ejpmr, 2019,6(9), 590-598

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF CHLORPHENIRAMINE AND LEVODROPROPIZINE IN PURE AND DOSAGE FORM BY RP HPLC METHOD

K. Sruthi* and D. Dhachinamoorthi

Department of Pharm.Analysis and Quality assurance, QIS College of Pharmacy, Ongole-523272.

***Corresponding Author: K. Sruthi**

Department of Pharm.Analysis and Quality assurance, QIS College of Pharmacy, Ongole-523272.

Article Received on 22/07/2019 **Article Revised on 12/08/2019** **Article Accepted on 02/09/2019**

ABSTRACT

A simple, Accurate, precise method was developed for the simultaneous estimation of the Chlorpheniramine and Levodropropizine in syrup dosage form. Chromatogram was run through Zodiasil C18 150 x 4.6 mm, 5µ. Mobile phase containing Buffer 0.01N Kh2po4: Acetonitrile taken in the ratio 65:35 was pumped through column at a flow rate of 1.0 ml/min.Optimized wavelength selected was 252 nm. Retention time of Chlorpheniramine and Levodropropizine were found to be 2.321 min and 2.948 min. %RSD of the Chlorpheniramine and Levodropropizine were and found to be 0.8 and 1.0 respectively. %Recovery was obtained as 99.59% and 99.29% for Chlorpheniramine and Levodropropizine respectively. LOD, LOQ values obtained from regression equations of Chlorpheniramine and Levodropropizine were 0.08, 0.23 and 0.48, 1.46 respectively. Regression equation of Chlorpheniramine is y = 13761x + 395.2. And y = 21327x +3227 of Levodropropizine. 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.

KEYWORDS: Chlorpheniramine, Levodropropizine, RP-HPLC.

INTRODUCTION

The quality and safety of a drug is generally assured by monitoring and controlling the assay and impurities effectively. While assay determines the potency of the drug and impurities will determine the safety aspect of the drug. Assay of pharmaceutical products plays an important role in efficacy of the drug in patients.

The wide variety of challenges is encountered while developing the methods for different drugs depending on its nature and properties. This along with the importance of achieving the selectivity, speed, cost, simplicity, sensitivity, reproducibility and accuracy of results gives an opportunity for researchers to come out with solution to address the challenges in getting the new methods of analysis to be adopted by the pharmaceutical industry and chemical laboratories. Different physico-chemical methods (1) are used to study the physical phenomenon that occurs as a result of chemical reactions. Among the physico-chemical methods, the most important are optical (refractometry, polarimetry, emission and fluorescence methods of analysis), photometry (photocolorimetry and spectrophotometry covering UV-Visible, IR Spectroscopy and nepheloturbidimetry) and chromatographic (column, paper, thin layer, gas liquid and high performance liquid chromatography) methods. Methods such as nuclear magnetic resonance (NMR) and para magnetic resonance (PMR) are becoming more and more popular. The combination of mass spectroscopy (MS) with gas chromatography is one of the most powerful tools available. The chemical methods include the gravimetric and volumetric procedures which are based on complex formation; acid-base, precipitation and redox reactions. Titrations in non-aqueous media and complexometry have also been used in pharmaceutical analysis. The number of new drugs is constantly growing. This requires new methods for controlling their quality. Modern pharmaceutical analysis must need the following requirements.

1. The analysis should take a minimal time.
2. The accuracy of the analysis should meet the demands of Pharmacopoeia.
3. The analysis should be economical.
4. The selected method should be precise and selective.

DRUG PROFILE[13-15]

Chlorphenamine

A histamine H1 antagonist used in allergic reactions, hay fever, rhinitis, urticaria, and asthma. It has also been used in veterinary applications. One of the most widely used of the classical antihistaminics, it generally causes less drowsiness and sedation than promethazine.

Structure

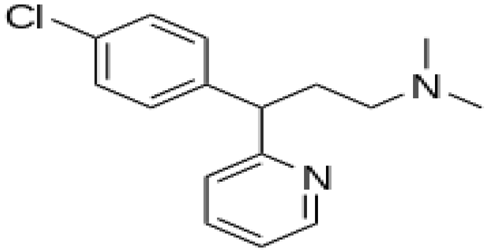


Fig: Chemical structure of Chlorphenarime.

LEVODROPROPIZINE

Description: Levodropropizine is a cough suppressant. It is the levo isomer of dropropizine. It acts as a peripheral antitussive, with no action in the central nervous system Levodropropizine is under investigation in clinical trial NCT01573663 (A Drug-Drug Interaction Study of Ambroxol and Levodropropizine).

Structure

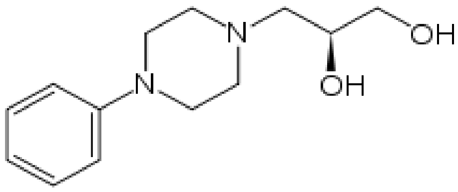


Fig: Structure of Levodropropizine.

MATERIALS AND METHODS

Materials

- Chlorpheniramine and Levodropropizine pure drugs (API), Combination Chlorpheniramine and Levodropropizine syrup (RESWAS), Distilled water, Acetonitrile, Phosphate buffer, Methanol, Potassium dehydrogenate ortho phosphate buffer, Ortho-phosphoric acid. All the above chemicals and solvents are from Rankem
  Instruments:
- Electronics Balance-Denver
- p^H meter -BVK enterprises, India
- Ultrasonicator-BVK enterprises
- WATERS HPLC 2695 SYSTEM equipped with quaternary pumps, Photo Diode Array detector and Auto sampler integrated with Empower 2 Software.
- UV-VIS spectrophotometer PG Instruments T60 with special bandwidth of 2 mm and 10mm and matched quartz cells integrated with UV win 6 Software was used for measuring absorbances of Chlorpheniramine and Levodropropizine solutions.

Methods

Diluent: Based up on the solubility of the drugs, diluent was selected, Acetonitrile and Water taken in the ratio of 50:50.

Preparation of Standard stock solutions: Accurately weighed 30mg of Chlorpheniramine, 2mg of Levodropropizine and transferred to individual 50 ml volumetric flasks separately. 3/4 th of diluents was added to both of these flasks and sonicated for 10 minutes. Flasks were made up with diluents and labeled as Standard stock solution 1and 2. (40µg/ml of Chlorpheniramine and 600µg/ml of Levodropropizine).

Preparation of Standard working solutions (100% solution): 1ml from each stock solution was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (4µg/ml Chlorpheniramine of and 60µg/ml of Levodropropizine).

Preparation of Sample stock solutions: Syrup equivalent to 30mg Chlorpheniramine and 2mg of Levodropropizine was transferred into a 50 ml volumetric flask, 20ml of diluents was added and sonicated for 25min, further the volume was made up with diluent and filtered by HPLC filters (40µg/ml of Chlorpheniramine and 600µg/ml of Levodropropizine).

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

Preparation of buffer

0.1% OPA Buffer: 1ml of Conc Ortho Phosphoric acid was diluted to 1000ml with water.

Validation

System suitability parameters

The system suitability parameters were determined by preparing standard solutions of Chlorpheniramine (4ppm) and Levodropropizine (60ppm) and the solutions were injected six times and the parameters like peak tailing, resolution and USP plate count were determined.

The % RSD for the area of six standard injections results should not be more than 2%.

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 Standard stock solutions: Accurately weighed 2mg of Chlorpheniramine, 30mg of Levodropropizine and transferred to individual 50 ml volumetric flasks separately. 3/4 th of diluents was added to both of these flasks and sonicated for 10 minutes. Flasks were made up with diluents and labeled as Standard stock solution 1and 2. (40µg/ml of Chlorpheniramine and 600µg/ml of Levodropropizine)

Preparation of Standard working solutions (100% solution): 1ml from each stock solution was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (4µg/ml Chlorpheniramine of and 60µg/ml of Levodropropizine)

Preparation of Sample stock solutions: Syrup equivalent to 30mg Chlorpheniramine and 2mg of Levodropropizine was transferred into a 50 ml volumetric flask, 20ml of diluents was added and sonicated for 25min, further the volume was made up

with diluent and filtered by HPLC filters (40µg/ml of Chlorpheniramine and 600µg/ml of Levodropropizine)
Preparation of Sample working solutions (100% solution): 1ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent. (4µg/ml of Chlorpheniramine and 60µg/ml of Levodropropizine)

Linearity
Preparation of Standard stock solutions: Accurately weighed 2mg of Chlorpheniramine, 30mg of Levodropropizine and transferred to individual 50 ml volumetric flasks separately. 3/4 th of diluents was added to both of these flasks and sonicated for 10 minutes. Flasks were made up with diluents and labeled as Standard stock solution 1and 2. (40µg/ml of Chlorpheniramine and 600µg/ml of Levodropropizine)
25% Standard solution: 0.25ml each from two standard stock solutions was pipetted out and made up to 10ml. (1µg/ml of Chlorpheniramine and 15 µg/ml of Levodropropizine)
50% Standard solution: 0.5ml each from two standard stock solutions was pipetted out and made up to 10ml. (2µg/ml of Chlorpheniramine and 30µg/ml of Levodropropizine)
75% Standard solution: 0.75ml each from two standard stock solutions was pipetted out and made up to 10ml. (3µg/ml of Chlorpheniramine and 45µg/ml of Levodropropizine)
100% Standard solution: 1.0ml each from two standard stock solutions was pipetted out and made up to 10ml. (4µg/ml of Chlorpheniramine and 60µg/ml of Levodropropizine)
125% Standard solution: 1.25ml each from two standard stock solutions was pipetted out and made up to 10ml. (5µg/ml of Chlorpheniramine and 75µg/ml of Levodropropizine)
150% Standard solution: 1.5ml each from two standard stock solutions was pipettede out and made up to 10ml (6µg/ml of Chlorpheniramine and 90µg/ml of Levodropropizine)

Accuracy
Preparation of Standard stock solutions: Accurately weighed 2mg of Chlorpheniramine, 30mg of Levodropropizine and transferred to individual 50 ml volumetric flasks separately. 3/4 th of diluents was added to both of these flasks and sonicated for 10 minutes. Flasks were made up with diluents and labeled as Standard stock solution 1and 2. (600µg/ml of Chlorpheniramine and 40µg/ml of Levodropropizine)
Preparation of 50% Spiked Solution: 0.5ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.
Preparation of 100% Spiked Solution: 1.0ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.
Preparation of 150% Spiked Solution: 1.5ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Acceptance Criteria
The % Recovery for each level should be between 98.0 to 102
Robustness: Small deliberate changes in method like Flow rate, mobile phase ratio, and temperature are made but there were no recognized change in the result and are within range as per ICH Guide lines.
Robustness conditions like Flow minus (0.9ml/min), Flow plus (1.1ml/min), mobile phase minus, mobile phase plus, temperature minus (25°C) and temperature plus (35°C) was maintained and samples were injected in duplicate manner. System suitability parameters were not much affected and all the parameters were passed. %RSD was within the limit.
LOD sample Preparation: 0.25ml each from two standard stock solutions was pipetted out and transferred to two separate 10ml volumetric flasks and made up with diluents. From the above solutions 0.1ml each of Chlorpheniramine, Levodropropizine, solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluents.
LOQ sample Preparation: 0.25ml each from two standard stock solutions was pipetted out and transferred to two separate 10ml volumetric flask and made up with diluent. From the above solutions 0.3ml each of Chlorpheniramine, Levodropropizine, and solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluent.

DEGRADATION STUDIES
Oxidation
To 1 ml of stock solution of Chlorpheniramine and Levodropropizine, 1 ml of 20% hydrogen peroxide (H2O2) was added separately. The solutions were kept for 30 min at 60^0c. For HPLC study, the resultant solution was diluted to obtain 4µg/ml&60µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Acid Degradation Studies
To 1 ml of stock solutions of Chlorpheniramine and Levodropropizine, 1 ml of 2N Hydrochloric acid was added and refluxed for 30mins at 60^0c. The resultant solution was diluted to obtain 4µg/ml&60µg/ml solution and 10 µl solutions were injected into the system and the chromatograms were recorded to assess the stability of sample.

Alkali Degradation Studies
To 1 ml of stock solution Chlorpheniramine and Levodropropizine, 1 ml of 2N sodium hydroxide was added and refluxed for 30mins at 60^0c. The resultant solution was diluted to obtain 4µg/ml&60µg/ml solution and 10 µl were injected into

the system and the chromatograms were recorded to assess the stability of sample.

Dry Heat Degradation Studies

The standard drug solution was placed in oven at 105°C for 6 h to study dry heat degradation. For HPLC study, the resultant solution was diluted to 4µg/ml&60µg/ml solution and10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

Photo Stability studies

The photochemical stability of the drug was also studied by exposing the 40µg/ml&600µg/ml solution to UV Light by keeping the beaker in UV Chamber for 1days or 200 Watt hours/m^2 in photo stability chamber. For HPLC study, the resultant solution was diluted to obtain 4µg/ml&60µg/ml solutions and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Neutral Degradation Studies

Stress testing under neutral conditions was studied by refluxing the drug in water for 1hrs at a temperature of 60°. For HPLC study, the resultant solution was diluted to 4µg/ml&60µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

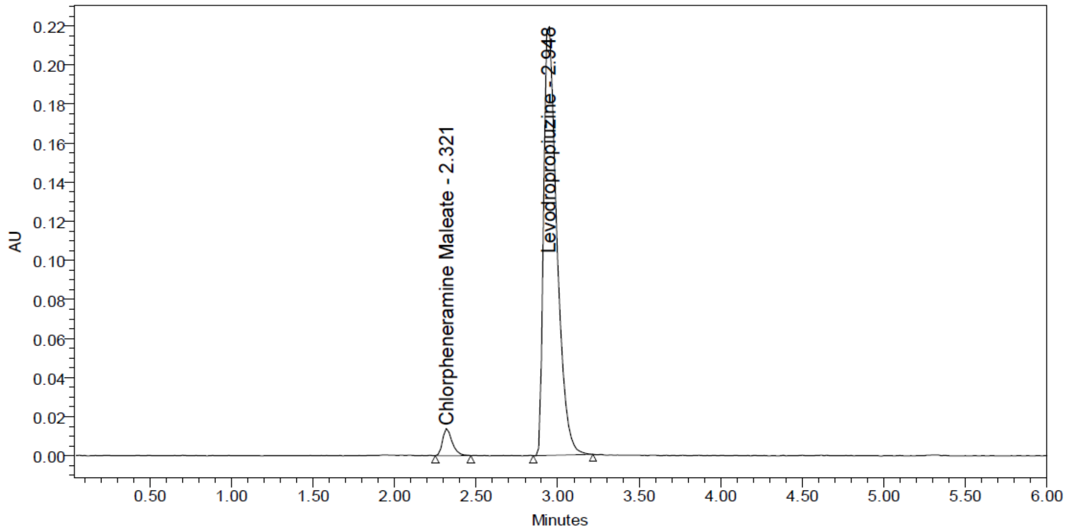
RESULTS AND DISCUSSION

Method development: Method development was done by changing various, mobile phase ratios, buffers etc.

Optimized conditions

Chromatographic conditions:

Mobile phase	:	0.01N KH_2PO_4: Methanol (65:35v/v)
Flow rate	:	0.7 ml/min
Column	:	Zodiasil C18 (4.6 x 150mm, 3.5µm)
Detector wave length	:	252nm
Column temperature	:	30°C
Injection volume	:	10µL
Run time	:	6 min
Diluent	:	Water and Acetonitrile in the ratio 50:50
Results	:	By changing Mobile phase condition As per ICH guidelines All the system suitability parameters are within the Limit and satisfactory. So this method was optimized.



System suitability parameters for Chlorpheniramine and Levodropropizine.

S no	Chlorpheniramine			Levodropropizine			
Inj	RT(min)	USP Plate Count	Tailing	RT(min)	USP Plate Count	Tailing	Resolution
1	2.331	7443	1.31	2.910	6367	1.53	4.5
2	2.333	7209	1.30	2.945	6249	1.50	4.6
3	2.334	7338	1.34	2.950	5831	1.53	4.5
4	2.336	7009	1.35	2.967	6093	1.50	4.7
5	2.337	7323	1.32	2.972	5980	1.50	4.7
6	2.337	6852	1.32	2.985	5555	1.51	4.7

Validation

Specificity

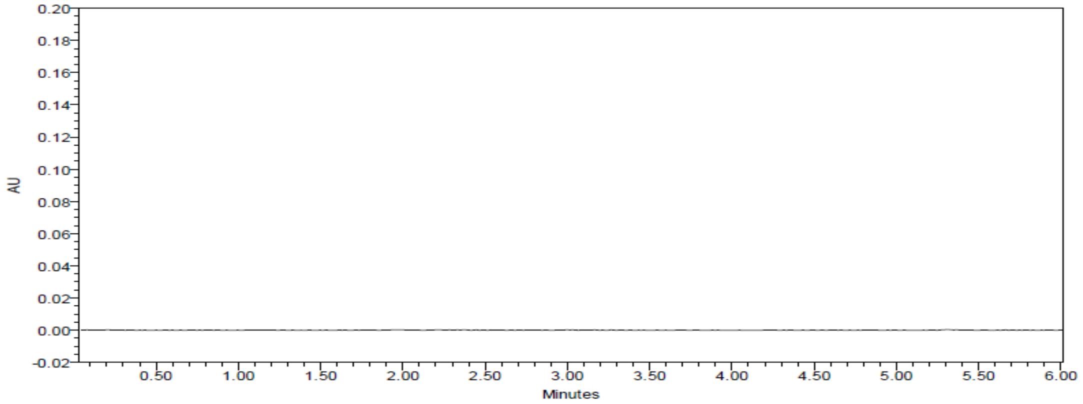


Figure No. 6.12: Chromatogram of blank.

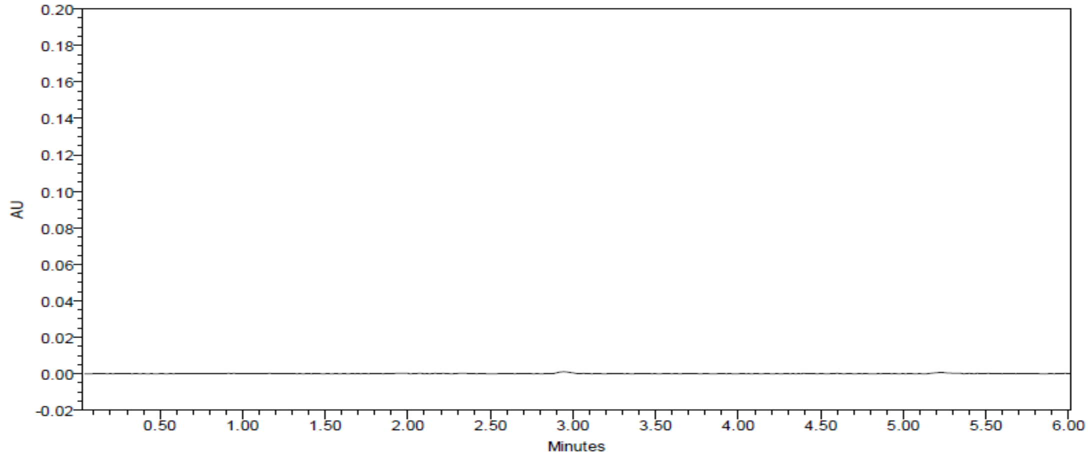


Figure No: Chromatogram of placebo.

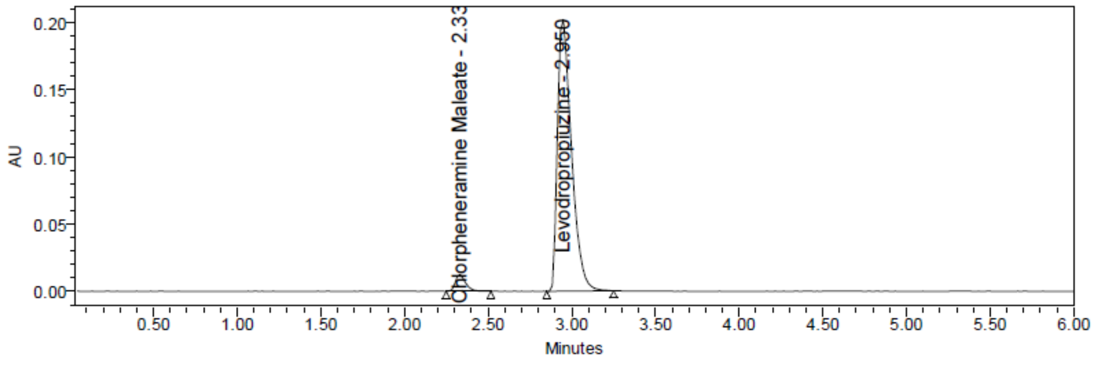


Fig No. 6.14: Typical Chlorpheniramine.

Linearity

Table 6.2: Linearity table for Chlorpheniramine and Levodropropizine.

Chlorpheniramine		Levodropropizine	
Conc (µg/mL)	Peak area	Conc (µg/mL)	Peak area
0	0	0	0
1	14079	15	318895
2	28126	30	647743
3	42288	45	962549
4	55521	60	1295822
5	69134	75	1599897
6	82601	90	1915799

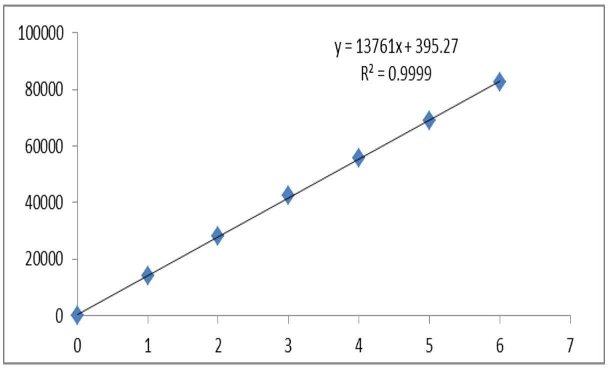


Fig No. 6.15: Calibration curve of Chlorpheniramine.

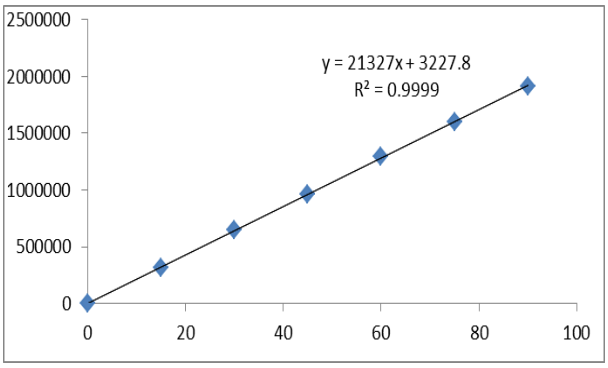


Fig No: Calibration curve of Levodropropizine.

Precision

System Precision

Table 6.3: System precision table of Chlorpheniramine and Levodropropizine.

S. No	Area of Chlorpheniramine	Area of Levodropropizine
1.	55148	1301522
2.	55736	1314073
3.	56532	1296434
4.	55773	1282682
5.	56214	1306711
6.	56409	1287966
Mean	55969	1298231
S.D	517.2	11696.8
%RSD	0.9	0.9

Intermediate precision (Day_ Day Precision)

Table 6.5 Intermediate precision table of Chlorpheniramine and Levodropropizine.

S. No	Area of Chlorpheniramine	Area of Levodropropizine
1.	54794	1274604
2.	54807	1288976
3.	55024	1283620
4.	54781	1286891
5.	55306	1287951
6.	54735	1296679
Mean	54908	1286454
S.D	219.6	7236.0
%RSD	0.4	0.6

Accuracy

Table 6.6: Accuracy table of Levodropropizine.

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	30	29.72	99.08	99.29%
	30	29.75	99.18	
	30	29.71	99.03	
100%	60	59.41	99.02	
	60	59.13	98.55	
	60	60.11	100.18	
150%	90	89.83	99.82	
	90	89.64	99.60	
	90	89.28	99.19	

Table 6.6: Accuracy table of Chlorpheniramine.

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	2	1.99	99.27	99.59%
	2	2.00	99.99	
	2	1.99	99.66	
100%	4	3.98	99.49	
	4	3.93	98.20	
	4	3.99	99.85	
150%	6	6.01	100.20	
	6	6.01	100.12	
	6	5.97	99.49	

Sensitivity table of Chlorpheniramine and Levodropropizine.

Molecule	LOD	LOQ
Chlorpheniramine	0.08	0.23
Levodropropizine	0.48	1.46

Table 6.9: Assay Data of Chlorpheniramine.

S.no	Standard Area	Sample area	% Assay
1	55148	55209	98.54
2	55736	55253	98.62
3	56532	55804	99.61
4	55773	56381	100.64
5	56214	55607	99.25
6	56409	55855	99.70
Avg	55969	55685	99.39
Stdev	517.2	435.1	0.78
%RSD	0.9	0.8	0.78

Table 6.10: Assay Data of Levodropropizine.

S. no	Standard Area	Sample area	% Assay
1	1301522	1317811	101.41
2	1314073	1305454	100.46
3	1296434	1280971	98.57
4	1282682	1304096	100.35
5	1306711	1300845	100.10
6	1287966	1291189	99.36
Avg	1298231	1300061	100.04
Stdev	11696.8	12682.1	0.98
%RSD	0.9	1.0	1.0

Degradation data

Type of degradation	Chlorpheniramine			Levodropropizine		
	Area	%recovered	% degraded	Area	%recovered	% degraded
Acid	54175	96.70	3.30	1227501	94.46	5.54
Base	53800	96.03	3.97	1216500	93.61	6.39
Peroxide	53216	94.99	5.01	1203723	92.63	7.37
Thermal	55247	98.61	1.39	1248038	96.04	3.96
Uv	54955	98.09	1.91	1267316	97.52	2.48
Water	55706	98.09	1.91	1287211	99.05	0.95

SUMMARY AND CONCLUSION

Parameters		Chlorpheniramine	Levodropropizine	LIMIT
Linearity Range (µg/ml)		1-6µg/ml	15-90 µg/ml	R< 1
Regressioncoefficient		0.999	0.999	
Slope(m)		13761	21327	
Intercept(c)		395.2	3227	
Regression equation (Y=mx+c)		y = 1371x + 395.2	y = 21327x + 3227.	
Assay (% mean assay)		99.39%	100.04%	90-110%
Specificity		Specific	Specific	No interference of any peak
System precision %RSD		0.9	0.9	NMT 2.0%
Method precision %RSD		0.8	1.0	NMT 2.0%
Accuracy %recovery		99.59%	99.29%	98-102%
LOD		0.08	0.48	NMT 3
LOQ		0.03	1.46	NMT 10
Robustness	FM	0.7	0.6	%RSD NMT 2.0
	FP	1.4	0.9	
	MM	1.6	0.4	
	MP	1	0.6	
	TM	1.3	1.4	
	TP	0.1	1.1	

CONCLUSION

A simple, Accurate, precise method was developed for the simultaneous estimation of the Chlorpheniramine and Levodropropizine in syrup dosage form. Retention time of Chlorpheniramine and Levodropropizine were found to be 2.321 min and 2.948 min. %RSD of the Chlorpheniramine and Levodropropizine were and found to be 0.8 and 1.0 respectively. %Recovery was obtained as 99.59% and 99.29% for Chlorpheniramine and Levodropropizine respectively. LOD, LOQ values obtained from regression equations of Chlorpheniramine and Levodropropizine were 0.08, 0.23 and 0.48, 1.46 respectively. Regression equation of Chlorpheniramine is y = 13761x + 395.2. And y = 21327x +3227 of Levodropropizine. 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.

REFERENCES

1. B.k Sharma, Instrumental methods of chemical analysis, Introduction to analytical chemistry, 23rd Edition Goel publication, Meerut, 2007.
2. Gurdeep R. Chatwal, Sham K. Anand, Instrumental Methods of Chemical Analysis, 2007; 2.566-2.638.
3. Douglas A Skoog, F. James Holler, Timothy A. Niemen, Principles of Instrumental Analysis, 725-760.
4. Dr.S. Ravi Shankar, Text book of Pharmaceutical analysis, Fourth edition, 13.1-13.2.
5. Lindholm.J, Development and Validation of HPLC Method for Analytical and Preparative purpose. Acta Universitatis Upsaliensis, pg, 2004; 13-14.
6. Rashmin, An introduction to analytical Method Development for Pharmaceutical formulations. Indoglobal Journal of Pharmaceutical Sciences, 2012; 2(2): 191-196.
7. Ashok Kumar, Lalith Kishore, navpreet Kaur, Anroop Nair. Method Development and Validation for Pharmaceutical Analysis. International Pharmaceutica Sciencia, Jul-Sep 2012; 2(3).
8. Kaushal.C, Srivatsava.B, A Process of Method Development: A Chromatographic Approach. J Chem Pharm Res, 2010; 2(2): 519-545.
9. Vibha Gupta, Ajay Deep Kumar Jain, N.S.Gill, Kapil, Development and Validation of HPLC method. International Research Journal of Pharmaeutical and Applied Sciences, Jul-Aug, 2012; 2: 4.
10. Hokanson GC. A life cycle approach to the validation of analytical methods during Pharmaceutical Product Development. Part 1: The Initial Validation Process. Pharm Tech, 1994; 92-100.
11. ICH, Validation of analytical procedures: Text and Methodology. International Conference on Harmonization, IFPMA, Geneva, 1996.
12. Indian Pharmacopoeia, Indian Pharmacopoeial Commission, Controller of Publication, Government of India, Ministry of health and Family Welfare, Ghaziabad, India, 2010; 2: 1657-1658.
13. https://www.drugbank.ca/drugs/DB01114
14. https://www.drugbank.ca/drugs/DB12472
15. https://www.scbt.com › Home › Chemicals › Other Chemicals › Antioxidants
16. Palakurthi Ashok kumar*1, Thummala Veera Raghava Raju, Dongala Thirupathi, Ravindra Kumar, Jaya Shree.Development and Validation of a Stability-Indicating LC-Method for the Simultaneous Estimation of Levodropropizine,

Levodropropizine, Methylparaben, Propylparaben, and Levodropropizine Impurities. Sci Pharm, 2013; 81: 139–150.

17. Wahba hassan,* Soheir abd el-fatah weshahy, Maissa salem yaaqob, Marianne nebsen morcos, Dina, nadia fayek youssef. Simultaneous determination of levodropropizine, methylparaben, and propylparaben in oral co-formulated syrup by rp-hplc method. International journal of pharmaceutical sciences and research. J. Chil. Chem. Soc., 2015; 60(4).
18. Alessandro Zanasi1*, Luigi Lanata, Giovanni Fontana, Federico Saibene, Peter Dicpinigaitis and Francesco De Blasio. Levodropropizine for treating cough in adult and children: a meta-analysis of published studies. Zanasi et al. Multidisciplinary Respiratory Medicine, 2015; 10: 19.
19. Zhang qing1, Liu Jun1*,Huang fang,zhou yi-bin. RP-HPLC and TLC method for testing related substances in levodropropizine. chinese new drugs journal 2001-06.
20. Lin Yan*,Tongling LiRongqin, ZhangXiaohong Xu, Pengcheng Zheng.HPLC determination and steady-state bioavailability study of levodropropizine sustained-release tablets in dogs. Archives of Pharmacal Research, June, 2006; 29(6): 514–519.
21. Gao hong-zhi*, Liang yu-guang, hao Guang-tao, Lin li-na,hu jin-chao, Liu ze-yuan. Pharmacokinetics of levodropropizine in healthy volunteers. Chinese Journal of New Drugs, 2008-16.