ANALYTICAL VALIDATION METHOD OF ANTIHYPERLIPIDEMIC DRUG USING RPHPLC

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Abstract

This study describes the analytical validation of a reverse-phase high-performance liquid chromatography (RP-HPLC) method for the simultaneous quantification of two antihyperlipidemic drugs, Pravastatin Sodium and Fenofibrate. The method was developed and validated following the guidelines of the International Conference on Harmonization (ICH) for specificity, linearity, accuracy, precision, robustness, and system suitability. The RP-HPLC method utilized an appropriate stationary phase and optimized mobile phase composition for efficient separation and quantification of Pravastatin Sodium and Fenofibrate. Specificity was demonstrated by analyzing the drugs in the presence of potential impurities and excipients commonly found in pharmaceutical formulations. Linearity was evaluated over a range of concentrations, and accuracy and precision were assessed through recovery studies and repeatability tests, respectively. Robustness of the method was evaluated by varying chromatographic conditions such as flow rate, column temperature, and mobile phase composition. System suitability parameters were determined to ensure consistent performance of the chromatographic system. The validated RP-HPLC method exhibited satisfactory results in terms of specificity, linearity, accuracy, precision, robustness, and system suitability, indicating its suitability for routine analysis of Pravastatin Sodium and Fenofibrate in pharmaceutical formulations. This validated method can serve as a reliable tool for quality control purposes in the pharmaceutical industry, particularly in the development and manufacturing of antihyperlipidemic drug products.

Introduction

The development of robust and reliable analytical methods is crucial for the quality control and assurance of pharmaceutical products. In the case of antihyperlipidemic drugs, such as Pravastatin Sodium and Fenofibrate, accurate quantification is essential to ensure therapeutic efficacy and patient safety. Reverse-phase high-performance liquid chromatography (RP-HPLC) has emerged as a powerful technique for the analysis of pharmaceutical compounds due to its high sensitivity, selectivity, and reproducibility.

This study focuses on the analytical validation of an RP-HPLC method for the simultaneous quantification of Pravastatin Sodium and Fenofibrate in pharmaceutical formulations. Analytical validation is a critical process that verifies the performance characteristics of an analytical method to ensure its suitability for routine use. The validation parameters include specificity, linearity, accuracy, precision, robustness, and system suitability.

The specificity of the method is evaluated by determining whether the chromatographic peaks corresponding to Pravastatin Sodium and Fenofibrate are distinct from potential impurities and excipients present in the sample matrix. Linearity is assessed by analyzing the drugs at different concentration levels and establishing a linear relationship between the analyte concentration and the detector response. Accuracy and precision are determined through

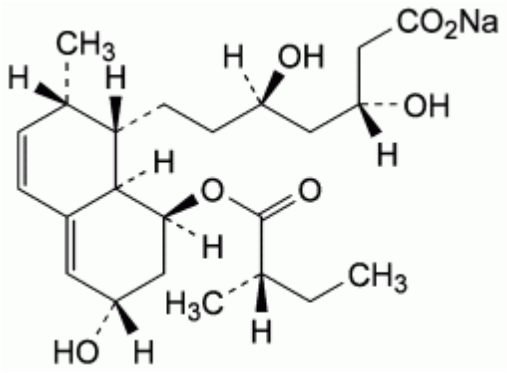
recovery studies and repeatability tests, respectively, to ensure the method provides reliable and reproducible results.

Robustness testing involves varying chromatographic conditions, such as flow rate, column temperature, and mobile phase composition, to evaluate the method's robustness against small variations in experimental parameters. System suitability parameters are also determined to ensure the consistent performance of the chromatographic system over time.

Overall, the analytical validation of the RP-HPLC method for Pravastatin Sodium and Fenofibrate provides a comprehensive assessment of its suitability for routine analysis in pharmaceutical formulations. This validated method can be utilized for quality control purposes in the pharmaceutical industry, contributing to the development and manufacturing of safe and effective antihyperlipidemic drug products.

Drug profile

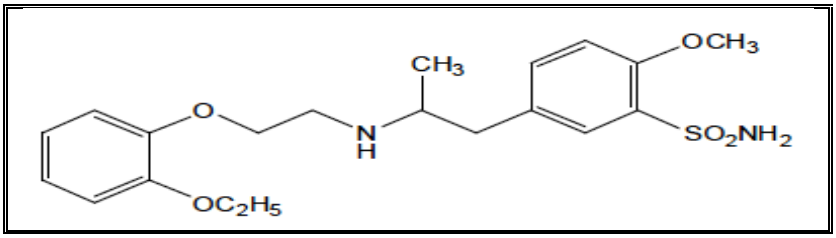
Pravastatin Sodium [1,2]

Official Status	:	USP, EP.
Structure	:	
Mol. Formula	:	$C_{23}H_{35}NaO_7$
Mol. Weight	:	424.528g/mol
CAS No.	:	81093-37-0
Chemical Name	:	9-Fluoro-11,17-dihydroxy-16-methyl-3,20-dioxopregna-1,4-dien-21-yl disodium phosphate
Appearance	:	White to yellowish white, crystalline powder.
Melting Point	:	45 - 50°C
Solubility	:	Freely soluble in water &methanol, sparingly soluble in Acetonitrile, slightly soluble in 2-propanol.
UV λmax	:	238 nm
Storage	:	Store protected from moisture.
Category	:	Hepatic,3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase

1.1.1 Fenofibrate [1,2]

Official Status : USP

Structure :



Mol. Formula : $C_{20}H_{21}ClO_4$

Mol. Weight : 360.84

CAS No. : 49562-28-9

Chemical Name : Isopropyl, 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate

Appearance : Off - White crystalline powder.

Melting Point : 79°C and 82°C.

Solubility : Soluble in DMSO to 100 mM and in ethanol to 100 mM, insoluble in water (saturation solubility 0.8 µg/ml)

UV λmax : 225, 279

Storage : Store at Room Temperature. The product can be stored for up to 12 months.

Category : Potent, selective PPAR-α agonist

1.2 Literature Review

Ref. No	Author	Instrument	Column	Mobile Phase	Flow rate (ml/ min)	Detection
6. 2. 1.	S. Pravallika, et al. [3]	HPLC	C 18	ACN THF : NH_4 acetate pH-4.5	1	UV
6. 2. 2.	Dillip Kumar Sahoo, et	HPLC	C 18	ACN : buffer pH 3	1	PDA

	al. [4]					
6. 2. 3.	Satish kumar Shetty A , et al. [5]	HPLC	C 18	ACN : buffer pH 3.6	1	PDA
6. 2. 4.	S. Brain-Isasi, et al. [6]	HPLC	C 18	ACN : buffer pH 2	1	PDA
6. 2. 5.	M.T. Zzaman, et al. [7]	HPLC	Lithosphere 60	ACN : buffer pH 6	0.7	UV
6. 2. 6.	B. Chinnappadu, et al. [8]	UV HPLC LC MS	C 18	ACN : buffer pH 6.8	0.8	UV
6. 2. 7.	S. D. Bhingea, et al. [9]	UV HPLC LC MS	C 18	ACN : buffer pH 4.1	1	UV
6. 2. 8.	E. Samyukta et al. [10]	HPLC	ODS	ACN : buffer pH 2.5	1.5	UV
6. 2. 9.	S.V. Mulgund, et al. [11]	HPLC	ODS	ACN : Water	1.5	UV
6. 2. 10.	Srinivasa RaoPolaganni, et al. [12]	HPLC	ODS	ACN : Water	0.8	UV
6. 2. 11.	Praveen Kumar S. et al. [13]	HPLC	C 18	MET : 0.1 % OPA	1	UV
6. 2. 12.	Grishma Trivedi, et al. [14]	UV		Water Methanol		240 nm
6. 2. 13.	Kunjan B. Bodiwala, et al. [15]	UV		Methanol		249 nm

6. 2. 14.	Wolfgang Jacobsen, et al. [16]	HPLC	C 8	ACN : Formic acid pH 4	1	UV

1.3 Analytical Method Development, Optimization and Validation

1.3.1 Chemicals and Solvents

The reference standard (RS) Pravastatin Sodium and Fenofibrate was obtained as gift sample from Glenmark Pharmaceuticals. Chemicals of analytical grade and solvents, like Methanol and Acetonitrile of LC grade purchased from SD Fine Chemicals were used.

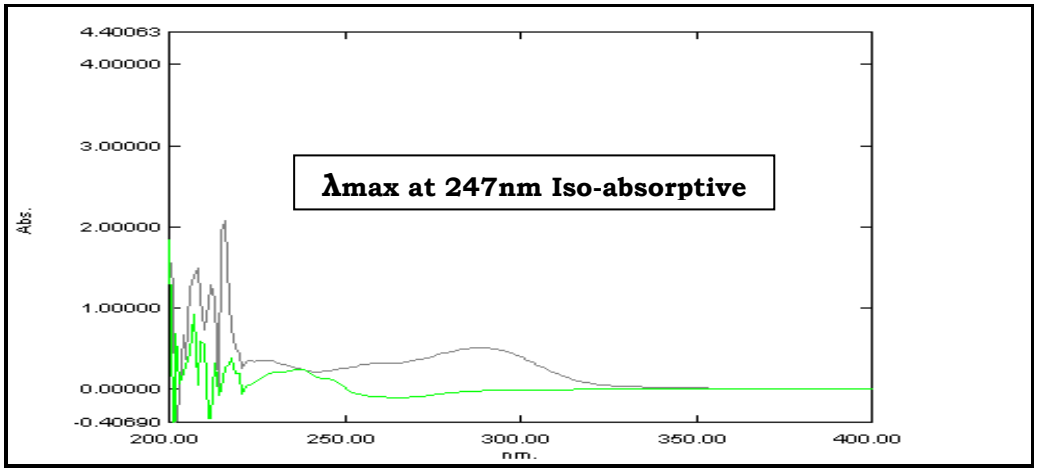
6.3.2 Preparation of Standard Stock Solution:

Accurately weighed quantity of 100mg of each Pravastatin Sodium and Fenofibrate was transferred into two separate100ml volumetric flasks. A 20ml portion of Mobile Phase i.e. Acetonitrile: KH_2PO_4 was added. This solution was sonicated for 10 minute and cooled to room temperature. Then the volume was made up to the mark with mobile phase to obtain standard stock solution of each drug of concentration 1000µg/ml. the stock solutions were filtered through a 0.45µm pore size Nylon 66 membrane filter.

6.3.3 Selection of Analytical Wavelength:

From the standard stock solution further dilutions were prepared using mobile phase and scanned over the range of 200-400 nm and the spectra were overlay in λmax of both the drugs was observed both the drugs showed considerable absorbance at 247nm. Therefore 247nm was selected as wavelength of analysis. Overlay in spectra of Pravastatin Sodium and Fenofibrate are shown in Figure 6.1 using mobile phase as solvent.

Figure 6.1 Overlay in spectra of Pravastatin Sodium and Fenofibrate



6.3.4 Preparation of Mobile Phase:

Phosphate buffer of pH 4 was prepared by dissolving 3.4g of potassium dihydrogen phosphate in 900mL HPLC grade water and the pH 4.0 was adjusted with o-phosphoric acid and volume was made up to 1000 ml with same solvent. Both the solvents Acetonitrile and Phosphate buffer were filtered through a 0.45µm pore size Nylon 66 membrane filter and then sonicated for 15 min. The mobile phase consisting of Acetonitrile and Phosphate buffer (80:20 v/v).

6.3.5 Optimization of Chromatographic Conditions:

The HPLC method was optimized with a view to develop a HPLC method for simultaneous estimation of Pravastatin Sodium and Fenofibrate in tablet dosage form. Number of mobile phases with different pH and compositions were tried. Mobile phase consisting of Acetonitrile: KH_2PO_4 (80:20 v/v), showed good resolution, peak shape and desired elution. Flow rate was set to 1ml/min. and UV detection was carried out at 247nm.

Chromatogram showed symmetrical peaks with good shapes; tailing factors for Pravastatin Sodium and Fenofibrate were within range and the resolution of the standard drugs was satisfactory. Retention time for Pravastatin Sodium and Fenofibrate were 1.877 and 6.319 minute respectively. Number of theoretical plates was also greater than 2000 at optimized conditions. The system suitability parameters observed by using this mobile phase are reported in Table 6.1.

Table 6.1 Selection of chromatographic parameters

1.	Column	:	C18 column 150 mm × 4.6 mm (5 µm)
2.	Mobile Phase	:	Acetonitrile : KH_2PO_4 (80:20 v/v) pH 6
3.	Flow Rate	:	1 ml/minute.
4.	Detection Wavelength	:	247 nm.
5.	Sample Injected	:	20 µl.

6.3.6 Preparation of standard calibration curves and selection of analytical concentration ranges:

For each drug, appropriate aliquots of standard stock solution were transferred to a series of 10 ml volumetric flasks. The volume was made up to the mark with distilled water to obtain working standard solutions for each drug of concentrations 2-20µg/ml and 8-80µg/ml for both Pravastatin Sodium and Fenofibrate resp. Three sets of each concentration of the drugs were prepared separately. The standard calibration curves of Peak area Vs Concentration were plotted using the mean of these three independent observations. The concentration range over, which the drugs obeyed Beer-Lambert's law was found to be between 2-20 µg/ml & 8-80µg/ml of Pravastatin Sodium and Fenofibrate respectively. The results are shown in Table 6.2.

Table 6.2 Standard Calibration Data for Pravastatin Sodium and Fenofibrate

Sr. No.	Pravastatin Sodium		Fenofibrate	
	Concentration (µg/ml)	Peak Area* (mAU)	Concentration (µg/ml)	Peak Area* (mAU)
1.	2	90010	8	471043
2.	4	155224	16	1004559
3.	6	239945	24	1554806
4.	8	300371	32	2033598
5.	10	396588	40	2702907
6.	12	476915	48	3109876
7.	14	549952	56	3574594
8.	16	629060	64	4003944
9.	18	699424	72	4426145
10.	20	757076	80	4933587

* Average of three determinations

Figure 6.2 Standard Calibration curve of Pravastatin Sodium

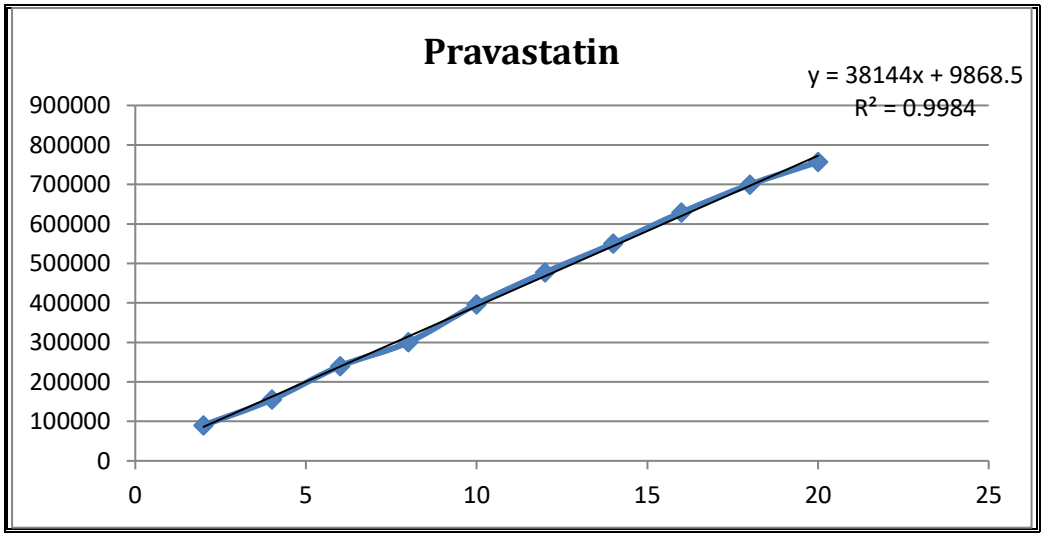
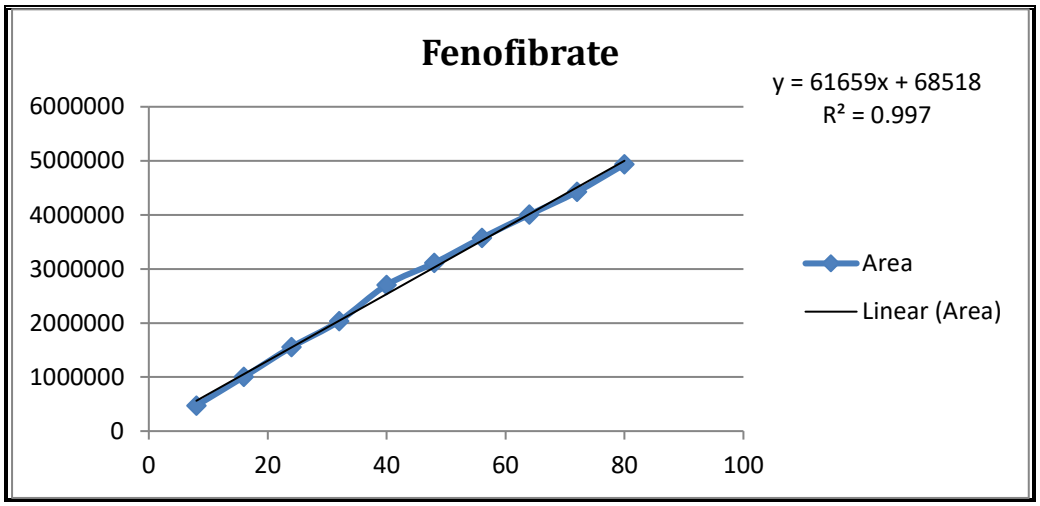


Figure 6.3 Standard Calibration curve of Fenofibrate



6.3.6 Analysis of Pure Mixed Standards:

The sample stock solutions of both the drugs were suitably diluted with mobile phase to get mixture with concentration of 16µg/ml of Pravastatin Sodium and 64µg/ml of Fenofibrate. Mixed standard solution of Pravastatin Sodium and Fenofibrate were injected to get the chromatogram.

The results are shown in Table 6.3 & 6.4.

Figure 6.4 Chromatogram of Pravastatin Sodium and Fenofibrate for Pure Mixed Standard

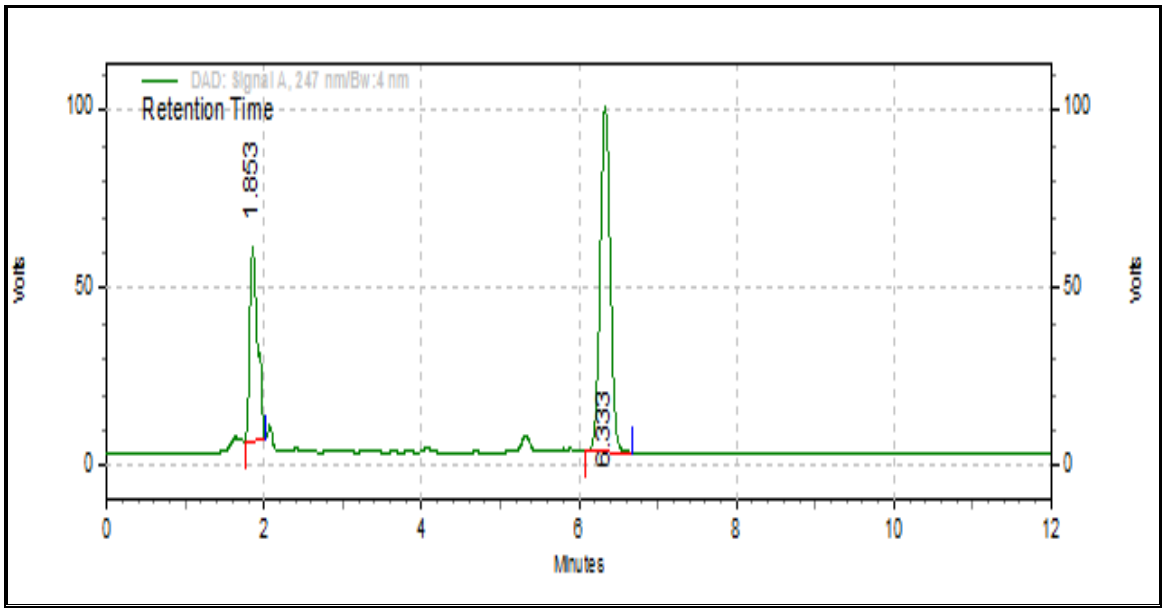


Table 6.3 System Suitability Parameters for Pure Mixed Standard

Drug	Conc taken (µg/ml)	RT (min)	Area (mAU)	Tailing Factor	Theoretical Plate
PRAVA	16	1.853	627817.17	0.82	3361.40

FENO	64	6.333	4370116	0.83	3565.37

Table 6.4 Analysis of Pure Mixed Standard of Pravastatin Sodium and Fenofibrate

Drugs	Conc. of Drug taken (µg/ml)	Conc. of Drug found (µg/ml)*	% Drug found*
PRAVA	16	15.65	97.84
FENO	64	64.75	101.17

* Average of six determinations

6.3.7 Analysis of Tablet Formulation:

Tablet containing 40 mg of Pravastatin Sodium, and 160 mg of Fenofibrate was prepared by dry granulation method using microcrystalline cellulose, magnesium stearate, sodium lauryl sulphate as dilutants. The mixture was passed through a sieve of 14 mesh size and compressed into tablet.

Twenty tablets, containing 40 mg of Pravastatin Sodium, and 160 mg of Fenofibrate together with excipients were accurately weighed, transferred to a clean and dry mortar and ground into a fine powder. The powder equivalent was accurately weighed, then transferred to a clean 10 ml volumetric flask, 10 ml of mobile phase i. e. Acetonitrile : KH_2PO_4 (80:20) mixture was added, and the flask was attached to a rotary shaker for 10 min to disperse the material completely. The mixture was then sonicated for 10 min and diluted to volume with mobile phase to give a solution containing 10µg/ml of Pravastatin Sodium and 40 µg/ml of Fenofibrate. This solution was filtered through a 0.45µm pore size Nylon 66 membrane filter. Solution of concentration 10µg/ml (Pravastatin Sodium) and 40µg/ml (Fenofibrate) of combination were prepared with mobile phase and injected, chromatogram was recorded and the amount of both the drugs was calculated. The chromatograms of Pravastatin Sodium and Fenofibrate in tablet formulation are shown in Figure 6.5. Results are shown in Table 6.5 & 6.6.

Table 6.5 Analysis data of Tablet Formulation

Label Claim (µg/tab)		Amount Found (µg /tab)*		% Label Claim*	
PRAVA	**FENO**	**PRAVA**	**FENO**	**PRAVA**	**FENO**
40	160	39.99	142.32	99.98	88.95

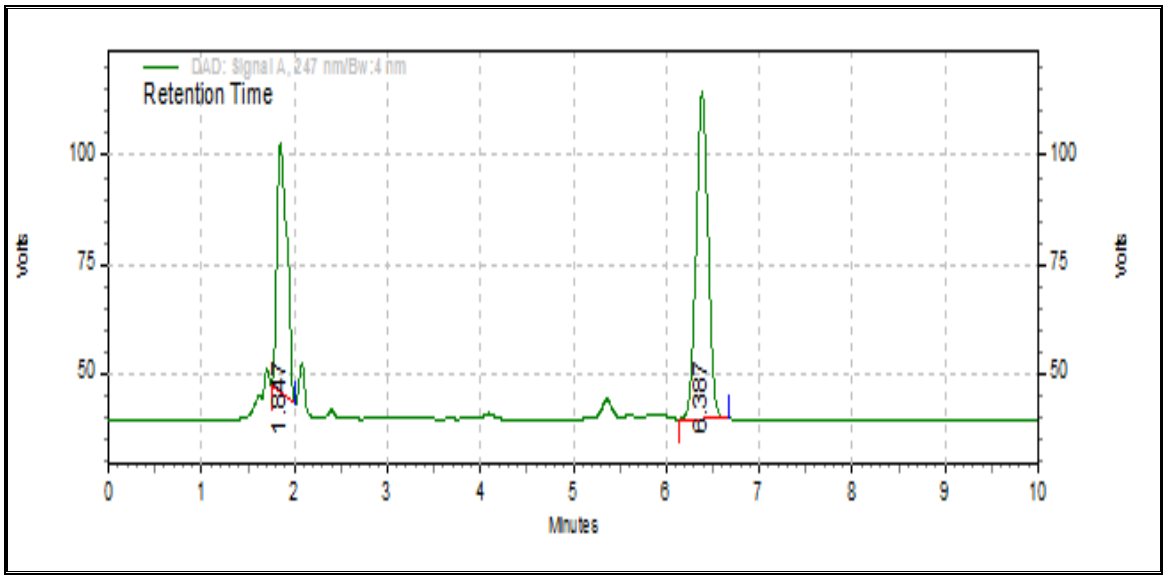
***** Average of six determinations

Table 6.6 System Suitability Parameters for Tablet Formulation

Drug	RT (min)*	Area (mAU)*	Tailing Factor*	Theoretical Plate*
PRAVA	1.903	1598644	0.82	3361.40
FENO	6.314	9546879	0.83	3565.37

* Average of six determinations

Figure 6.5 Chromatogram of Pravastatin Sodium and Fenofibrate in tablet formulation



6.3.9 METHOD VALIDATION:

1) PRECISION

a) Repeatability:

The results are shown in Table 6.7.

Table 6.7 Repeatability Data

Repeatability						
Drug	**Conc. taken in (µg/ml)***	**Area**	**Conc. found in (µg/ml)***	**% Purity***	**S. D.**	**% R. S. D.**
PRAVA	16	608604	15.17	94.83	0.950	1.002
FENO	64	436285	64.64	101.00	0.978	0.968

* Average of six determinations

b) Intermediate Precision:

The Inter-day precision was obtained by the assay of sample sets on different days. The results of the analysis are shown in Table 6.8 & 6.9.

Table 6.8 Intra-day Precision Study Data

Interval	Drug	Conc. taken (µg/ml)*	Area	Conc. found (µg/ml)*	% Purity*	S.D.	% R. S. D.
Morning	PRAVA	16	635334	16.51	99.58	1.124	1.129
	FENO	64	4256763	63.86	99.78	0.4064	0.407
Afternoon	PRAVA	16	645555	16.10	100.62	0.789	0.784
	FENO	64	4323196	64.05	100.07	0.519	0.519
Evening	PRAVA	16	656727	16.38	102.37	0.868	0.847
	FENO	64	4344338	64.36	100.57	1.274	1.267

* Average of six determinations

Table 6.9 Inter-day Precision Study Data

Interval	Drug	Conc. Taken (µg/ml)*	Area	Conc. Found (µg/ml)*	% Purity*	S. D.	% R. S. D.
Day 1	PRAVA	16	635334	16.51	99.58	1.124	1.129
	FENO	64	425676	63.86	99.78	0.406	0.407
Day 2	PRAVA	16	596023	14.85	92.86	0.728	0.784
	FENO	64	4371395	64.77	101.20	0.947	0.935
Day 3	PRAVA	16	608604	15.17	94.83	0.951	1.002
	FENO	64	4362857	64.64	101.00	0.978	0.968

* Average of six determinations

2. ACCURACY:

Accuracy studies were carried out by applying the method to the pure mixed standards it was assessed using 9 determination of three concentrations (three replicates of each concentration) covering the specified range. The results of accuracy study are shown in Table 6.10.

Table 6.10 Accuracy Study Data

Drug	Conc. of drugs taken (µg/ml)*	Conc. of drugs found (µg/ml)*	% Drug found *	S. D.	% R. S. D.
PRAVA	12	12.01	100.13	0.7333	0.7324
FENO	48	48.80	101.68	0.6038	0.5937
PRAVA	16	15.65	97.84	0.9623	0.9834
FENO	64	64.75	101.17	1.2554	1.2408
PRAVA	20	19.89	99.46	1.0637	1.0694
FENO	80	79.91	99.89	1.0998	1.0997

* Average of three determinations

3. Recovery:

Recovery studies were carried out by applying the method to drug contents present in the tablet formulation to which known amount of standard Pravastatin Sodium and Fenofibrate was added at 80%, 100% and 120% levels. The results of recovery study are shown in Table 6.11& 6.12.

Table 6.11 Recovery Study Data

Level of Recovery	Drug	Present Amount of Drug (µg/ml)*	Amount of Std. added (µg/ml)*	Amount of Drugs Recovered (µg/ml) *	% Drug Found *
80 %	PRAVA	16	14	29.50	96.50
	FENO	64	62	125.08	98.54
100 %	PRAVA	16	16	32.19	101.21
	FENO	64	64	127.79	99.68
120 %	PRAVA	16	18	34.23	101.32
	FENO	64	66	128.93	98.39

* Average of three determinations at each level of recovery

Table 6.12 Statistical Validation of Recovery Study

Level of Recovery	% Mean Recovery*		S. D.		% R. S. D.	
	PRAVA	FENO	PRAVA	FENO	PRAVA	FENO
80 %	96.50	98.54	0.8849	1.8469	0.9171	1.8741
100 %	101.21	99.68	1.0686	0.4528	1.050	0.4543
120 %	101.32	98.39	1.0961	0.5778	1.0880	0.5781

*Average of three determinations at each level of recovery

4. Robustness:

To evaluate the robustness, deliberate variations were made in the method parameters such as change in pH of the mobile phase, flow rate and ratio of the organic and aqueous component of the mobile phase. The results are shown in Table 6.13.

Table 6.13 Robustness Study (Flow Rate)

Robustness Study (Flow Rate)						
Drug	**Conc. of drugs taken (µg/ml)***	**Flow Rate (ml/min)**	**R. T. (min)***	**% Content***	**S. D.**	**% R. S. D.**
PRAVA	16	**0.8**	1.862	97.84	1.0155	0.9834
FENO	64	**0.8**	6.443	101.00	0.9786	0.9689
PRAVA	16	**1.2**	1.318	100.74	0.6869	0.681

FENO	64	**1.2**	5.82	99.09	1.1017	1.111
Robustness Study (pH Change)						
PRAVA	16	**4.5**	1.482	98.51	1.138	1.155
FENO	64	**4.5**	6.693	99.32	1.259	1.267
PRAVA	16	**5.0**	1.544	96.18	0.964	1.003
FENO	64	**5.0**	7.169	99.32	1.259	1.267

***Average of six determinations

5. Limit of Detection (LOD) & Limit of Quantitation (LOQ):

The LOD and LOQ were separately determined based on the standard deviation of response of the calibration curve. The results are shown in Table 6.14.

Table 6.14 LOD & LOQ values

Drug	**Parameters**	
	LOD (µg/ml)	**LOQ (µg/ml)**
PRAVA	1.122	3.402
FENO	1.198	3.631

6.5 RESULT & DISCUSSION

A simple, economic and validated RP-HPLC method was developed for the simultaneous estimation of Pravastatin and Fenofibrate in bulk and combined dosage form. The optimized parameters for HPLC and the results of the system suitability studies and validation are given in Table No. 6.17.

Table 6.17 Validation and System Suitability Studies

Parameters	**PRAVA**	**FENO**
Linearity Range (µg/ml)	2-20	8-80
Correlation Coefficient	0.984	0.997
LOD (µg/ml)	1.122	1.198
LOQ (µg/ml)	3.402	3.631
Precision **Inter-Day (%RSD)** **Intra-Day (%RSD)**	 0.97 0.92	 0.77 0.73
Tailing Factor	0.82	0.83
Mean % Recovery	99.67	98.87
Theoretical plates	3361	3565

The above validation and system suitability studies suggest that the developed RP-HPLC method can be employed successfully for the estimation Pravastatin and Fenofibrate in the bulk and combined dosage form.

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