Development and Validation of HPLC Method Using Hydrotropic Mobile Phase for the Estimation of Raloxifene Hydrochloride

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Hydrotropy, RP-HPLC, HPTLC, UV Spectroscopy, Raloxifene Hydrochloride

Abstract:

Hydrotropy is a molecular phenomenon that significantly enhances the solubility of sparingly or poorly water-soluble drugs. In hydrotropy, a hydrotrope (e.g., urea, nicotinamide, sodium benzoate, sodium citrate) is added to a solvent, which serves as the mobile phase in RP-HPLC analysis. This approach reduces the need for harmful and costly organic solvents, making drug analysis more eco-friendly and economical. In this study, a method was developed using 3% sodium benzoate (pH 6.2) as the single mobile phase. The analysis was conducted with a Lichrosphere® RP-18e (C18) (250 × 4.6 mm, 5 µm particle size) column as the stationary phase, with a flow rate of 1 ml/min, and detection at 286 nm using a PDA detector. The retention time was 5.029 minutes, and the method demonstrated linearity over a concentration range of 50–400 µg/ml, with a correlation coefficient of 0.9991. The developed method was validated according to ICH Q2 (R1) guidelines, confirming its suitability for routine analysis of Raloxifene Hydrochloride in bulk and pharmaceutical dosage forms. The objectives of the study were successfully achieved

1.INTRODUCTION

Hydrotropy refers to the process of enhancing a solute's solubility in water by introducing a chemical agent known as a hydrotrope (7-9). Hydrotropic solutions are commonly utilized as solvents in analytical techniques like spectrophotometry and chromatography, allowing for precise, rapid, and accurate drug analysis (9-13). This study applies the principle of hydrotropy to the mobile phase in RP-HPLC, providing a safer, eco-friendly, and more cost-effective alternative to the traditionally used toxic and expensive organic solvents (2-5). Hydrotropes are amphiphilic compounds with hydrophilic functional groups that facilitate the solubilization of poorly soluble substances in aqueous solutions. These organic salts in aqueous environments can significantly improve the solubility of hydrophobic compounds in the water phase. Typical examples of hydrotropes include hydroxybenzenes, hydroxybenzoates, benzenesulfonates, sodium benzoate, urea, and sodium citrate (15-18).

Raloxifene hydrochloride (RLX) is the chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl) benzo [b] thien-3-yl]-[4-[2-(l-piperidinyl) ethoxy] phenyl]-, hydrochloride. Raloxifene hydrochloride1 is an anti osteoporotic drug, first selective estrogen receptor modulator (SERM) for the prevention and treatment of osteoporosis in postmenopausal women. It affects the cycle of bone formation and breakdown in the body and reduces loss of bone tissue. It produces estrogen-like effects on bone, reducing re sorption of bone and increasing bone mineral density in postmenopausal women. It is a poly hydroxylated non-steroidal benzothiophene compound.

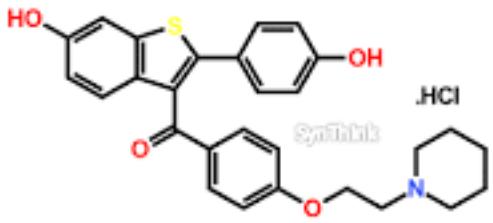


Figure 1: Structure of Raloxifene hydrochloride (RLX)

2. MATERIALS ANDMETHODS

2.1 Instrument

The study utilized a Waters 600 E Infinity HPLC instrument equipped with a diode array detector and controlled by Empower-2 software. The stationary phase was a Lichrosphere® RP-18e (C18) column (250 × 4.6 mm, 5 µm particle size). All drugs and chemicals were weighed using a Mettler Toledo XPR106DUH semi-microbalance, and pH measurements were conducted with a Mettler Toledo SevenCompact pH meter S220. The mobile phase and samples were sonicated with an Ultrasonicator from EIE Instruments Pvt. Ltd., India.

2.2 Reagents and Chemicals

- Raloxifene Hydrochloride standard obtained from the Indian Pharmacopoeia Commission (IPRS)
- HPLC-grade water (Milli-Q)
- Sodium benzoate, analytical grade, from Rankem India
- Methanol, HPLC grade, from Rankem India
- Glacial acetic acid from Rankem India

2.3 Preparation of Stock Solutions of Raloxifene Hydrochloride:

Raloxifene Hydrochloride (100 mg) was accurately weighed and transferred to a 100 ml volumetric flask. Methanol was added, and the mixture was sonicated to dissolve the drug. The volume was then adjusted to the mark with methanol to prepare a standard stock solution with a concentration of 1000 µg/ml. From this stock solution, 1 ml was transferred to a 100 ml volumetric flask, and the volume was made up to 100 ml with the same methanol to obtain a working standard solution with a concentration of 100 µg/ml.

2.4 Method Development and Optimization

The concentration and pH of the mobile phase influence the resolution, selectivity, and efficiency of separation. In RP-HPLC, organic solvents, which are often toxic, volatile, and costly, are typically used as mobile phases. However, this study aimed to develop an eco-friendly, cost-effective, and non-volatile hydrotropic mobile phase for estimating the poorly water-soluble drug Raloxifene Hydrochloride. Mobile phase selection was conducted using a

trial-and-error approach, testing various concentrations of sodium benzoate solution at different pH levels. Among these, a 3% sodium benzoate solution at pH 6.2 (adjusted with glacial acetic acid) produced a sharp peak for Raloxifene Hydrochloride. Thus, the optimized mobile phase was finalized as 3% sodium benzoate solution (pH 6.2).

2.5 Solubility of Raloxifene Hydrochloride

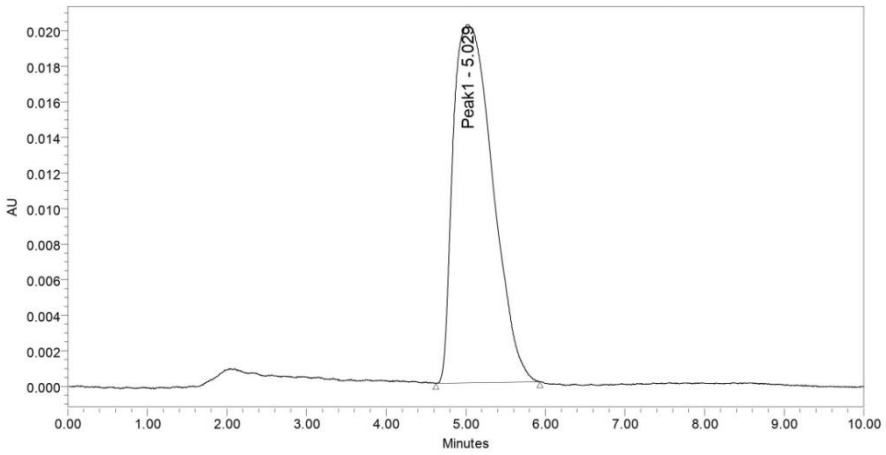
Evaluation of hydrotropic agent for Raloxifene Hydrochloride Table-1

S.No.	Hydrotropic agents	Conc. of hydrotropic agent	Solubility of drug(mg/ml)
1.	Sodium Salicylate	1M	3.822
2.	Sodium Benzoate	1M	1.081
3.	Sodium Citrate	1M	4.728
4.	Urea	1M	3.682
5.	Sodium Acetate	1M	7.409

2.6 Mobile Phase selection Table-2

S.No.	Mobile phase	Flow rate	Conclusion
1.	5% Urea Solution	1.0 ML/Min	Unstable baseline
2.	3%w/v Sodium Benzoate Solution	1.0 ML/Min	Most Suitable
3.	6% w/v Sodium Acetate	1.0 ML/Min	No peak found

Optimization of Chromatographic Conditions for Raloxifene Hydrochloride



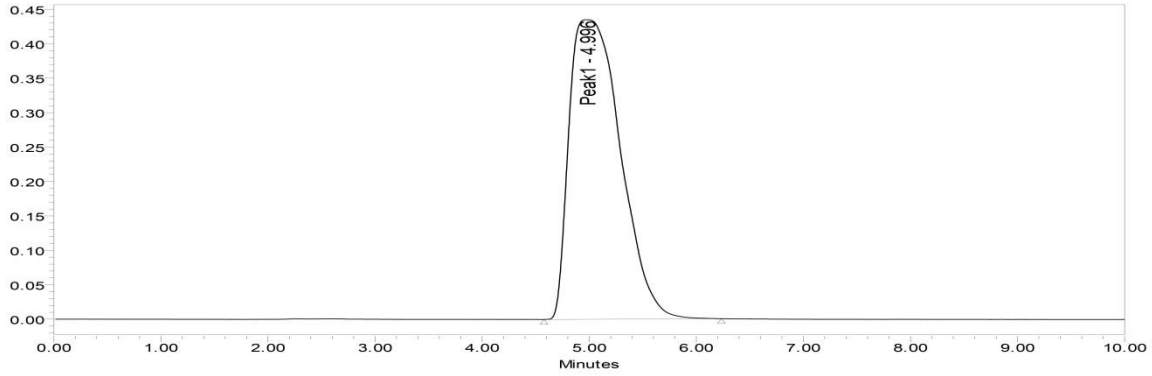
	Peak Name	RT	Area	% Area	Height	USP Plate Count	Symmetry Factor
1	Peak1	5.029	696643	100.00	20161	559.03	1.59

	USP Tailing	K Prime
1	1.59	4.028928e+000

Figure 2: HPLC Graph Raloxifene Hydrochloride

Flow rate	pH	Mobile phase	Remark
1.ml/min.	6.2	3%w/v Sodium Benzoate Solution	Only single peak observed

Condition-1



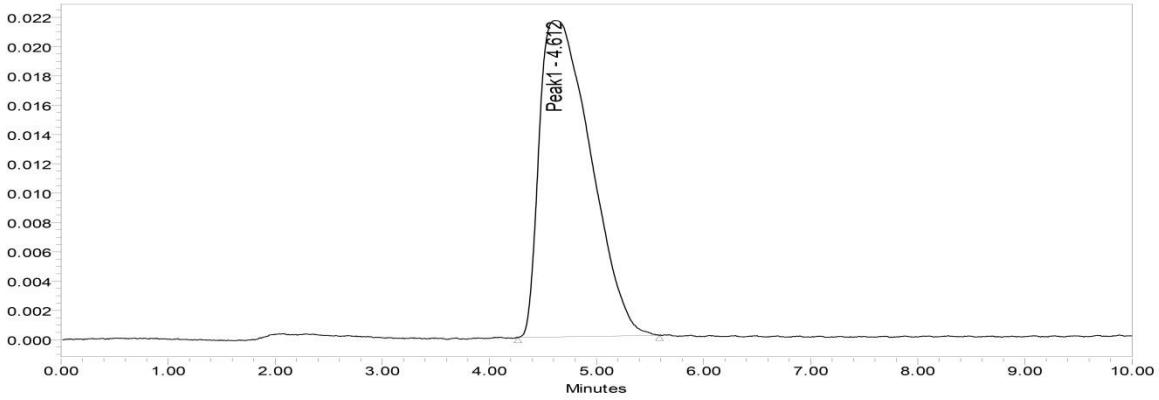
	Peak Name	RT	Area	% Area	Height	USP Plate Count
1	Peak1	4.996	14489610	100.00	434995	659.06

	Symmetry Factor	USP Tailing	K Prime
1	1.57	1.57	3.995575e+000

Figure 3: HPLC Graph Raloxifene Hydrochloride

Flow rate	pH	Mobile phase	Remark
0.8 ml/min.	6.2	2 %w/v Sodium Benzoate Solution	R_T Change Observe

Condition- 2



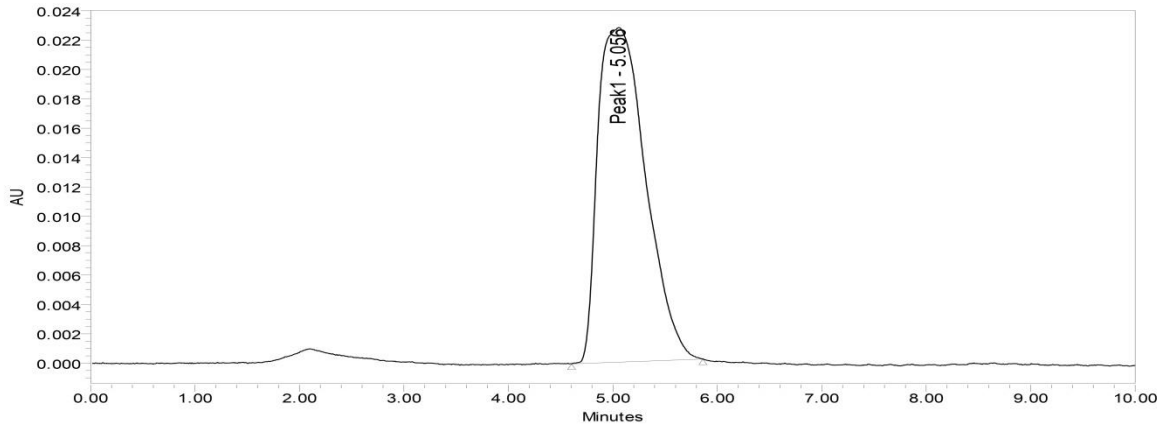
	Peak Name	RT	Area	% Area	Height	USP Plate Count	Symmetry Factor
1	Peak1	4.612	717375	100.00	21610	466.62	1.86

	USP Tailing	K Prime
1	1.86	3.611901e+000

Figure 4: HPLC Graph Raloxifene Hydrochloride

Flow rate	pH	Mobile phase	Remark
1 ml/min.	5.0	2 %w/v Sodium Benzoate Solution	R_T Change Observe

Condition-3



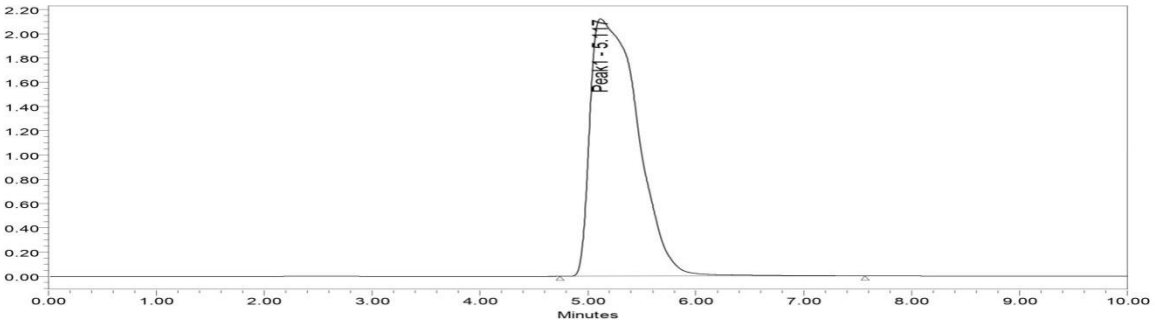
	Peak Name	RT	Area	% Area	Height	USP Plate Count	Symmetry Factor
1	Peak1	5.056	724671	100.00	22782	701.65	1.44

	USP Tailing	K Prime
1	1.44	4.056226e+000

Figure 5: HPLC Graph Raloxifene Hydrochloride

Flow rate	pH	Mobile phase	Remark
1 ml/min.	6.2	3%w/v Sodium Benzoate Solution	Only single peak observed

Condition- 4



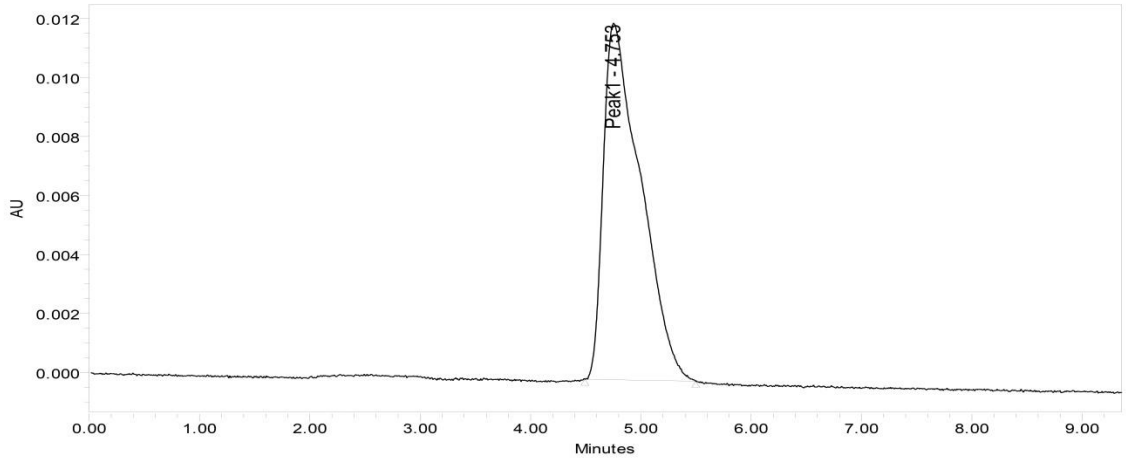
	Peak Name	RT	Area	% Area	Height	USP Plate Count
1	Peak1	5.117	64880546	100.00	2123290	878.91

	Symmetry Factor	USP Tailing	K Prime
1	2.29	2.29	4.117308e+000

Figure 6: HPLC Graph Raloxifene Hydrochloride

Flow rate	pH	Mobile phase	Remark
1 ml/min.	5.0	3%w/v Sodium Benzoate Solution	Only single peak observed

Condition- 5

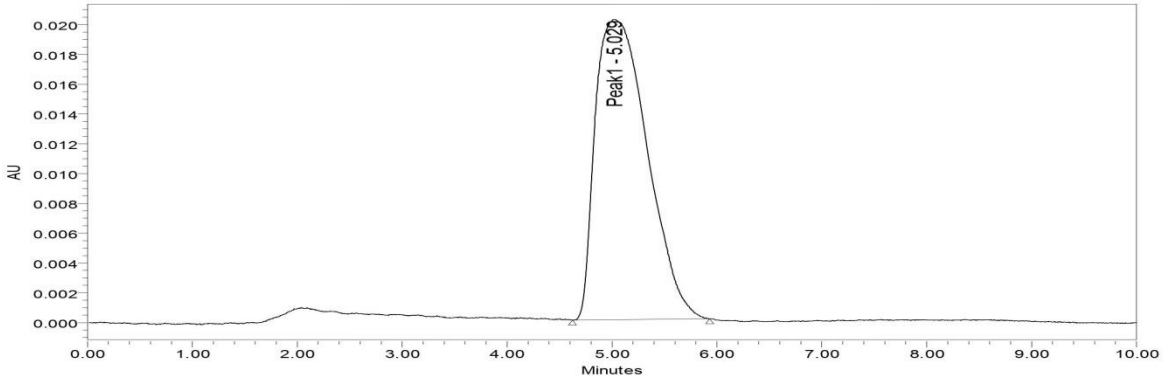


	Peak Name	RT	Area	% Area	Height	USP Plate Count	Symmetry Factor	USP Tailing	K Prime
1	Peak1	4.753	284345	100.00	12094	529.74	1.99	1.99	3.753051

Figure 7: HPLC Graph Raloxifene Hydrochloride

Flow rate	pH	Mobile phase	Remark
1 ml/min.	6.2	1%w/v Sodium Benzoate Solution	R_T Change Observe

Condition - 6



	Peak Name	RT	Area	% Area	Height	USP Plate Count	Symmetry Factor
1	Peak1	5.029	696643	100.00	20161	559.03	1.59

	USP Tailing	K Prime
1	1.59	4.028928e+000

Figure 8: HPLC Graph Raloxifene Hydrochloride

Flow rate	pH	Mobile phase	Remark
1 ml/min.	5.0	1%w/v Sodium Benzoate Solution	Only single peak observed

2.7 HPLC Operating Conditions

- **Column**: Lichrosphere® RP-18e (C18) (250 × 4.6 mm, 5 µm particle size)
- **Detector**: Diode Array Detector (DAD)

- **Injection Volume**: 20 µl
- **Flow Rate**: 1 ml/min
- **Temperature**: Ambient
- **Run Time**: 10 minutes
- **Mobile Phase**: 3% sodium benzoate solution
- **Wavelength**: 286 nm

2.8 Preparation of Working Standard Solution

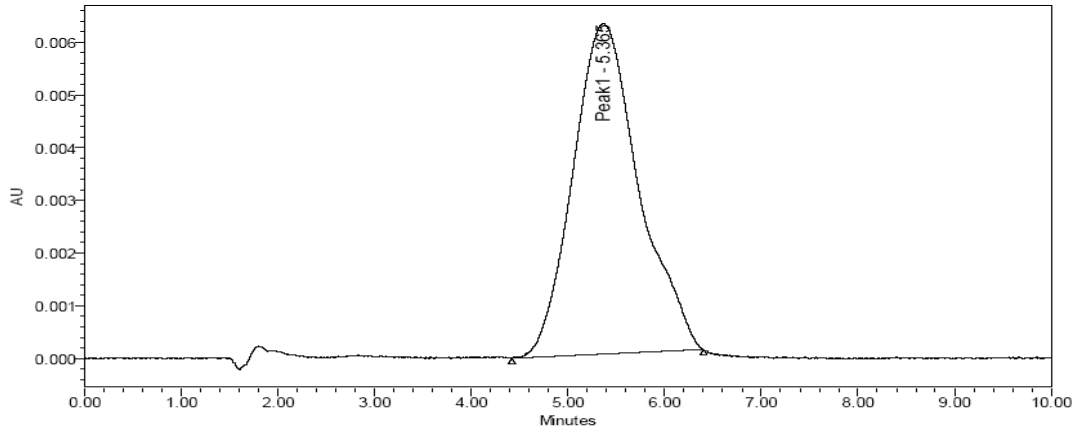
From the standard stock solution of Raloxifene Hydrochloride (100 µg/ml), 1 ml was accurately pipetted and transferred into a 10 ml volumetric flask, then diluted to volume with methanol. This prepared solution contained 10 µg/ml of Raloxifene Hydrochloride. Additional solutions with concentrations ranging from 10–100 µg/ml were prepared in a similar manner. The 10 µg/ml concentration solution was used for the System Suitability Test (SST) and for preparing the standard chromatogram for the assay.

3. RESULTSANDDISCUSSION

3.1 System Suitability Test

System suitability was evaluated by injecting a 10 µg/ml Raloxifene Hydrochloride standard. The results confirmed that all parameters were within the acceptable range. Raloxifene Hydrochloride was consistently retained and well-separated with a retention time of 5.029 minutes. The tailing factor for the Raloxifene Hydrochloride peak remained below 1.1, indicating good peak symmetry (acceptance limit < 2), ensuring effective column performance throughout the separation process. These results confirm that the developed method is reliable and suitable for method validation. The chromatogram of the system suitability test is shown in Figure 2, with data presented in Table 13.

Chromatogram of Raloxifene Hydrochloride



	Peak Name	RT	Area	% Area	Height	USP Plate Count	Symmetry Factor	USP Tailing	K Prime
1	Peak1	5.365	297422	100.00	6280	307.49	1.16	1.16	4.365388

Figure 9: HPLC Graph Raloxifene Hydrochloride

3.2 Method validation

- The proposed method was validated as per ICH guidelines [19].
- The validation parameters studied included linearity, accuracy, precision, specificity, robustness, ruggedness, limit of detection (LOD), and limit of quantitation (LOQ).
- Linearity& Range (Preparation of Calibration Curve):
  Standard solutions were prepared in the concentration range of 50–400 µg/mL. Each concentration was injected, and the corresponding chromatograms were recorded.

3.2.1 PREPARATION OF CALIBRATION CURVE

Table No.3: Data of Calibration Curve Raloxifene Hydrochloride

Con. (ug/ml)	day 1	day 2	day 3	Mean	SD	%RSD
50	847038	847183	847420	847213	187.8376	0.032496
100	1661617	1662086	1661762	1661822	230.1257	0.014875
150	2467166	2469357	2469416	2468646	1292.346	0.065945
200	3294270	3297247	3296660	3296059	1676.874	0.057841
250	4029336	4028145	4027417	4028299	868.7643	0.04398
300	4810746	4811684	4815495	4812642	2575.173	0.053371
350	5643598	5643933	5646422	5644651	1642.851	0.027333
400	6895035	6797422	6998903	6597120	2051.604	0.032409
Slop			**15973**			
Regression Coefficient			**R^2=0.9991**			
Regression Equation			**Y=15973x+51562**			

The calibration graph was plotted between the Conc. V/s Area. The calibration of Raloxifene Hydrochloride was plotted between the conc. range of 50 - 400 µg/ml. The R^2 was found to be 0.9991. Slop and intercept was found to be 15973 and 51562 respectively.

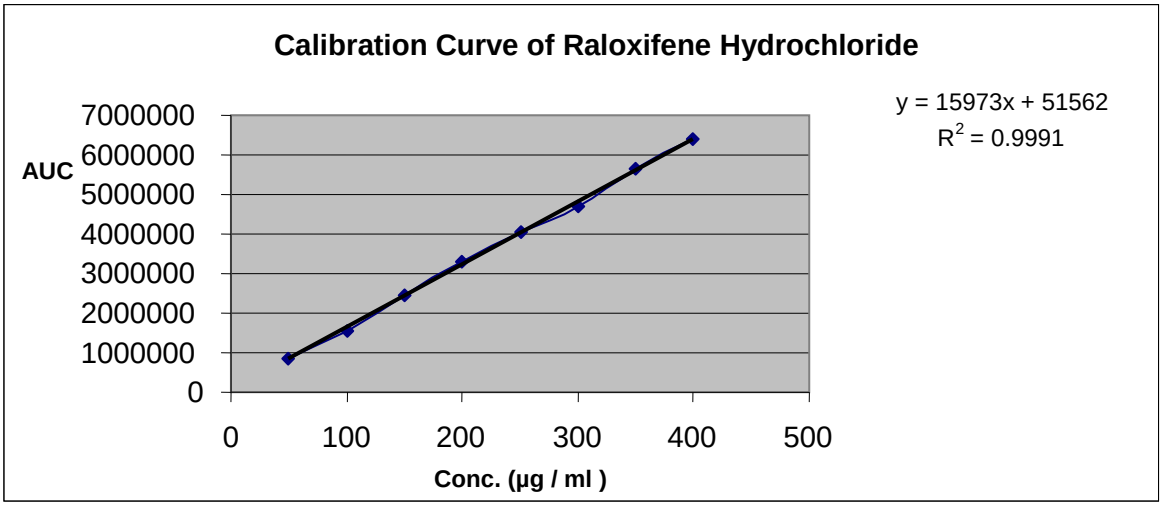


Fig. No.2 Calibration graph of Raloxifene Hydrochloride

3.2.2 ESTIMATION OF DRUGS IN FORMULATION

Table No.4: Data of drugs estimation in Raloxifene Hydrochloride formulation

S.No.	Name of Product	Claim Amt	Found Amt	% Purity	SD	RSD
1.	Cipla's Ralista	60mg.	59.40mg.	99.5	2.541	0.871

3.3 VALIDATION OF PROPOSED METHOD AS PER ICH GUIDELINE

The proposed method was validated in accordance with ICH guidelines [19].

The validation parameters evaluated included linearity, accuracy, precision, specificity, robustness, ruggedness, limit of detection (LOD), and limit of quantitation (LOQ).

3.3.1 Linearity& Range (Preparation of Calibration Curve):

A calibration curve was plotted, as shown in Figure 2, with the corresponding data presented in Table 3.

3.3.2 Accuracy

The accuracy of the method was assessed by calculating the recovery of Raloxifene Hydrochloride using the standard addition method. Known amounts of Raloxifene Hydrochloride (48, 60, and 72 µg/mL) from standard stock solutions were added to a pre-quantified standard sample (60 µg/mL).

Three replicates of each solution were injected into the HPLC system and analyzed using the proposed method. The amount of Raloxifene Hydrochloride was determined by measuring the peak areas and applying these values to the straight-line equation of the calibration curve, as presented in Table 5.

Table No.5: Recovery data for Raloxifene Hydrochloride

Level	Con. (µg/ ml)	Con. before spiking (µg/ml)	Con. of std add (µg/ml)	Con. after spiking (µg/ml)	% recover y	Mean	SD	% RSD
80%	60	60.6	48.0	108.6	98.75	99.84667	1.053107	1.054724
80%	60	60.9	48.0	108.9	100.85			
80%	60	60.5	48.0	108.5	99.94			
100%	60	60.4	60.0	120.4	101.36	100.6433	0.832606	0.827284
100%	60	60.8	60.0	120.8	99.73			
100%	60	60.5	60.0	120.5	100.84			
120%	60	60.2	72.0	132.2	98.77	99.71	0.878408	0.880962
120%	60	60.1	72.0	132.2	100.51			
120%	60	60.4	72.0	132.4	99.85			

The above table shows the results of recovery studies of Raloxifene Hydrochloride. The percent recovery of analyte is 99.84%, 100.64 % and 99.71 % for low, medium and high level respectively.

3.3.3 Precision

A) Inter-day Precision:

Inter-day precision refers to the measurement of the response for three different concentrations over three consecutive days. The method demonstrated precision, with %RSD values ranging from 1.77% to 1.98%, as shown in Table 6. Since the %RSD of Furosemide was less than 2%, it indicates that the developed method is precise.

Conc. (µg/ml)	Peak Area			Mean	SD	%RSD
	Day 1		Day 3			

		Day 2				
50	2467166	2517233	2429881	2471426.66	43831.58	1.77
75	2821591	2909273	2919881	2883581	53946.66	1.87
100	3094270	3100587	2992626	3062494.33	60590.13	1.98

Table No.6: Data of Inter-day precision for Raloxifene Hydrochloride

The above result shows the % RSD for precision sets for Raloxifene Hydrochloride were 1.77, 1.87 and 1.98 forlow, medium and high concentration level, which is less than 2% stated by ICH.

B) Intra-day Precision

Intra-day precision refers to the measurement of the response for three different concentrations, repeated three times within the same day. The method demonstrated precision, with %RSD values ranging from 0.29% to 1.54%, as shown in Table 7. Since the %RSD of Raloxifene Hydrochloride was less than 2%, it confirms that the developed method is precise.

Table No.7: Data of Intraday precision for Raloxifene Hydrochloride

Conc. (µg/ml)	Peak Area			Mean	SD	%RSD
	Trial 1	Trial 2	Trial 3			
50	2422585	2419881	2409273	2417246	7036.22	0.29
75	2821591	2842062	2813381	2825678	14770.8	0.52
100	3094270	3190587	3152626	3145828	48517.0	1.54

The above result shows the % RSD for intra-day precision sets for Raloxifene Hydrochloride were 1.29, 0.52 and 1.54 for low, medium and high concentration level, which is less than 2% stated by ICH.

C) Repeatability (System Stability Study)

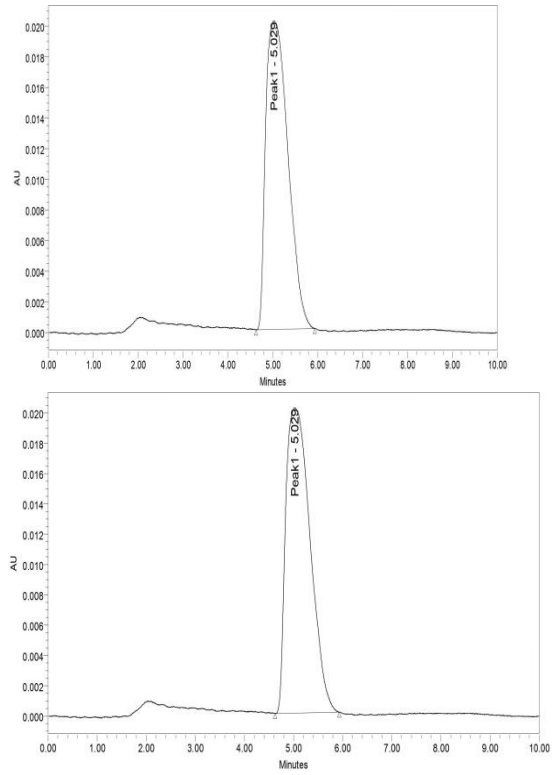
The repeatability of sample application was assessed by analyzing Raloxifene Hydrochloride (60 µg/mL) six times, and the corresponding peak areas were recorded. The percent relative standard deviation (%RSD) of the mean peak areas is presented in Table 8.

Table No.8: Repeatability Data for Raloxifene Hydrochloride

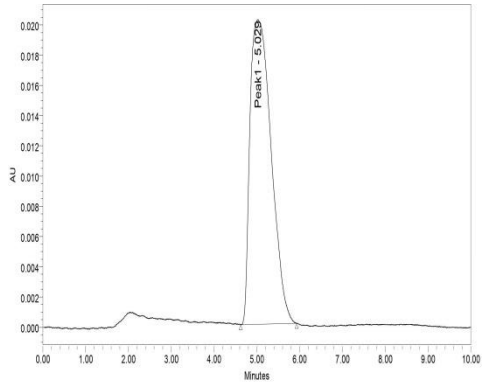
Sr.no.	Conc.(µg/ml)	AUC	Con. found. (µg/ml)	SD	%RSD
1	60	2821591	59.58	53288.81	1.90
2	60	2873048	59.81		
3	60	2842062	60.86		
4	60	2714953	59.85		
5	60	2813381	59.05		
6	60	2804454	59.49		
Mean	60	2811581.5	59.94		

The above table shows the repeatability data for Raloxifene Hydrochloride. The %RSD was found to be 1.90.

Repeatability Graphs of Raloxifene Hydrochloride-



(A)



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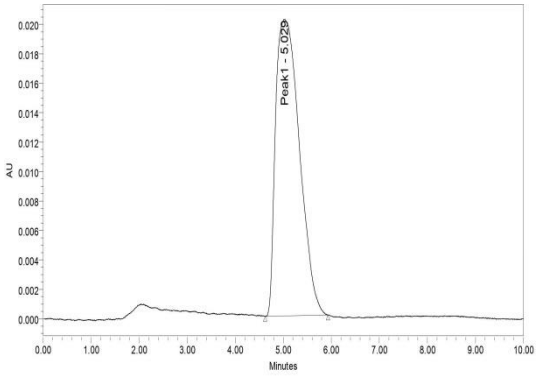

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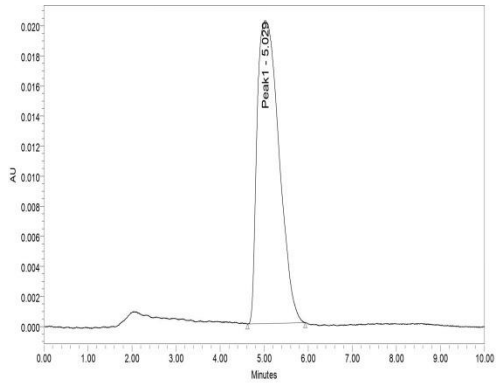

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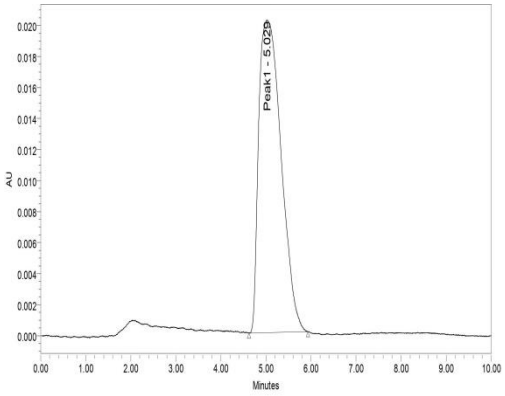

(F)

3.3.4 Specificity

Specificity refers to the ability of the method to analyze the analyte unequivocally in the presence of excipients or impurities that may cause interference. The results presented in Table 9 indicate that the recovery of the drug was above 99%, demonstrating that the developed method is specific.

Table No.9: Results of Specificity

S.No.	Amout of drug taken (µg/ml)	Amount of drug found (µg/ml)(n=3)	%amount of drug found	Mean of %amount of drug found±SD
1.	60	59.56	99.12	
2.	60	59.42	98.84	**99.06±0.53**
3.	60	59.61	99.22	

3.3.5 Robustness

To evaluate robustness, small deliberate changes were introduced to the chromatographic conditions, including variations in mobile phase composition, flow rate, mobile phase pH, column temperature, and wavelength. The effects of these changes on the results were examined.

The robustness of the method was assessed at a concentration level of 55 µg/mL of Raloxifene Hydrochloride. The mean and %RSD values of the peak areas were calculated, and the results are presented in the table-10.

Table No.10: Data for Robustness of method

S.No.	**Parameter**	**Drug**	**AUC**	**Conc.**	**% assay**	**SD**	**%RSD**
1.	MP Composition Concentration of sodium benzoate	Raloxifene Hydrochloride	2808744	53.76	99.29	0.418	0.24056
2.	MP Composition Concentration of sodium benzoate	Raloxifene Hydrochloride	2756957	50.50	97.42	0.0370	0.21706
3.	Flow Rate	Raloxifene	2809273	53.79	99.30	0.655	0.37689

	(+0.1%)	Hydrochloride					
4.	Flow Rate (-0.1%)	Raloxifene Hydrochloride	2822884	54.65	99.80	0.330	0.18894
5.	Mobile phase PH (+0.1)	Raloxifene Hydrochloride	2860424	57.02	101.15	0.173	0.09772
6.	Mobile phase PH (-0.1)	Raloxifene Hydrochloride	2802323	53.36	99.06	0.773	0.44589
7.	Coloum Temp. (+1̊C)	Raloxifene Hydrochloride	2822098	54.60	99.77	0.388	0.2222
8.	Coloum Temp. (-1̊ C)	Raloxifene Hydrochloride	2804323	53.48	99.13	0.462	0.26631
9.	Wavelength (+3nm)	Raloxifene Hydrochloride	2812209	53.98	99.41	0.388	0.22301
10.	Wavelength (-3nm)	Raloxifene Hydrochloride	28502323	56.37	100.78	0.573	0.32488

The table shows results of robustness. The robustness was found by varying several conditions i.e. M.P. composition, flow rate and wavelength. The results obtained were satisfactory so that the developed method was robust.

3.3.6 Ruggedness

Inter-day variations were assessed by performing six replicate injections of sample solutions, prepared and analyzed by different analysts on three separate days over one week. Ruggedness was evaluated in terms of %RSD, and statistical analysis showed no significant differences between the results obtained by different analysts. The findings are presented in Table 11.

Table No.11: Results of Ruggedness

S.NO.	Parameter	Concentration(µg/mL)	Peak area	Mean peak area	Standad Deviation	%RSD
1.	Analyst-1	60	2873048	2,857,555	21,910.4	0.767%
			2842062			
2.	Analyst-2	60	2714953	2,719,167	5,959.5	0.219%
			2723381			

3.3.7 Limit of Detection and Quantitation(LOD and LOQ)

Table No.12: Limit of quantification and limit of detection for Raloxifene Hydrochloride

SD of calibration curve	Mean S.D.	Slope	LOD	LOQ
182.8376	1283.822	15873	0.355907	0.700821
340.1257				
1282.346				
1476.874				
979.7643				
2615.173				

1782.851				
1951.604				

The proposed method effectively demonstrates the suitability of using a hydrotropic solution as the mobile phase in HPLC. This approach is safe, cost-effective, and eco-friendly. A 3% sodium benzoate solution was found to be optimal, providing sharp and accurate peaks for Raloxifene Hydrochloride with a retention time of 5.029 minutes. Therefore, this method can be reliably used for the analysis of marketed formulations of Raloxifene Hydrochloride.

4. Analysis of marketed formulation

An aliquot of Raloxifene Hydrochloride tablet equivalent to 10 mg of standard Raloxifene Hydrochloride was transferred into a 10 mL volumetric flask, and the volume was adjusted to 10 mL with HPLC-grade methanol, resulting in a concentration of 1000 µg/mL. The solution was sonicated for 5 minutes and filtered through a Whatman filter.

Next, a 1 mL aliquot of the above solution was transferred to a 10 mL volumetric flask, and the volume was made up with methanol to achieve a concentration of 100 µg/mL. A 0.5 mL sample was then transferred to a 10 mL volumetric flask and diluted with methanol to obtain a final concentration of 5 µg/mL.

The solution was injected into the HPLC system, which had been equilibrated with the optimized chromatographic conditions. Peak area and retention time were recorded, and quantification was carried out using the regression equation provided in Table 13.**Table No. 13:SummaryofResults.**

S. NO.	Parameters	Raloxifene Hydrochloride
	Absorption maxima(nm)	286
	Retension time(min)	5.029
	Concentration range(µg/ml)	50-400
	Regression equation(y=mx+c)	Y=15973x+51562
	Correlationcoefficient	0.9991
	Specificity	Nointerferenceofanypeaks
	Tailingfactor	1.37
	NumberofTheoreticalplates	
	Accuracy(%RSD)	
	80%	1.054724
	100%	0.827284
	120%	0.880962
	LOD(µg/ml)	0.355907
	LOQ(µg/ml)	0.700821
	Intra-day Presicion(%RSD)	
	1st run	0.29

	2nd run	0.52
	3rd run	1.54
	Interday Presicion	
	Day1	1.77
	Day2	1.87
	Day3	1.98
	Percentage recovery	99
	Robustness(%RSD)	
	Flowrate	<2
	Mobile phase composition	<2
	Ruggedness(%RSD)	
	Analyst1	**0.767%**
	Analyst2	**0.219%**

5. Conclusion

In conclusion, the proposed HPLC method using a hydrotropic solution as the mobile phase is a novel, eco-friendly, specific, accurate, precise, and robust RP-HPLC method for the determination of Raloxifene Hydrochloride, employing the concept of hydrotropy. Unlike the reported methods for Raloxifene Hydrochloride estimation, which rely on organic solvents that are toxic to the environment and expensive, the developed method uses a 3% sodium benzoate solution (pH 6.2) as the mobile phase. This avoids the need for costly and corrosive organic solvents.

The method was validated according to ICH Q2 (R1) guidelines. Detection was carried out at 286 nm using a diode array detector, with a retention time of 5.029 minutes for Raloxifene Hydrochloride. The method showed linearity over a concentration range of 50–400 µg/mL, with a correlation coefficient of 0.999. Therefore, this developed method can be effectively used for the analysis of Raloxifene Hydrochloride formulations.

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