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STABILITY INDICATING RP-HPLC METHOD FOR COMBINATION OF PSEUDOEPHEDRINE SULPHATE AND LORATADINE HYDROCHLORIDE IN PHARMACEUTICAL FORMULATION

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Keywords:

Pseudoephedrine Sulphate (PSE), Loratadine Hydrochloride (LOR), Stability indicating method, Reverse Phase - High performance liquid chromatographic (RP - HPLC), Assay

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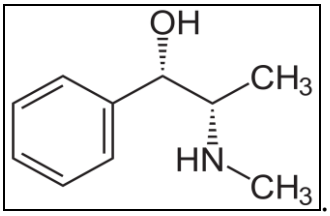
ABSTRACT: Reverse Phase - High performance liquid chromatographic (RP - HPLC) method was described for determination of Pseudoephedrine Sulphate (PSE) and Loratadine Hydrochloride (LOR). The chromatographic separation was achieved using mobile phase mixture of Acetonitrile: 0.05 M Potassium Dihydrogen Phosphate Buffer: (pH 2.8 adjusted with Ortho Phosphoric Acid Solution): Methanol in the ratio of 30:35:35 (%v/v/v) with column Zorbax Eclipse XDB C_{18}, (150 x 4.6 mm i.d), Particle size 5 µm at 1.2 ml/min flow rate. 10 µL of standard preparation containing 150 µg/ml PSE and 6.25 µg/ml LOR was injected into the column and the component was separated by carrying out elution for a run time of 10 minutes and detected at 254 nm wavelength. The described method shows excellent linearity over a range of 120 to 180 µg/ml and 5 to 7.5 µg/ml for PSE and LOR, respectively. PSE and LOR were subjected to stress degradation conditions of hydrolysis (acid and base), oxidation, Heat and UV light degradation. Stressed samples were analysed by the developed method. The proposed method was readily applied for the assay of pharmaceutical formulations and the results were found to be accepted, therefore the proposed method can be adopted for the routine analysis of any quality control laboratory.

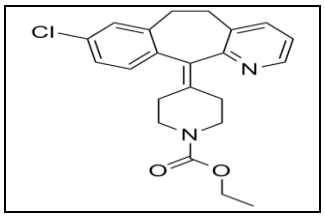
INTRODUCTION: Pseudoephedrine Sulphate with Loratadine Hydrochloride is used for the treat sneezing, runny or stuffy nose, itchy or watery eyes, hives, skin rash, itching, and other symptoms of allergies and the common cold. Pseudoephedrine Sulphate is a Vasocnstrictor agent. Its chemical name is (1S,2S)-2-(methyl amino)-1-phenylpropan-1-ol Sulphate (**Fig. 1**).



.SO_4

FIG. 1: PSEUDOEPHEDRINE SULPHATE

Loratadine Hydrochloride is an anti Histaminic and Anti allergic agent. Its chemical name is Ethyl4-{13-chloro-4-azatricyclo[9.4.0.0^{3,8}] pentadeca-1(11),3,5,7,12,14-hexaen-2-ylidene}piperidine-1-carboxylate (**Fig. 2**).



.HCl

FIG. 2: LORATADINE HYDROCHLORIDE

This combination is available in 5 mg of Loratadine Hydrochloride and 120 mg of Pseudoephedrine Sulphate dose. Thus it is inevitable to develop such a sensitive, accurate, precise, rapid and economical method for routine analysis of this combination in pharmaceutical dosage form successfully.

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MATERIALS AND METHODS:

Instrumentation: A high performance liquid chromatography system consisting of Agilent technologies 1260 infinity Module with Photo Diode Array detector was used. Chemicals were weighed using Analytical balance Mettler Toledo model MS105DU. All pH measurements were done on pH meter Systronics- model µpH System 361.

Reagents and Chemicals: HPLC grade solvents Methanol, Acetonitrile and Water, Potassium Dihydrogen Phosphate were obtained from Merck Pvt. Ltd. India. Water was deionised and further purified by means of Milli-Q plus water purification system, Millipore Ltd (U.S.A). Hydrochloride acid AR, Sodium Hydroxide AR, Hydroxide Peroxide AR Grade was obtained from Rankem Pharmaceuticals India Ltd. India.

Chromatographic Conditions and Measurement Procedure:

Buffer Preparation: Weighed and dissolved 6.8 gm Potassium Dihydrogen Phosphate Buffer into 1000 ml Water. Adjusted pH to 2.8 with Ortho Phosphoric Acid and mixed. Filtered Buffer solution through 0.45 µm filter paper under vacuum.

Preparation of Mobile Phase: Buffer Solution, Acetonitrile and Methanol was mixed in the ratio of 35:30:35 % v/v/v, sonicated to degas the mixture and used as mobile phase.

Standard Preparation: Accurately weighed PSE (600 mg) and LOR (25 mg) and transferred to a 50 ml volumetric flask. Added 25 of mobile phase and sonicated to dissolved. Volume was made up to the mark with diluent to give a solution containing 12000 µg/ml PSE and 500 µg/ml LOR. From this solution 5 ml was transfer to 100 ml volumetric flask. The volume was adjusted to the mark with the mobile phase to give a solution containing 600µg/ml PSE and 25 µg/ml LOR. From this solution further diluted 5.0 ml to 20 ml with mobile phase to prepare standard solution containing 150 µg/ml PSE and 6.25 µg/ml LOR.

Sample Preparation: Twenty tablets were weighed and finely powdered. The powder equivalent to 600 mg PSE and 25 mg LOR was accurately weighed. These PSE and LOR powder was transferred to volumetric flask of 50 ml capacity and dissolved in 25 ml of mobile phase. The flask was sonicated for 10 minute. The flask was shaken and volume was made up to the mark with mobile phase.

The above solution was filtered through whatmann filter paper (0.45µ). This solution is expected to contain PSE - 12000 µg/ml and LOR - 500µg/ml. From this, 5 ml of aliquot was taken and transferred to volumetric flask of 100 ml capacity and volume was made up to the mark with the Diluent to give a solution containing 600 µg/ml PSE and 25 µg/ml LOR. From this solution further diluted 5.0 ml to 20 ml with mobile phase to prepare solution containing 150 µg/ml PSE and 6.25 µg/ml LOR. This solution was used for the estimation of PSE and LOR.

Selection of Wavelength Maxima: The sensitivity of HPLC method that uses UV detection depends upon proper selection of detection wavelength. An ideal wavelength is the one that gives good response for the drugs that are to be detected. In the present study individual drug solutions of 150 µg/ml PSE and 6.25 µg/ml LOR were prepared in solvent mixtures of 35 volume of Water, 30 volume of Acetonitrile and 35 volume of methanol. These drug solutions were than scanned in the UV region of 200 - 400 nm and spectrum was recorded (**Fig. 3** and **4**).

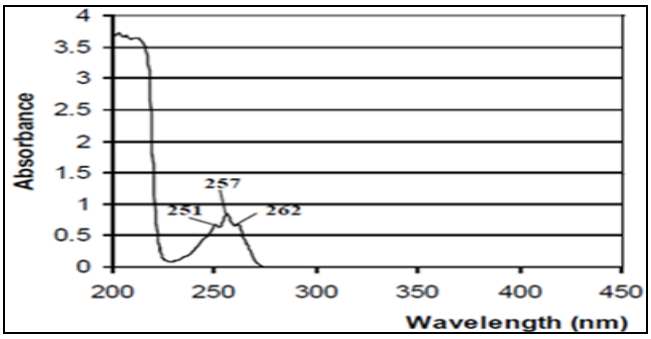

FIG. 3: UV SPECTRUMS OF PSE

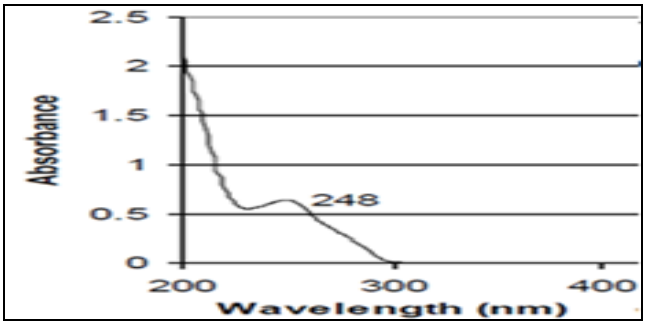

FIG. 4: UV SPECTRUM OF LOR

Method Development: By using the chromatographic conditions that were used for assay of Antihistamine drug as reference, various trials were made. Each trial mixture of known components were injected and observed for resolution and tailing factor of the peaks. Various proportions of buffer, Methanol and Acetonitrile were tried as mobile phase and 35 volume of 0.05 M Dihydrogen Phosphate Buffer (KH_2PO_4 Buffer = 6.8 gm KH_2PO_4 Buffer into 1000 ml Water and pH adjusted to 2.8 with Ortho Phosphoric Acid), 30 volume of Acetonitrile and 35 volume of methanol improved peak symmetry and resolution.

Different flow rates of the mobile phase were tried for good resolution. Both the drugs PSE and LOR were found to be soluble and stable in a mixture of 35 volume of 0.05 M Dihydrogen Phosphate Buffer (KH_2PO_4 Buffer = 6.8 gm KH_2PO_4 Buffer into 1000 ml Water and pH adjusted to 2.8 with Ortho Phosphoric Acid), 30 volume of Acetonitrile and 35 volume of Methanol. Finally the chromatographic conditions were optimized at flow rate 1.2 ml/min, injection volume of 10 µL, run time of 10 minutes, at column oven temp 50 °C with mobile phase (sonicated and degased) as diluent in a Zorbex Eclipse XDB C_{18}, (150 x 4.6 mm i.d), Particle size 5 µm.

The Retention time for both the drugs PSE and LOR were found to be 1.157 and 6.049 respectively and tailing factor was 1.16 and 1.12 for PSE and LOR respectively (**Table 1**).

TABLE 1: SYSTEM SUITABILITY TEST PARAMETER

System Suitability Parameters	Proposed Method	
	PSE	LOR
Retention times (R_t) (min)	1.157 ± 0.0025	6.049 ± 0.0220
Theoretical plates (N)	898790	15092783
Resolution (R_S)	40.257 ± 0.293	
Tailing factor (A_S)	1.16 ± 0.033	1.12 ± 0.012
Capacity factor	10.61 ± 0.072	59.42 ± 0.37

Absorption maximum was found to be 254 nm and peaks shape was good. The method was further validated under the chromatographic conditions.

Method Validation: Once chromate-graphic conditions were established, the method was validated in compliance with ICH guidelines. The following parameters like system suitability along with specificity, linearity, precision and accuracy, limits of detection and limit of quantification were performed for validation. The specificity of the method was described as the ability to discriminate the analyte from all potential interfering substances (*i.e.* excipients) in the tablet dosage form. This test was performed by recording chromatograms of placebo blank solution and drug mixture spiked in the placebo solution. The placebo blank solution was prepared by mixing the corresponding tablet excipients. It can be seen from the chromatogram, that no peaks were observed in the placebo blank solution and percentage recovery of drugs spiked in placebo blank solution indicating that no interference due the excipients for the recovery of the analytes occurred.

A study to evaluate the interference of placebo was conducted. Samples were prepared in duplicate by taking placebo equivalent to the weight present in portion of test preparation as per the test method and injected into the HPLC system. It was observed that there were no peaks interfering with the analyte peak. The chromatogram indicates that the peak is homogeneous, there is no interference from the excipients at the retention time of analyte peak and has no co-eluting peaks indicating specificity of the method. For the analytical method, determination of assay specificity was also demonstrated by performing force degradation study of placebo and drug product under various stress conditions like Acid degradation, Alkali degradation, Oxidative degradation, UV degradation and Thermal degradation.

Forced Degradation Studies:

Degradation with 3% H_2O_2: Weighed and transferred about 1250 mg of sample in to 50 mL volumetric flask. Add 5.0 mL 3% v/v Hydrogen peroxide to the flask. Store flask at 60 ºC for 1 hour. After the stipulated time period remove the flask from water bath and cool the content. Dilute to volume with diluent; mix evenly. Prepare diluent and placebo preparation simultaneously and chromatogram obtained. (150 µg/ml PSE and 6.25 µg/ml LOR) (**Fig. 4**).

Degradation with 0.1M HCl: Weighed and transferred about 1250 mg of sample in to 50 mL volumetric flask. Add 5.0 mL 0.1 M Hydrochloric acid to the flask. Store flask at 60 °C for 1 day. After the stipulated time period remove the flask from water bath and cool the content.

Add 5.0 mL 0.1 M Sodium hydroxide. Dilute to volume with diluent; mix evenly. Prepare diluent and placebo preparation simultaneously and chromatogram obtained. (150 µg/ml PSE and 6.25 µg/ml LOR) (**Fig. 5**).

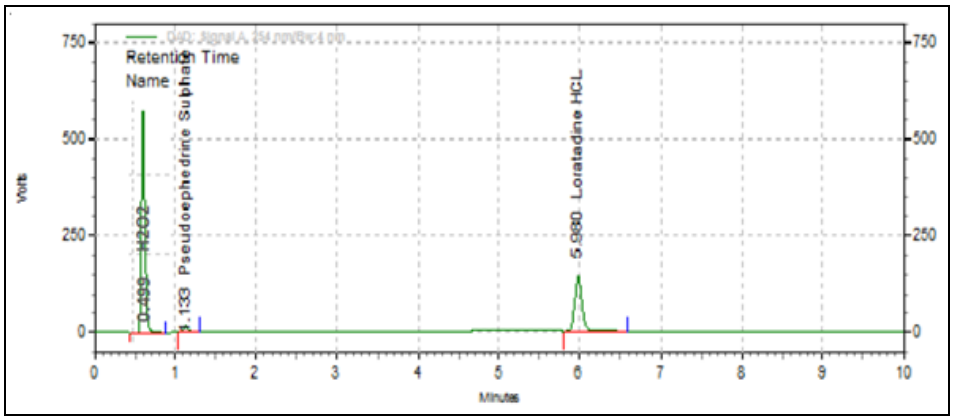

FIG. 4: CHROMATOGRAPH OF FORCED DEGRADATION STUDY ON SAMPLE SOLUTION CONTAINING PSE AND LOR USING 3 % H_2O_2 SOLUTION

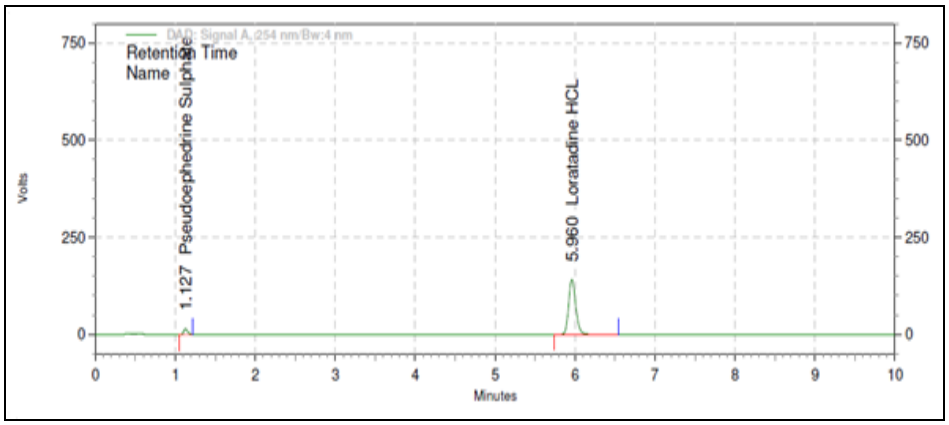

FIG. 5: CHROMATOGRAPH OF FORCED DEGRADATION STUDY ON SAMPLE SOLUTION CONTAINING PSE AND LOR USING 0.1 M HCl SOLUTION

Degradation with 0.1M NaOH: Transfer an accurately weighed quantity of about 1250 mg of sample solution in to 50 mL volumetric flask Add 5.0 mL 0.1 M Sodium hydroxide to the flask. Store flask at 60 °C for 1 day. After the stipulated time period remove the flask from water bath and cool the content. Add 5.0 mL 0.1 M Hydrochloric acid. Dilute to volume with diluent; mix evenly. Prepare diluent & placebo preparation simultaneously and chromatogram obtained. (150 µg/ml PSE and 6.25 µg/ml LOR) (**Fig. 6**).

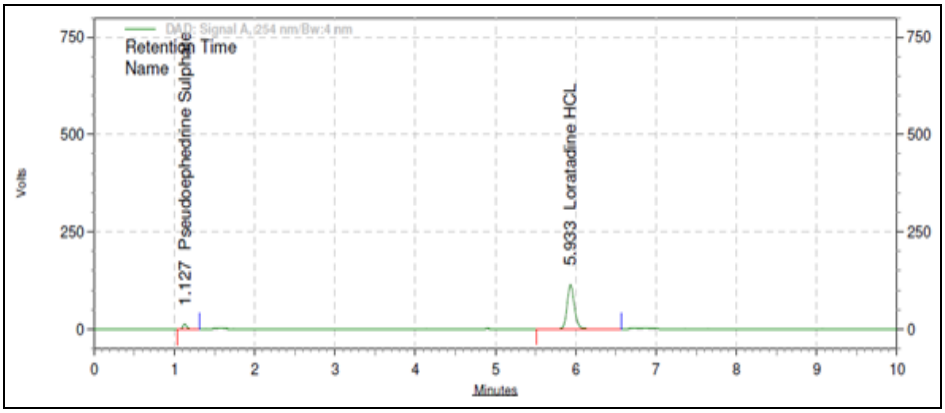

FIG. 6: CHROMATOGRAPH OF FORCED DEGRADATION STUDY ON SAMPLE SOLUTION CONTAINING PSE AND LOR USING 0.1 M NaOH SOLUTION

Exposed to Heat: Accurately weigh and transfer about 1250mg of sample exposed under heat at 80ºC for 12 hours in 50 ml volumetric flask, Add about 20 ml of mobile phase and sonicated to dissolve it completely and make volume up to the mark with mobile Phase. Dilute 2.5 ml of this solution to 50 ml with the mobile phase. Further dilute 5 ml this solution to 20 ml with mobile phase and chromatogram obtained. (150 µg/ml PSE and 6.25 µg/ml LOR) (**Fig. 7**).

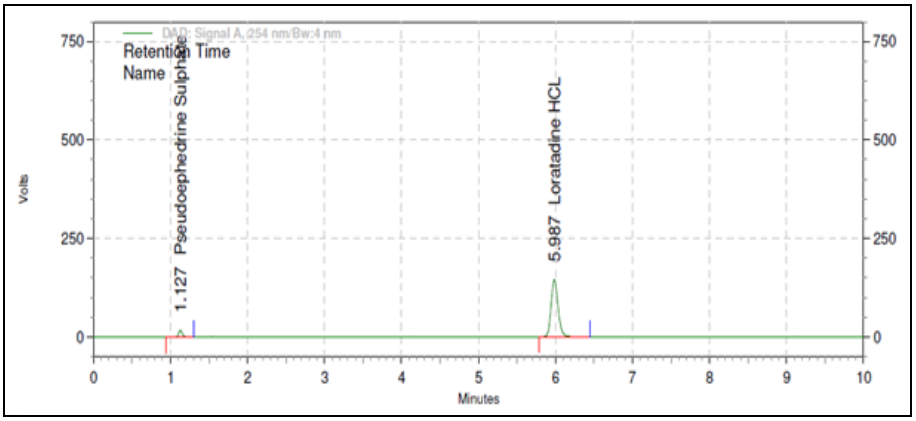

FIG. 7: CHROMATOGRAPH OF FORCED DEGRADATION STUDY ON SAMPLE SOLUTION CONTAINING PSE AND LOR USING HEAT TREATMENT

Exposed to UV Light: Accurately weigh and transfer about 1250mg of sample exposed UV radiation for 24 hours in 50 ml volumetric flask, Add about 20 ml of mobile phase and sonicated to dissolve it completely and make volume up to the mark with mobile Phase. Dilute 2.5 ml of this solution to 50 ml with the mobile phase. Further dilute 5 ml this solution to 20 ml with mobile phase and chromatogram obtained. (150 µg/ml PSE and 6.25 µg/ml LOR) (**Fig. 8**).

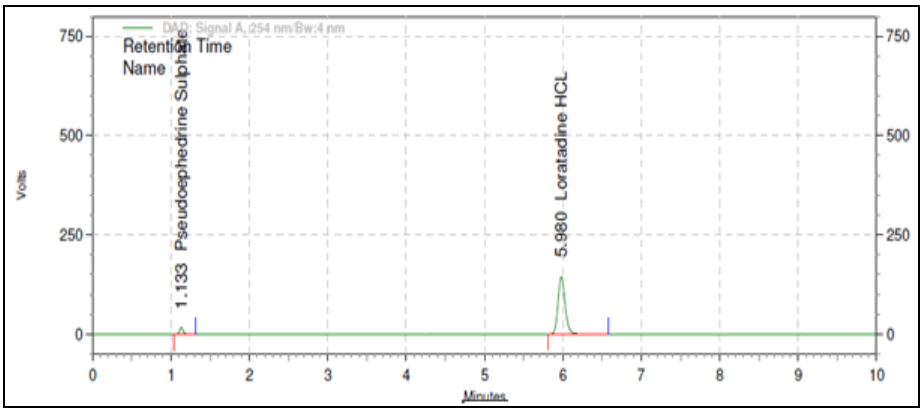

FIG. 8: CHROMATOGRAPH OF FORCED DEGRADATION STUDY ON SAMPLE SOLUTION CONTAINING PSE AND LOR USING UV LIGHT

RESULTS AND DISCUSSION:

System Suitability: The standard solution was prepared by using working standard as per the method. For six replicate injections system suitability parameters like number of theoretical plates, USP Tailing and % RSD were found to be within specified limits (**Table 2**).

TABLE 2: SYSTEM SUITABILITY TEST PARAMETER

System Suitability Parameters	Proposed Method	
	PSE	LOR
Retention times (R_t) (min)	1.157 ± 0.0025	6.049 ± 0.0220
Theoretical plates (N)	898790	15092783
Resolution (R_S)	40.257 ± 0.293	
Tailing factor (A_S)	1.16 ± 0.033	1.12 ± 0.012
RSD of all Replicates area of Standard Solution	0.45 %	0.2 %

Specificity: A study was carried out by determining peak purity. It observed that there were no peaks interfering with the analyte which was evident from the purity data.

Linearity: Linearity of detector response was established by plotting graph between concentrations versus average area counts of the analytes. Data shown in **Table 3** and represented graphically in Graph **(Fig. 9** and **Fig. 10)** indicate that the response is linear over the specified range.

TABLE 3: LINEARITY

Linearity Level (%)	Final Conc. (µg/mL)		Mean Area	
	PSE	LOR	PSE	LOR
80	120	5.000	715893	12332610
90	135	5.625	807665	13677550
100	150	6.250	902441	15390547
110	165	6.875	991879	16837735
120	180	7.500	1084638	18142250

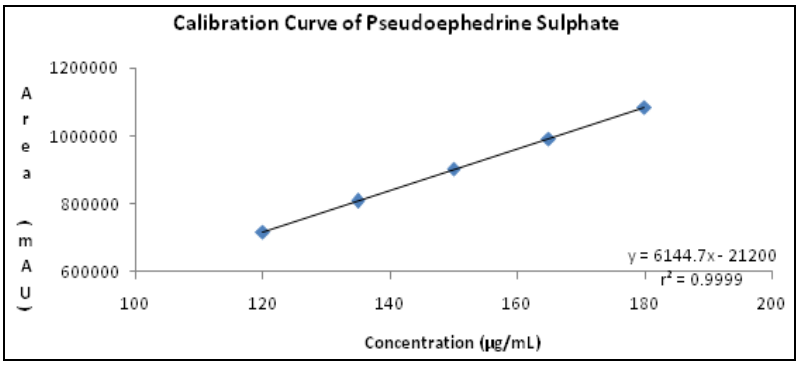

FIG. 9: CALIBRATION CURVE OF PSEUDOEPHEDRINE SULPHATE

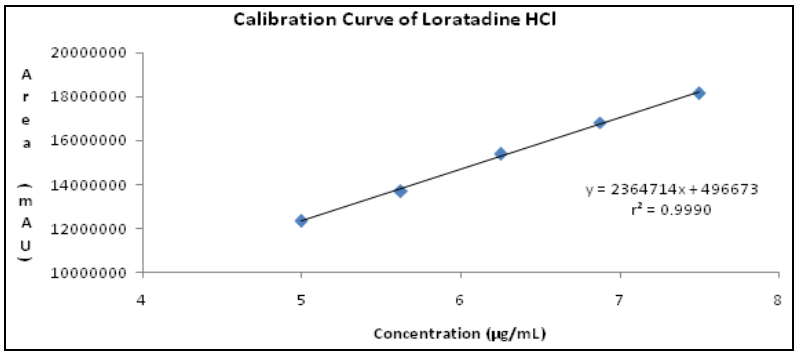

FIG. 10: CALIBRATION CURVE OF LORATADINE HCl

Accuracy: A study of accuracy (recovery) was performed on known amount of placebo by spiking active pharmaceutical ingredient. Samples were prepared as per the proposed method at 80% to 120% of the sample concentration. Data shown in **Table 4** indicate that the method has an acceptable level of accuracy.

TABLE 4: ACCURACY

Accuracy Level	Theoretical amount (ppm)		Practical amount (ppm)		% Recovery		Mean	
	PSE	LOR	PSE	LOR	PSE	LOR	PSE	LOR
80 % Set - 1	120.0	5.00	119.0	5.2	99.1	103.0	99.3	102.4
80 % Set - 2	120.0	5.00	119.2	5.1	99.4	102.0		
80 % Set - 3	120.0	5.00	119.4	5.1	99.5	102.3		
100 % Set - 1	150.0	6.25	149.1	6.3	99.4	100.2	99.3	101.8
100 % Set - 2	150.0	6.25	148.8	6.6	99.2	105.2		
100 % Set - 3	150.0	6.25	149.0	6.2	99.3	100.0		
120 % Set - 1	180.0	7.50	178.3	7.5	99.1	100.3	99.4	101.3
120 % Set - 2	180.0	7.50	180.1	7.8	100.0	103.5		
120 % Set - 3	180.0	7.50	178.2	7.5	99.0	100.2		

Precision:

System Precision: Six replicate injections of standard solution were injected into the HPLC system. The %RSD for six replicated injections was found to be in the limits.

Method Precision: The precision of test method was evaluated by analysing assay for six individual samples prepared from same batch by the proposed method. The average %Assay and the relative standard deviation for the six sample preparation were found to be in the specified limits **Table 5**.

TABLE 5: METHOD PRECISION

	Injections	Mean Area		% Assay	
		PSE	LOR	PSE	LOR
Concentration	1	894915	15312952	99.2	101.2
PSE	2	897711	15116508	99.6	99.9
(150 ppm)	3	896307	15141466	99.6	99.9
LOR	4	896363	15389241	99.5	101.8
(6.25 ppm)	5	898880	15119343	99.7	99.9
	6	894168	15176341	99.3	100.4
		Mean		99.5	100.5
		% RSD		0.20	0.80

Intermediate Precision (Ruggedness): The ruggedness of method was verified by conducting the precision study by using different HPLC, different columns of same make by different analyst on different days. Six samples of same batch were prepared and analysed by the proposed method. The mean, standard deviation, and %RSD for the two sets of data are shown in **Table 6**. Ruggedness of the method is indicated by the overall RSD between the two sets of data.

TABLE 6: INTERMEDIATE PRECISION

	Injections	Mean Area		% Assay	
		PSE	LOR	PSE	LOR
Concentration	1	895097	15170151	99.2	100.2
PSE	2	897807	15094242	99.6	99.8
(150 ppm)	3	896332	15071106	99.3	99.5
LOR	4	896267	15210892	99.5	100.6
(6.25 ppm)	5	898842	15054434	99.7	99.5
	6	894121	15148158	99.3	100.2
		Mean		99.4	100.0
		% RSD		0.20	0.44
% Difference between Method Precision and Intermediate Precision				0.1	0.5

Robustness: Robustness of the method was investigated **Table 7** by varying the instrumental conditions such as flow rate (± 0.2), column oven temperature (± 2%) and pH of buffer in mobile phase (0.2). Standard solution was prepared and analysed as per the test procedure monitored the system suitability results.

TABLE 7: ROBUSTNESS STUDY FOR PSE AND LOR

Factors		Retention time (min)		Asymmetry (A_s)		Resolution
		PSE	LOR	PSE	LOR	
pH of mobile	2.6	1.156	5.988	1.662	1.123	40.22
phase	2.8	1.157	6.049	1.160	1.120	40.25
	3.0	1.155	5.983	1.178	1.124	40.29
	Mean ± SD	1.156 ± 0.001	6.006 ± 0.036	1.333 ± 0.284	1.122 ± 0.002	40.25 ± 0.035
Temp (^{o}C)	48	1.156	6.058	1.179	1.145	40.07
	50	1.157	6.049	1.160	1.120	40.25
	52	1.155	5.924	1.170	1.142	40.22
	Mean ± SD	1.156 ± 0.001	6.010 ± 0.075	1.169 ± 0.010	1.135 ± 0.014	40.18 ± 0.096
Flow rate	1.0	1.386	6.938	1.190	1.129	40.89
	1.2	1.157	6.049	1.160	1.120	40.25
	1.4	0.989	5.313	1.147	1.129	39.25
	Mean ± SD	1.177 ± 0.199	6.100 ± 0.813	1.165 ± 0.022	1.126 ± 0.005	40.13 ± 0.826

Stability of Sample Solution: The sample solution was stable up to 24 hours and did not show any appreciable change in sample area **Table 8**.

TABLE 8: SOLVENT SUITABILITY

Time points (hour)	PSE % Difference		LOR % Difference	
	Standard Preparation	Test Preparation	Standard Preparation	Test Preparation
0 Hours	NA	NA	NA	NA
6 Hours	0.47	0.02	0.44	0.20
12 Hours	0.48	0.44	1.09	0.69
18 Hours	0.62	0.19	1.11	0.94
24 Hours	0.93	0.60	1.05	1.12

Forced Degradation Study: The Data for Forced degradation are tabulated in **Table 9**. There was no interference of any peak at the retention time of analyte peaks from blank and placebo, Peak purity of all forced degradation treated samples were passed.

TABLE 9: FORCED DEGRADATION STUDY

S. no.	Condition applied	Area		% Assay		% Degradation	
		PSE	LOR	PSE	LOR	PSE	LOR
1	Untreated Sample	810872	15489146	99.4	101.3	---	---
2	HCl Treated	789274	13892608	89.8	90.8	10.2	9.2
3	NaOH Treated	829837	13097827	91.9	85.6	8.1	14.4
4	H_2O_2 Treated	769274	12390489	85.2	81.0	14.8	19.0
5	Thermal Treated	789274	13280483	87.4	86.8	12.6	13.2
6	UV Light Treated	776302	13792073	85.9	90.2	14.1	9.8

Summary of Validation Parameters are tabulated in **Table 10**.

TABLE 10: SUMMARY OF VALIDATION PARAMETERS OF RP-HPLC

Parameters	PSE	LOR
Recovery %	99.3 – 99.4	101.8 – 102.4
Method precision	0.20	0.80
Intermediate precision	0.20	0.44
Specificity	Specific	Specific
Solvent suitability	Solvent suitable for 24 hrs	Solvent suitable for 24 hrs

Estimation of Marketed Formulation: Estimation of Marketed Formulation was carried out in **Table 11.** From this study it has been concluded that the proposed method is specific and stability indicating for the estimation of PSE and LOR, in the tablet dosage form.

TABLE 11: ASSAY RESULTS OF MARKETED FORMULATION

Formulation	Drug	Label claim (mg)	Amount Taken (µg/ml) (n = 3)	Amount Found (µg/ml) (n = 3)	% Label claim ± S.D
LORFAST-D	PSE	120	150	149.25	99.50 ± 0.26
	LOR	5	6.25	6.31	100.96 ± 0.97

CONCLUSION: This intended study can be concluded as the proposed method is simple, highly fast, economical, sensitive and reliable and is found to be more precise, accurate, specific, stability indicating, rugged and robust. Hence it can be employed for routine estimation of tablets containing PSE and LOR. Conventional reported chromatographic methods may be replaced by the proposed stability indicating HPLC method because of its superiority in cost effectiveness, short analysis time per sample and better detection. For faster samples testing routinely in QC lab the validated method may be used.

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CONFLICT OF INTEREST: Nil

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