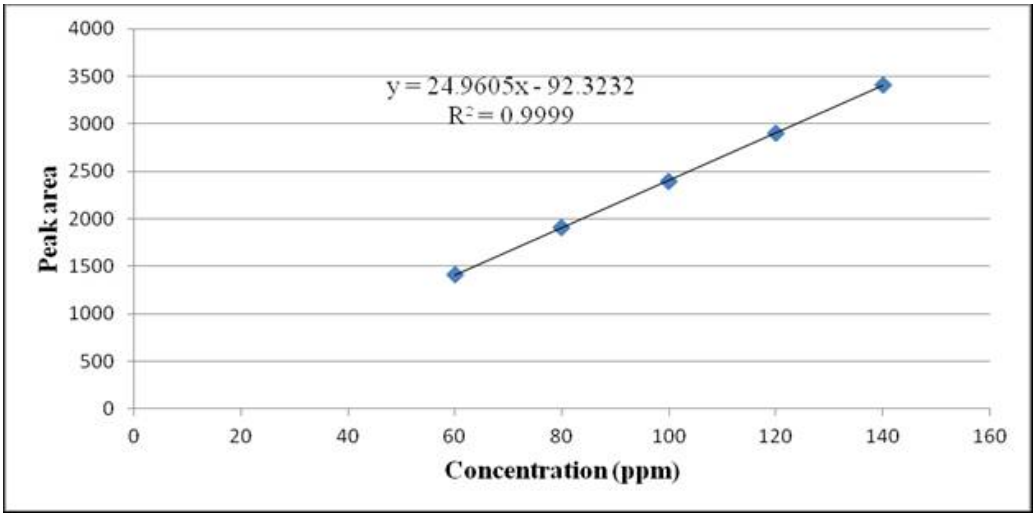

Fig. 3: Calibration graph for fenofibrate (60-140 ppm)

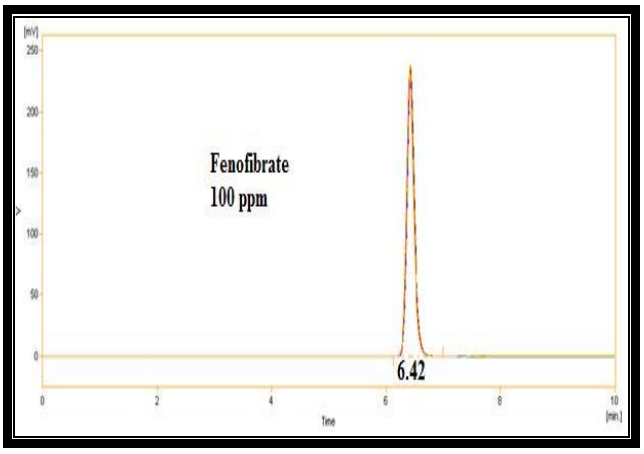

Fig. 4: Chromatogram showing fenofibrate repeatability (100 ppm)

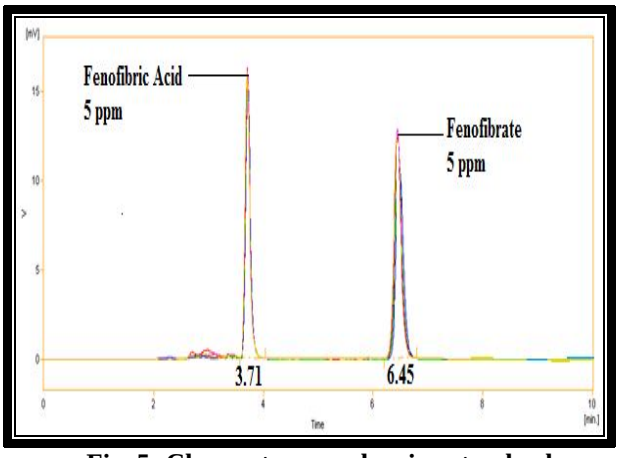

Fig. 5: Chromatogram showing standard solution mixture repeatability

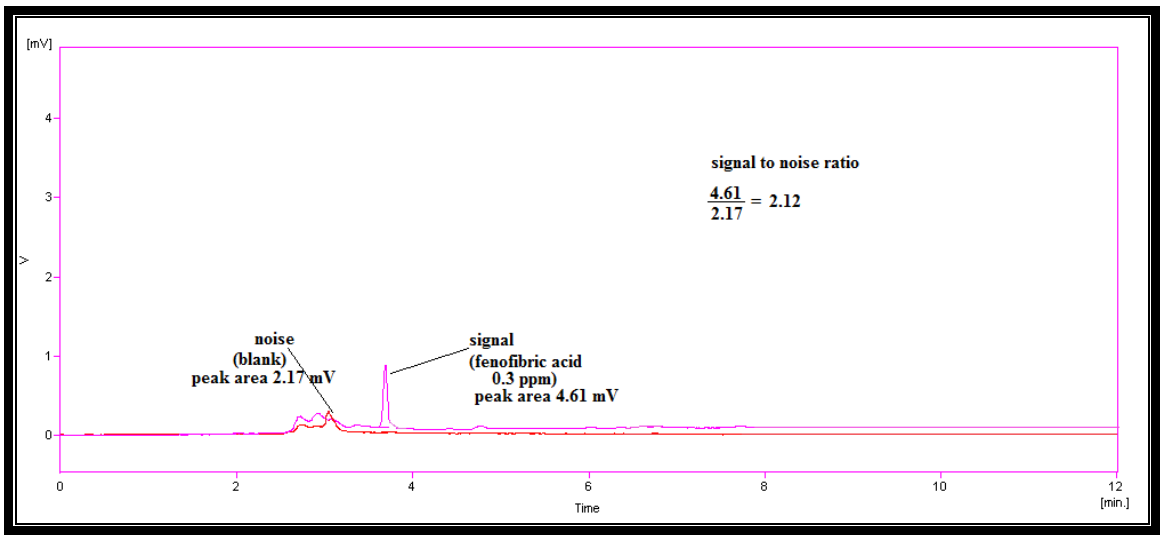

Fig. 6: Chromatogram showing LOD for fenofibric acid

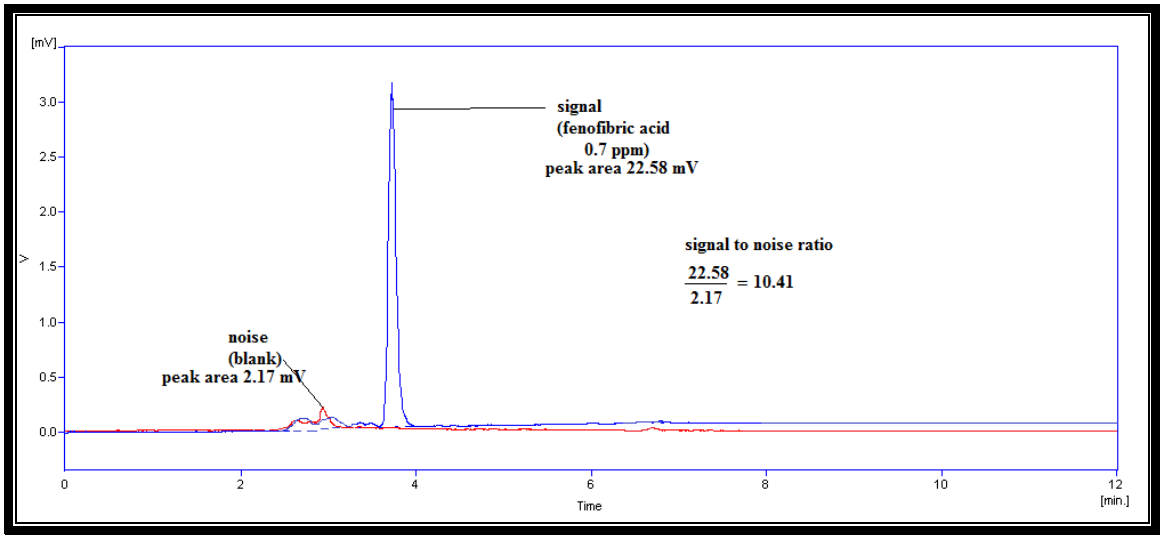

Fig. 7: Chromatogram showing LOQ for fenofibric acid

DISCUSSION

The compendial reversed phase high performance liquid chromatography method was validated and successfully applied to marketed formulations of fenofibrate for quantitative analysis of fenofibrate and fenofibric acid (related substance).

The related substance peak was well resolved from drug peak (R_s = 9.96). The plot of area versus respective concentrations of fenofibrate was found to be linear in the concentration range of 60-140 ppm with correlation coefficient 0.9999. The intraday and interday precision of the method in terms of % R.S.D. were ranging from 0.11-0.96% and 0.81-1.87% respectively. The limits of detection for fenofibric acid and fenofibrate were 0.3 and 2.47 ppm respectively. The limits of quantification for fenofibric acid and fenofibrate were 0.7 and 7.51 ppm respectively. Recovery of fenofibric acid and fenofibrate ranged from 99.77-100.39% and 99.48-100.18% respectively.

Results of marketed formulation analysis show that from 21 different batches of seven fenofibrate formulations, all batches complied with the assay test while 6 batches failed to comply with the test for related substance (table 13).

CONCLUSION

It is clear that almost 30 % batches failed in the test for related substance. This may be due to improper synthesis of fenofibrate causing the starting material fenofibric acid to be carried forward to the formulations. It is also possible that degradation may have occurred during manufacturing of tablets. Care should be taken at synthesis stage as well as at formulation manufacturing stage so that fenofibric acid remains within acceptance limit in marketed formulations.

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