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RP-HPLC METHOD DEVELOPMENT AND VALIDATION FOR THE SIMULTANEOUS ESTIMATION OF LEVODROPROPIZINE AND CHLORPHENIRAMINE MALEATE IN PHARMACEUTICALFORMULATIONS

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Key Words

Levodropropizine, Chloropheniramine, RP-HPLC, Validation.

ABSTRACT

Simple, accurate, precise method was developed for the simultaneous estimation of the Levodropropizine and Chlorpheniramine Maleate in syrup dosage form. Chromatogram was run through Std Kromosil C18 250 x 4.6 mm, 5µ. Mobile phase containing Buffer 0.1% OPA (2.2pH): Acetonitrile taken in the ratio 50:50 was pumped through column at a flow rate of 0.8 ml/min. Buffer used in this method was 0.1% OPA. Temperature was maintained at 30°C. Optimized wavelength selected was 215 nm. Retention time of Levodropropizine and Chloropheniramine were found to be 2.250 min and 3.588 min. %RSD of the Levodropropizine and Chloropheniramine were and found to be 0.2 and 0.5 respectively. %Recovery was obtained as 99.30% and 99.45% for Levodropropizine and Chloropheniramine respectively. LOD, LOQ values obtained from regression equations of Levodropropizine and Chloropheniramine were 0.15, 0.44 and 0.03, 0.09 respectively. Regression equation of Levodropropizineis y = 19120x + 12415. And y = 30379x + 1297. of Chloropheniramine. Retention times were decreased and run time was decreased, so the method developed was simple and economical that can be adopted in regular quality control test in Industries.

INTRODUCTION:

Chlorpheniramine is a histamine H1 antagonist used been used in veterinary applications. One of the most widely used of the classical antihistaminic, it generally causes less drowsiness and sedation than promethazine. In allergic reactions, hay fever, rhinitis, urticaria, and asthma. Chemically it is [3-(4- chlorophenyl)-3-(pyridin-2-yl) propyl] dimethylamine. Molecular formula is ($C_{16}H_{19}ClN_2$). Mechanism of action of Chlorpheniramine ties to the histamine H1 receptor. These obstructs the activity of endogenous histamine, which in this way prompts brief alleviation of the negative indications expedited byhistamine [5].

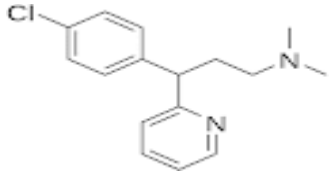


Figure.1: Structure of Chlorpheniramine

Levodropropizineis under investigation in clinical trial NCT01573663 (A Drug-Drug Interaction Study of Ambroxol and Levodropropizine). Molecular formula: $C_{13}H_{20}N_2O_2$. Chemical Name: (-) - (S)-3-(4-Phenyl-1-piperazinyl)-1,2-propanediol. Mechanism of action of Levodropropizineis the levo- rotatory(S)-enantiomer of dropropizine, a racemic non-opiate antitussive agent. Levodropropizine acts throughamainlyperipheraltracheobronchialantitussiveeffectbyinhibitionofvagalC-fibreand itssensor neuro peptide[6].

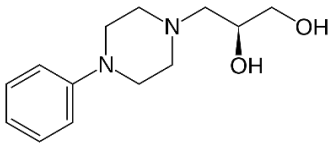


Figure.2: Structure of Levodropropizine

Literature survey the various work carried out on the topic reviewed, and several analytical methods for combination dosage forms of contain Levodropropizine and Chlorpheniramine by RP-HPLC Technique. So, there is no reported method of analysis by High Performance Liquid Chromatography for determination of syrup dosage form containing Levodropropizine and Chlorpheniramine. Hence, HPLC method in the present work and validated.[1-4]

Materials and Methods:

Levodropropizine and Chloropheniramine pure drugs (API), Combination Levodropropizine and Chloropheniramine syrup (RESWAS) dosage form were obtained from Dr. Reddy's Laboratories, HPLC grade water, Acetonitrile-HPLC grade, Phosphate buffer, Methanol, Potassium dehydrogenate ortho phosphate buffer-AR grade, Ortho-phosphoric acid-AR grade. All the above chemicals and solvents are from Rankem.

Instrumentation: Analysis was carried out in WATERSHPLC2695 System furnished with quaternary pumps, PDA Detector and Auto sampler incorporated with Empower 2 Software. Separation has been carried out using Std Kromosil C18 (4.6 x 250 mm, 5µm) column.

Preparation of test stock solution: Syrup equivalent to 30mg Levodropropizine and 2mg of Chloropheniramine was transferred into a 50 ml volumetric flask, 20 ml of diluents was added and sonicatedfor25min, further the volume was made up with diluent and filteredby HPLC filters (600µg/ml of Levodropropizine and 40 µg/ml ofChloropheniramine).

Preparation of Sample working solutions (100% solution): 1 ml of filtered test stock solution was transferredto10mlvolumetricflaskandmade upwithdiluent.(60µg/mlofLevodropropizineand4µg/ml of Chloropheniramine).

Method Validation: System suitability variables: The system suitability variable was estimated by preparing standard solutions of Levodropropizine (60 ppm) and Chloropheniramine (4 ppm) and the solutions were injected 6 times and the variableslikepeaktailing, resolution and USP plate count were estimated. The % RSD for the area of 6 standard injections results should not be more than2%.

Specificity: Checking of the interference in the optimized method. We should not find interfering peaks in blank and placebo at retention times of these drugs in this method. So, this method was said to be specific.

Precision:

Preparation of test stock solutions: Syrup equivalent to 30 mg Levodropropizine and 2 mg of Chloropheniramine was transferred into a

50 ml volumetric flask, 20 ml of diluents was added and sonicatedfor25 min, further the volume was made up with diluents and filtered by HPLC filters (600µg/ml of Levodropripazine and 40 µg/ml of Chloropheniramine).

Preparation of Sample working solutions (100% solution): 1 ml of filtered sample stock solution was transferred to 10 ml volumetric flask and made up with diluent. (60 µg/ml of Levodropropizine and 4 µg/ml of Chloropheniramine)

Linearity: From the standard stock solution (600 µg/ml of Levodropropizine and 40 µg/ml of Chloropheniramine) prepare fallowing concentrations.

25% Standard solution: 0.25ml every from two standard stock solutions was pipetted out and made up to 10 ml. (15 µg/ml of Levodropropizine and 1 µg/ml of Chloropheniramine)

50% Standard solution: 0.5ml every from two standard stock solutions was pipetted out and made up to 10 ml. (30 µg/ml of Levodropropizine and 2 µg/ml of Chloropheniramine)

75% Standard solution: 0.75ml every from two standard stock solutions was pipetted out and made up to 10 ml. (45 µg/ml of Levodropropizine and 3 µg/ml of Chloropheniramine)

100% Standard solution: 1 ml every from two standard stock solutions was pipetted out and made up to 10 ml. (60 µg/ml of Levodropropizine and 4 µg/ml of Chloropheniramine)

125%Standardsolution:1.25mleveryfro mtwostandardstocksolutionswaspipettedo utandmadeup to 10 ml. (75 µg/ml of Levodropropizine and 5 µg/ml ofChloropheniramine)

150% Standard solution: 1.5 ml every from two standard stock solutions was pipetted out and made up to 10 ml (90 µg/ml of Levodropropizine and 6 µg/ml of Chloropheniramine)

Accuracy:

Preparation of Standard stock solutions: Accurately weighed 30 mg of Levodropropizine, 2mg of Chloropheniramine and transferred to independent 50ml volumetric flasks separately. 75%ofdiluentswas added to both of these flasks and sonicated for 10minutes.Flaskswerемadeupwithdiluent sandlabelled as Standard stocksolution1and2.(600µg/ml of Levodropropizine and 40µg/ml of Chloropheniramine)

Preparation of 50% Spiked Solution: 0.5 ml of sample stock solution was taken into a10ml volumetric flask, tothat1ml fromeverystandardstocksolutionwaspipett edout, and madeuptothe markwithdiluent.

Preparation of 100% Spiked Solution: 1 ml of sample stock solution was taken into a 10 ml volumetric flask,tothat1mlfromeverystandardstocksolutionwaspipettedout,andmadeuptothe markwithdiluent.

Preparationof150%SpikedSolution:1.5 mlofsamplestocksolutionwastakenintoa10 mlvolumetric flask, to that 1ml from every standard stock solution was pipetted out, and made up to the mark with diluent.

Acceptance Criteria: The % Recovery for every level should be between 98.0 to 102.0

Robustness: Little ponder changes in, temperature less (25°C) and temperature in addition to (35°C) was kept up strategy like stream rate, portable stage proportion, and temperature are made yet there was no perceived change in the outcome and are inside range according to ICH rules. Strength conditions like Flowless(0.9ml/min), Flow in additionto (1.1ml/min), portable stage less, versatile

stage in addition and tests were infusedin copy way. Frameworkreasonablenessvariableswerev erylittleinfluencedandevery one of the variables were passed. %RSD was inside the breakingpoint.

LOD sample Preparation: 0.25 ml every from two standard stock arrangements was pipetted out and exchanged to two separate 10 ml volumetric carafes and made up with diluents. From the above arrangements 0.1 ml every one of Levodropropizine, Chloropheniramine, arrangements separately were exchanged to 10 ml volumetric cups and made up with similardiluents.

LOQsamplePreparation:andexchangedt otwoseparate10mlvolumetric jarand madeupwithdiluent. From the above arrangements 0.3 ml every one of Levodropropizine, Chloropheniramine, and arrangements separately were exchanged to 10 ml volumetric jars and made up with a similardiluent.

Degradation studies:

Acid Degradation Studies: To 1ml of stock solution of Levodropropizine and Chloropheniramine, 1 ml of2NHCLwasaddedandkeptfor 30minsat600c.Theobtainedsolutionwasdil utedtoobtain35µg/ml, 30 µg/ml and 100 µg/ml of all constituent and 10 µl solutions were injected into the HPLC and the chromatograms were note to estimation the stability of thetest.

Alkali Degradation Studies: To 1ml of stock solution of Levodropropizine and Chloropheniramine,1ml of 2N NaOH were added and kept for 30 mins at 600c. The obtained solution was diluted to obtain 35µg/ml,30 µg/mland 100 µg/mlofallconstituentand10 µlsolutionswereinjectedintotheHPLCandt he chromatograms were note to estimation the stability of thetest.

Oxidation: To 1ml of stock solution of Levodropropizine and Chloropheniramine, 1 ml of 20% H_2O_2 was added individually. The solutions were kept for 30 min at 600 c. The obtained solution was diluted to obtain 35µg/ml, 30µg/ml and 100µg/ml of all constituent and 10 µlsolutions were injected into the HPLC and the chromatograms were note to estimation the stability of thetest.

Dry Heat Degradation Studies: The standard drug solution was placed in oven at 1500c for one hour to monitor dry heat degradation. For HPLC analysis, the obtained solution was diluted to get 35µg/ml, 30µg/ml and 100µg/ml of all constituent and 10µl solutions were injected into the HPLC and the chromatograms were note to estimation the stability of the test.

Photo Stability Studies: The photo chemical stability of the drug was also studied by exposing the 250µg/ml, 800 µg/ml and 200 µg/ml solution to UV Light by keeping the beaker in UV chamber for 1 day or 200-Watt hour/m2 in photo stability chamber for HPLC study, the obtained solution was diluted to get35µg/ml,30µg/m land100µg/ml of all constituent and 10µl solutions were injected into the HPLC and the chromatograms were note to estimation the stability of thetest.

Neutral Degradation Studies: Stress testing under neutral conditions was studied by refluxing the drug in water for 6 hours at a temperature of 600c. For HPLC study, the obtained solution was diluted to get 35µg/ml,30µg/mland 100µg/mlofallconstituentand10µlsolution swereinjected intothesystemand the chromatograms were note to estimation the stability of thetest.

RESULTS AND DISCUSSION

Method Optimization:

Chromatographic conditions:

Mobile phase: 50% 0.1% OPA buffer: 50%Acetonitrile
Flowrate: 0.8ml/min
Column: Std Kromosil C18 (4.6 x 250mm,5µm)
Detector wavelength: 215 nm
Column temperature: 30°C
Injection volume: 10µl
Runtime: 5 min
Results: Both peaks show acceptable USP tailing factor, Theoretical plate count and resolution.

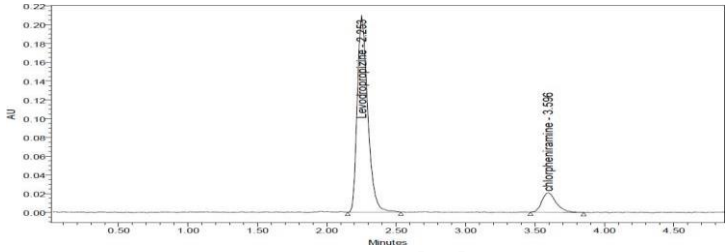


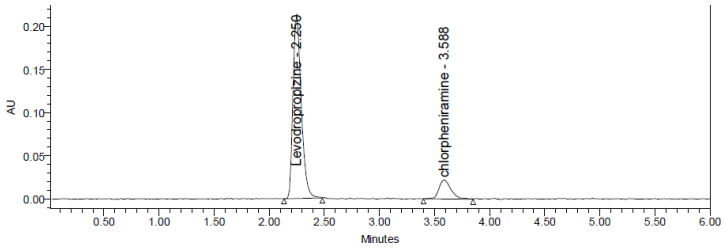
Figure.3: Optimized Chromatogram

System suitability: All the system suitability variables were within the limits and acceptable as per ICH guidelines

Table.1: System suitability variables for Levodropropazine and Chloropheniramine

S. no	Levodropropazine			Chloropheniramine			
Inj	RT (min)	USP Plate Count	Tailing	RT (min)	USP Plate Count	Tailing	Resolution
1	2.249	4148	1.32	3.588	6429	1.31	8.4
2	2.250	4032	1.33	3.588	5899	1.41	8.0
3	2.256	4425	1.34	3.597	6098	1.25	8.2
4	2.258	4494	1.32	3.598	5872	1.39	8.0
5	2.258	4505	1.32	3.599	6926	1.16	8.1
6	2.262	4519	1.28	3.601	6766	1.39	8.1

Figure.4: System Suitability Chromatogram



Specificity:

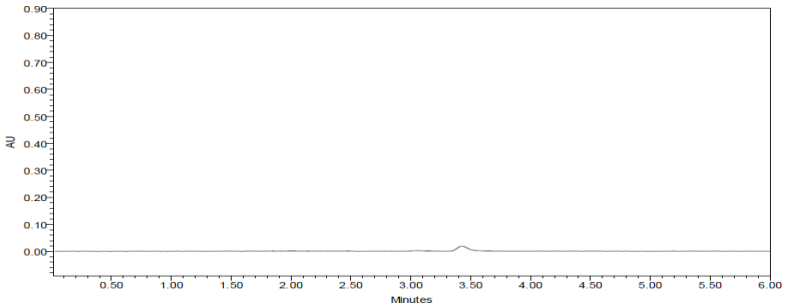


Figure.5: Chromatogram of blank

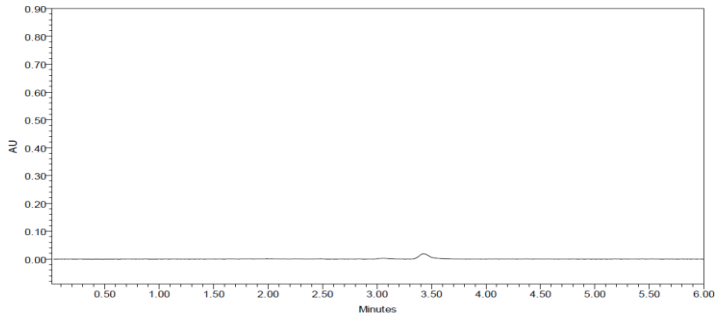


Figure.6: Chromatogram of placebo

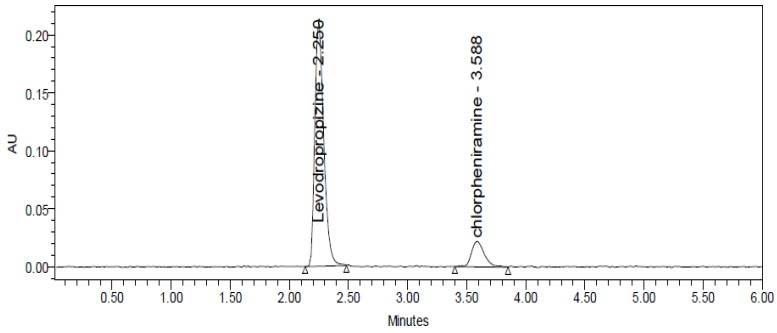


Figure.7: Optimized chromatogram

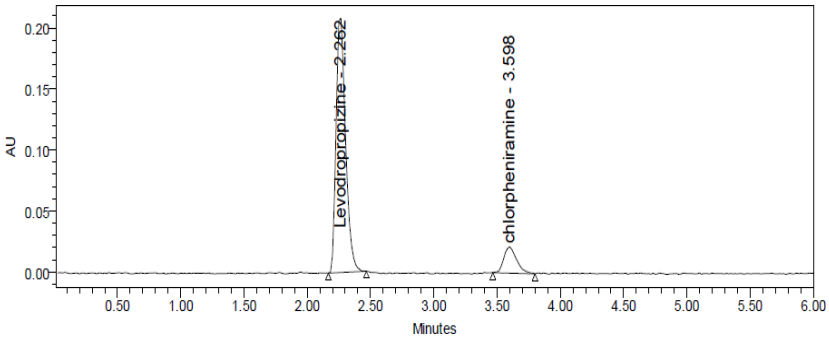


Figure.8: System precision chromatogram

Precision: System Precision:

Table.2: System precision table of Levodropropazine and Chloropheniramine

S. No	Area of Levodropropazine	Area of Chloropheniramine
1.	1187241	127537
2.	1193731	125563
3.	1179080	125508
4.	1196379	125681
5.	1184070	127869
6.	1189432	126739
Mean	1188322	126483
SD	6325.6	1052.4
%RSD	0.5	0.8

Table.3: Linearity table for Levodropropazine and Chloropheniramine.

Levodropropazine		Chloropheniramine	
Conc (µg/mL)	Peak area	Conc (µg/mL)	Peak area
0	0	0	0
15	319483	1	32088
30	576718	2	61487
45	883921	3	93447
60	1159098	4	125947
75	1424619	5	151893
90	1745954	6	182179

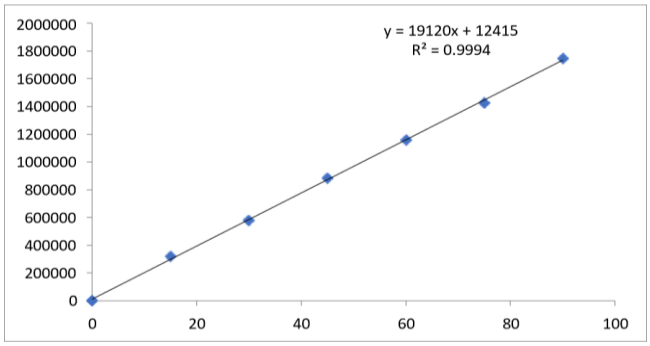


Figure.9: Calibration curve ofLevodropropazine

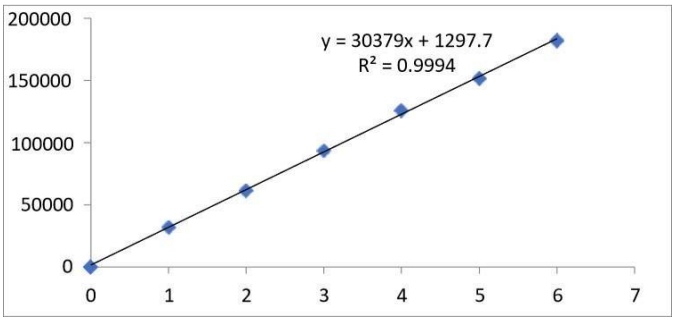


Figure.10: Calibration curve ofChloropheniramine

Repeatability:

Table.4: Repeatability table of Levodropropazine and Chloropheniramine

S. No	Area of Levodropropazine	Area of Chloropheniramine
1.	1185768	126564
2.	1188518	125892
3.	1182670	124635
4.	1185217	125889
5.	1182100	125944
6.	1183430	125355
Mean	1184617	125713
SD	2384.9	652.8
%RSD	0.2	0.5

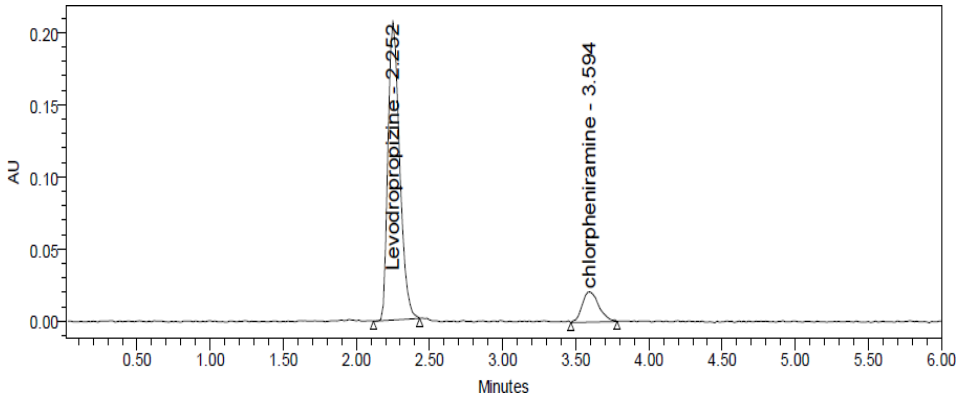


Figure.11: Repeatability chromatogram

Intermediate precision:

Table.5: Intermediate precision table of Levodropropazine and Chloropheniramine

S. No	Area of Levodropropazine	Area of Chloropheniramine
1.	1142541	123686
2.	1143272	121371
3.	1121506	123126
4.	1136047	122811
5.	1142215	123467
6.	1131153	121178
Mean	1136122	122607
SD	8576.4	1075.6
%RSD	0.8	0.9

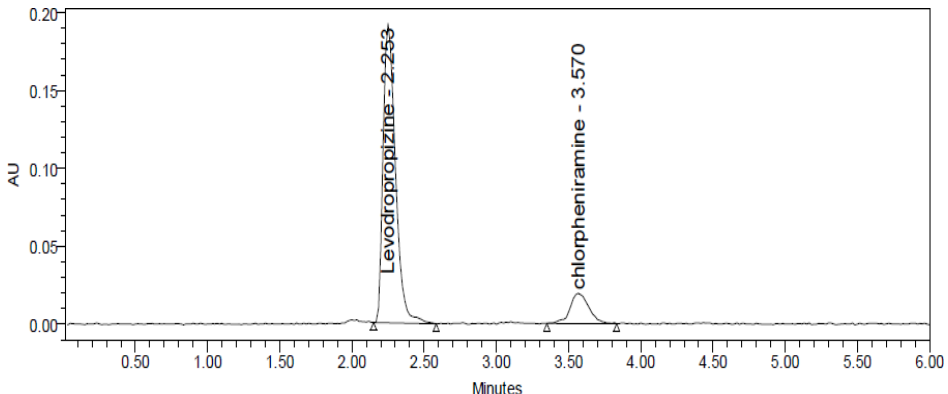


Figure.12: Intermediate precision Chromatogram

Accuracy:

Table.6: Accuracy table of Levodropropazine

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	30	29.88	99.61	99.45%
	30	29.89	99.65	
	30	29.85	99.49	
100%	60	59.91	99.85	
	60	59.58	99.29	
	60	59.97	99.96	
150%	90	89.50	99.45	
	90	89.41	99.34	
	90	88.58	98.42	

Table.7: Accuracy table of Chloropheniramine

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	2	2.00	99.90	99.30%
	2	1.98	98.95	
	2	1.98	99.19	
100%	4	3.95	98.64	
	4	3.98	99.48	
	4	3.97	99.17	
150%	6	5.96	99.26	
	6	6.00	99.94	
	6	5.95	99.13	

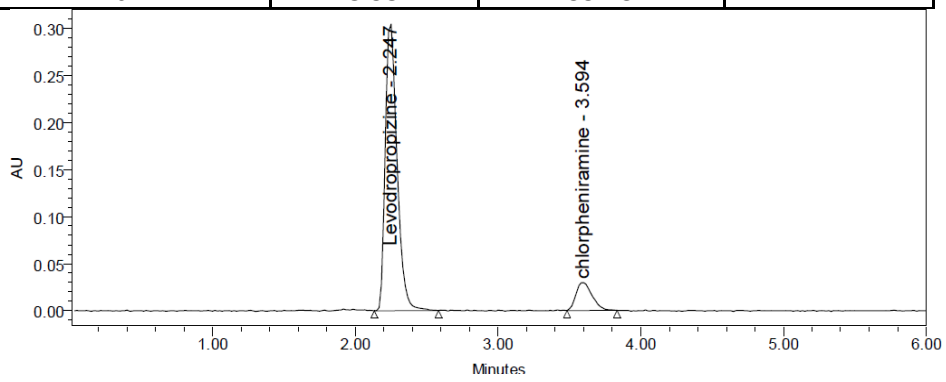


Figure.13: Accuracy 50% Chromatogram

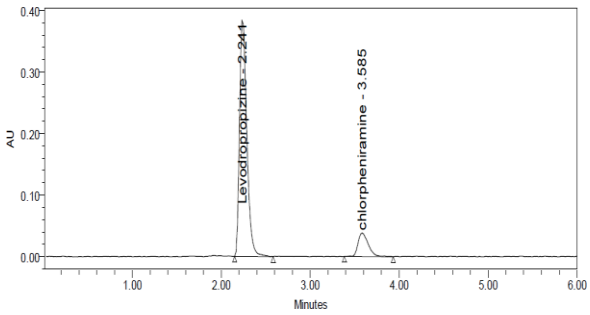


Figure.14: Accuracy100%Chromatogram

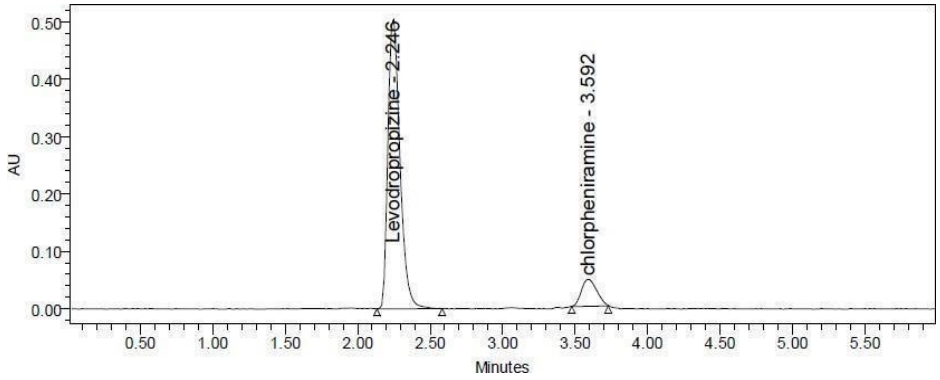


Figure.15: Accuracy150%Chromatogram

Sensitivity:

Table.8: Sensitivity table of Levodropropazine and Chloropheniramine

Molecule	LOD (µg/mL)	LOQ (µg/mL)
Levodropropazine	0.15 µg/mL	0.44 µg/mL
Chloropheniramine	0.06 µg/mL	0.09 µg/mL

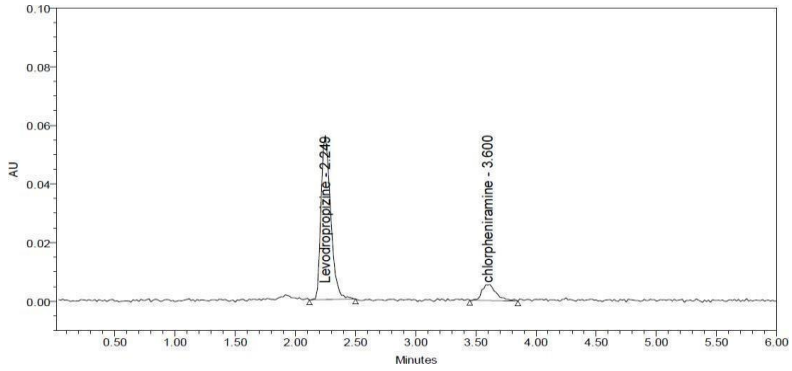


Figure.16: LOD Chromatogram of Standard

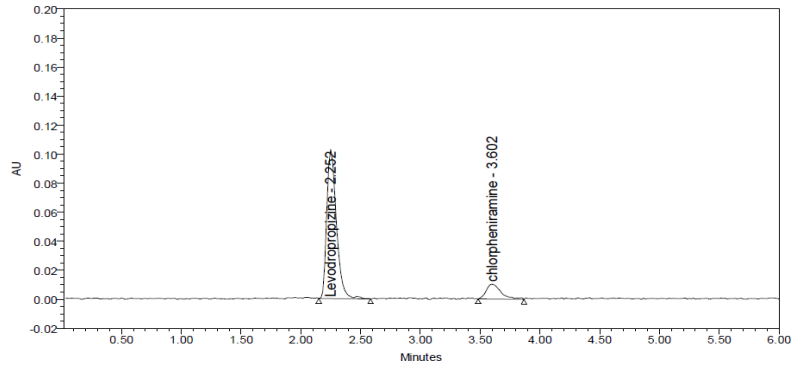


Figure.17: LOQ Chromatogram of Standard

Table.9: Robustness data for Levodropropazine and Chloropheniramine.

S.No	Condition	%RSD of Levodropropazine	%RSD of Chloropheniramine
1	Flow rate (-) 0.7ml/min	0.5	0.3
2	Flow rate (+) 0.9ml/min	0.8	0.8
3	Mobile phase (-) 45B:55A	1.0	0.7
4	Mobile phase (+) 55B:45A	0.6	0.5
5	Temperature (-) 25°C	0.9	0.9
6	Temperature (+) 35°C	0.7	0.3

Robustness

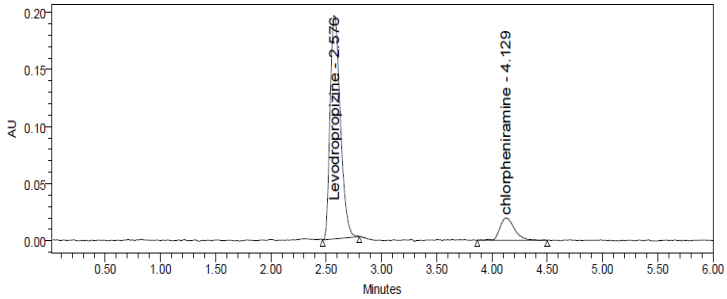


Figure.18: Flow minus Chromatogram

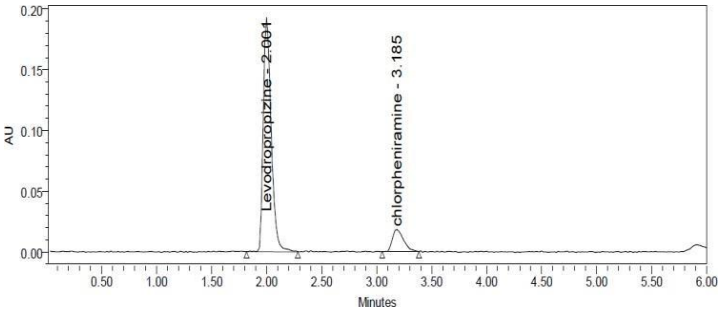


Figure.19: Flow plus Chromatogram

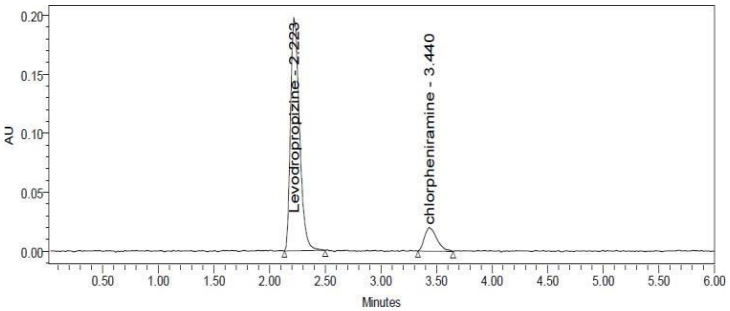


Figure.20: Mobile phase minus Chromatogram

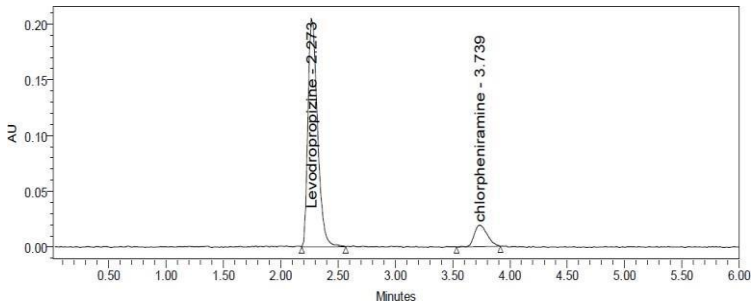


Figure.21: Mobile phase Plus Chromatogram

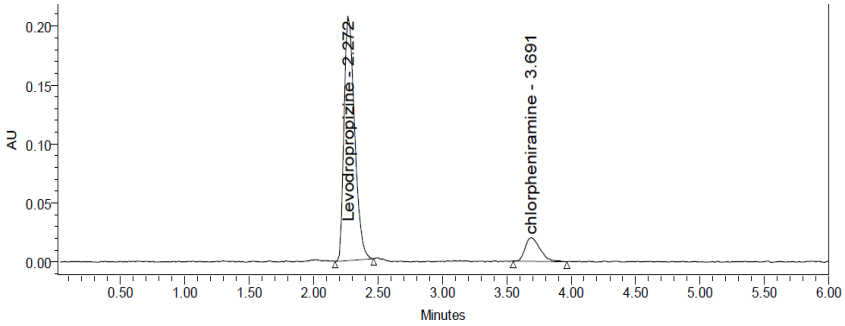


Figure.22: Temperature minus Chromatogram

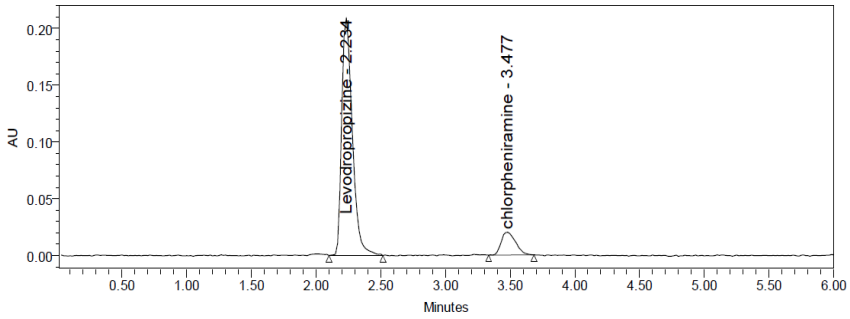


Figure.23: Temperature plus Chromatogram

Table.10: Assay Data of Levodropropazine

S.no	Standard Area	Sample area	% Assay
1	1187241	1185768	99.69
2	1193731	1188518	99.92
3	1179080	1182670	99.42
4	1196379	1185217	99.64
5	1184070	1182100	99.38
6	1189432	1183430	99.49
Avg	1188322	1184617	99.59
St dev	6325.6	2384.9	0.20
%RSD	0.5	0.2	0.20

Table.11: Assay Data of Chloropheniramine

S. no	Standard Area	Sample area	% Assay
1	127537	126564	99.96
2	125563	125892	99.43
3	125508	124635	98.44
4	125681	125889	99.43
5	127869	125944	99.47
6	126739	125355	99.01
Avg	126098	125713	99.29
St dev	1052.4	652.8	0.52
%RSD	0.8	0.5	0.5

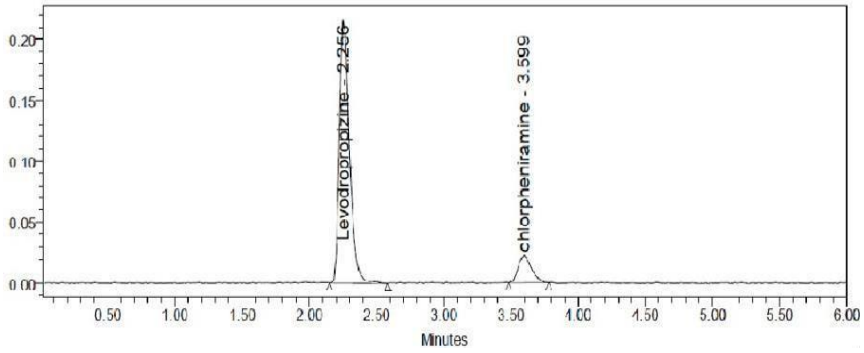


Figure.24: Chromatogram of working standard solution

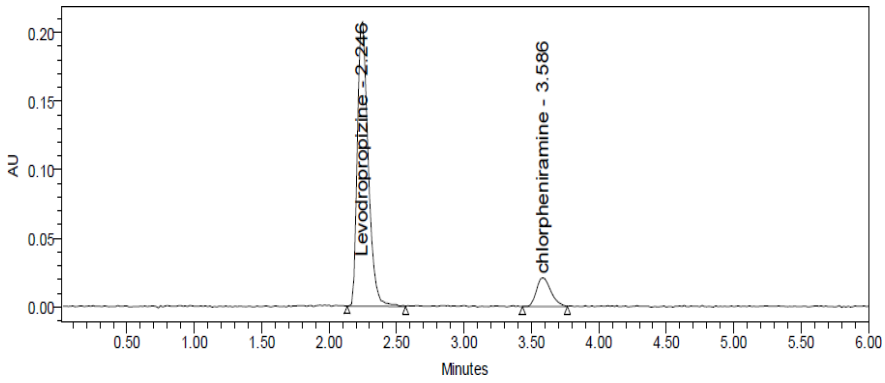


Figure.25: Chromatogram of working sample solution

Table.12: Degradation data

Type of degradation	Levodropropazine			Chloropheniramine		
	Area	% recovered	% degraded	Area	% recovered	% degraded
Acid	1119893	94.15	5.85	119832	94.65	5.35
Base	1138960	95.75	4.25	120979	95.55	4.45
Peroxide	1153746	96.99	3.01	122112	96.45	3.55
Thermal	1165490	97.98	2.02	123282	97.37	2.63
Uv	1168436	98.23	1.77	124880	98.63	1.37
Water	1179282	98.23	1.77	125614	99.21	0.79

Degradation chromatograms:

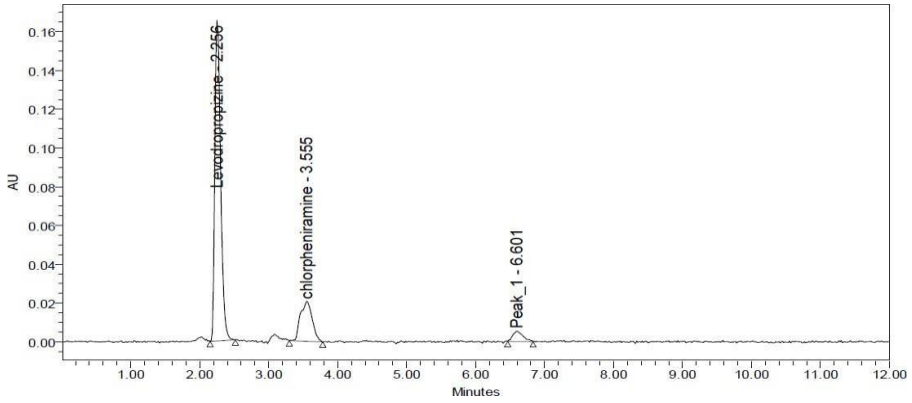


Figure.26: Aciddegradation chromatogram

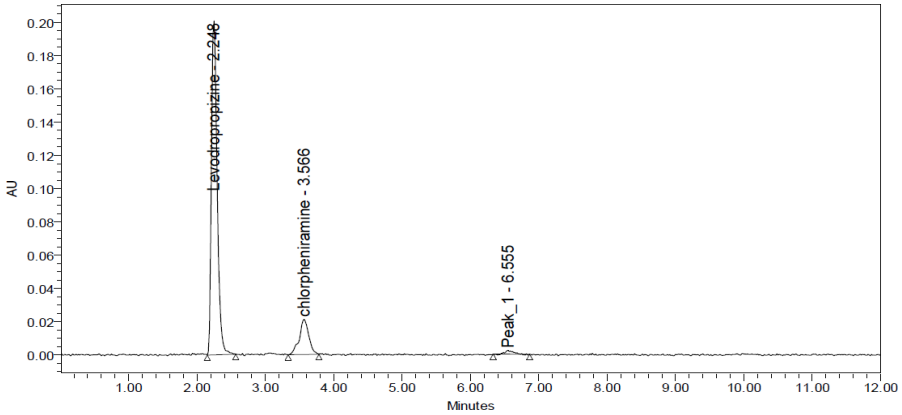


Figure.27: Base degradation chromatogram

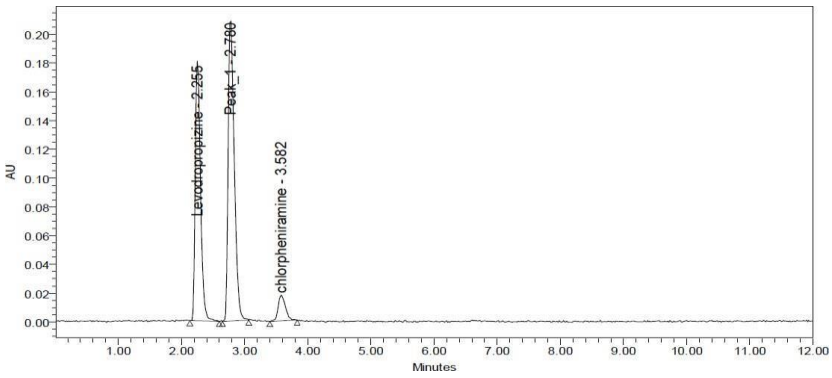


Figure.28: Peroxide degradationchromatogram

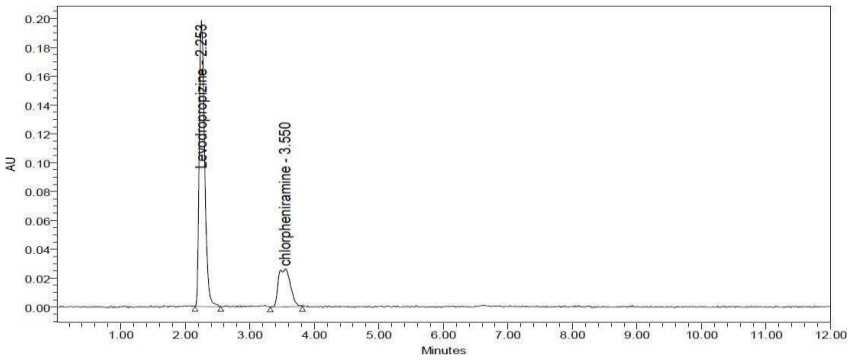


Figure.29: Thermal degradationchromatogram

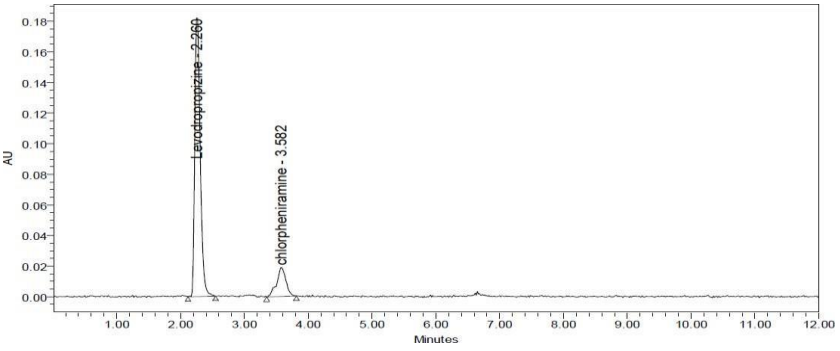


Figure.30: UV degradation chromatogram

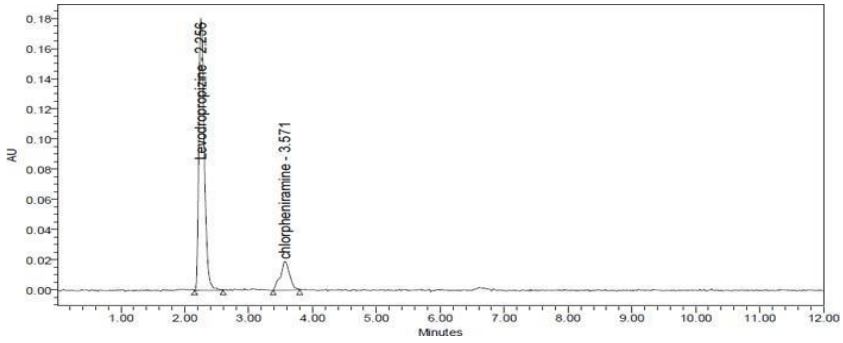


Figure.31: Water degradation chromatogram

Method validation:

System suitability: Asper to ICH limits plate count should be greater than 2000, tailing factor should be less than 2 and resolution must be greater than 2. All the system suitable variables were passed and were within the range. Show in Table 1 and Figure 4.

Specificity: Retention times of Levodropropizine and Chloropheniramine were2.250 min and 3.588 min jointly. We did not find disturb peaks in blank and placebo at retention times of these drugs in this technique. So, this technique was said to be exactly. Show in Figures5,6,7.

Precision: From a single volumetric flask of working standard solution 6 injections were given and the acquire areas were disclosing above. Average area, SD and% RSDwerecalculatedfor two drugs. % RSD gained as 0.5% and 0.8% jointly for Levodropropizine and Chloropheniramine.AsthelimitofPrecisionwaslessthan"2"thesystemprecisionwaspassed in this method. Show in Table 2 and Figure8.

Linearity: Six linear concentrations of Levodropropizine (15-90µg/ml) and Chloropheniramine (1-6µg/ml) were injected in a duplicate manner. Average areas were mentioned above and linearity equations obtained for Levodropropizine was y = 19120x + 12415 and of Chloropheniramine was y = 30379x + 1297.7 Correlation coefficient obtained was 0.9994 for the two drugs. Show in Table 3 and Figures 9,10.

Repeatability: Various testing froman example stock arrangement was done and six working example arrangements of same fixations were readied, every infusion from every working examplearrangementwasgivenandgotregionswe resaidintheabovetable.Normalterritory, standard deviation and % RSD were figured for two medications and acquired as 0.2% and 0.5% separately for Levodropropazine and Chloropheniramine. As the point ofconfinement of Precision was under "2" the framework accuracy was passed in this strategy. Show in Table 4 and Figure11.

Intermediate precision: Several sampling from a test stock solution was done and 6 working test solutions of same concentrations were prepared, every injection from every working test solution was given on the next day of the test preparation and acquire areas were disclose in theabovetable.Averagearea,SDand%RSDwerecalculatedfor2drugsandacquireas0.8% and 0.9% jointly for Levodropropazine and Chloropheniramine. As the limit of Precision was < "2" the system precision was preceded in this technique. Show in Table 5 and Figure 12.

Accuracy: Three levels of Accuracy samples were prepared by standard addition technique. 3 injections were given for every level of accuracy and mean % Recovery was acquired as 99.45% and 99.30% for Levodropropizine and Chloropheniramine jointly. Show in Tables6,7 and Figures13,14,15.

Sensitivity: The LOD and LOQ chromatograms were prepared and acquire. The LOD of Levodropropizine and Chloropheniramine were found to be 0.15µg/mL and 0.06µg/mL and LOQ was found to be 0.44µg/mL and 0.09µg/mL. As the limit of LOD and LOQ was NMT 3 µg/mLandNMT10µg/mLjointly.So,thesystemwaspassedinthistechnique.ShowinTable 8 and Figures16, 17.

Robustness: Robustness variables like Flow minus (0.9ml/min), Flow plus (1.1ml/min), mobile phase minus (45B:55A), mobile phase plus (55B:45A), temperature minus (25°C) and temperature plus (35°C) was carry on and tests were injected in duplicate manner. System suitability variables were not much overdone and all the variables were passed. %RSD was within the range. Show in Table 9 and Figures 18, 19, 20,21,22,23.

Assay: The label claim Levodropropizine 30mg, Chloropheniramine 2mg. Assay was do with theabovedosageform.Average%assayforLevodropropizineandChlorophenirameneacquire was

99.59% and 99.29% jointly. Show in Tables 10,11 and Figures24,25.

Degradation studies: It was evaluated by using the different stress conditions like acid, base, peroxide, thermal, UV and water to assess the degradation. Calculated their degradation in terms of %. Show in Table 12 and Figures 26,27,28,29,30,31.

Conclusion: A simple, accurate, precise method was developed for the simultaneous determination of the Levodropropizine and Chloropheniramine in syrup dosage form. Retention time of Levodropropizine and Chloropheniramine were found to be 2.250 min and
3.588 min. % RSD of the Levodropropizine and Chloropheniramine were and gained to be 0.2 and 0.8 jointly. % Recovery was acquired as 99.45 % and 99.30 % for Levodropropizine and Chloropheniraminejointly. LOD, LOQ values acquire from regression equations of Levodropropizine and Chloropheniramine were 0.15, 0.44 and 0.06, 009 jointly. Regression equation of Levodropropizineis y = 19120x + 12415 and y = 30379x + 1297 of Chloropheniramine. Retention times were decreased and that run time was decreased, so the method developed was simple and economical that can be adopted in regular Quality control test in Industries.

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