IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
March 2020 Vol.:17, Issue:4

Stability Indicating RP-HPLC Method for Simultaneous Determination of H_1-Histamine Receptor Antagonist and Mucolytic Agent in Marketed Formulation

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INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
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Submission: 25 February 2020
Accepted: 2 March 2020
Published: 30 March 2020

Keywords: Ambroxol hydrochloride and Levocetirizine dihydrochloride, Stability Indicating RP-HPLC

ABSTRACT

RP-HPLC method has been developed for simultaneous determination of Stability indicating HPLC method was developed for the simultaneous estimation of Ambroxol hydrochloride and Levocetirizine dihydrochloride in marketed formulation. The HPLC system used was SHIMADZU UFLC-2000 Prominence LC-20AD SPDM 20A Binary Gradient System with Rheodyne injector 20 µL and the column Enable C18 250 x 4.6 mm, 5 µm. The mobile phase comprised of Phosphate buffer (pH 3.0): Methanol in the ratio of 20:80 v/v and flow rate of 1.0 mL/min with PDA detection at 236 nm produced peaks of Ambroxol hydrochloride and Levocetirizine dihydrochloride in the chromatogram which was well resolved with a retention time of 3.4 min and 4.7 min respectively. The developed HPLC method was validated for various parameters like accuracy, precision, specificity, LOD, LOQ, linearity, range, and robustness as per ICH guidelines. The results obtained were well within the acceptance criteria for all the parameters. The proposed method was applied for the simultaneous estimation of Ambroxol hydrochloride and Levocetirizine dihydrochloride in marketed formulations (capsule). The assay results conformed to the label claim of the formulation. Hence the proposed method can be used for the routine analysis of Ambroxol hydrochloride and Levocetirizine dihydrochloride in their marketed capsule dosage formulations. Forced degradation studies were carried out in Acidic medium, Alkaline medium, Oxidation condition, Thermal condition, and Photostability condition and it was found that the degradation and the peaks of degraded products did not interfere with the method. Hence the developed and validated HPLC method can be employed for routine analysis of Ambroxol hydrochloride and Levocetirizine dihydrochloride in marketed formulations. The results obtained were within the acceptance criteria for the parameter. The proposed methods were applied for the estimation of Ambroxol hydrochloride and Levocetirizine dihydrochloride in marketed formulations. Hence the proposed method was found to be satisfactory and could be used for the routine analysis of Ambroxol hydrochloride and Levocetirizine dihydrochloride in their marketed capsule dosage formulations.

INTRODUCTION

Pharmaceutical product quality [1] is of vital importance for patient safety. The presence of impurities may influence the efficacy and safety of pharmaceuticals. Impurities and potential degradation products can cause the changing of chemical, pharmacological and toxicological properties of drugs having a significant impact on product quality and safety. Drug stability is considered to be a secure way to ensure the delivery of therapeutic values to the patients.

Stability is defined as the capacity of a drug substance to remain within the established specifications to maintain its identity, strength, quality, and purity throughout the retest or expiration dating period.

The stability of a pharmaceutical/medicinal product is defined as the capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications. Pharmaceutical products are expected to meet their specifications for identity, purity, quality, and strength throughout their defined storage period at specific storage conditions.

Stability [2] is an essential factor in the quality, safety, and efficacy of a drug substance. A drug substance, which is not of sufficient stability, can result in changes in physical (like appearance, melting point, clarity and color of the solution, water, crystal modification(polymorphism) or particle size) as well as chemical characteristics (increase in impurities and decrease in the assay) and microbiological attributes (Total bacterial count, fungal count and for pathogenic microbes).

The purpose of stability testing is to provide evidence on how the quality of a drug substance varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a retest period for the drug substance and recommended storage conditions. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period.

Stability [3] plays an important role in the drug development process. It explains several factors that affect the expiration dating of drug products, including the chemical and physical stability during the pre-clinical formulation stages, process development, packaging development, and post-marketing life. The evaluation of the physicochemical stability of a

given product requires an understanding of the physical and chemical properties of the drug substance. The two main aspects of a drug product that play an important role in shelf life determination are assay of active drug and degradants generated during the stability studies.

The container closure system must be evaluated for compatibility with the drug substance and drug product to ensure that the container and closure system does not contribute to degradation or contamination.

STABILITY TESTING METHODS [4]:

(i) Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, can be used to assess longer-term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

(ii)Intermediate testing: Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long-term at 25°C.

(iii)Long-term testing: Stability studies under the recommended storage condition for the retest period or shelf-life proposed (or approved) for labeling.

IMPORTANCE OF STABILITY TESTING [5]:

- Stability testing is a routine procedure performed on drug substances and products to develop a stable dosage form.

- Stability testing is the primary tool used to asses expiration dating and storage conditions for pharmaceutical products.

- Stability studies are linked to the establishment and assurance of safety, quality and efficacy of the drug product.

- To study drug decomposition kinetics.

- To establish an expiration date.
- Its physical and chemical properties.

STABILITY INDICATING METHOD [6]:

As its name suggests, an assay method is regarded as stability-indicating only if it is sufficiently sensitive and selective to discriminate between the active (intact) pharmaceutical ingredient (API) and the degradation product(s) and quantify one or more degradation products formed during the stability study. It is employed to supervise the stability of pharmaceutical dosage forms during stability study in various stages such as the investigational phase of drug development, once the drug is marketed and, for the ongoing stability studies.

The[7] 1998 draft guidelines of *US-FDA defines* stability-indicating methods as: *'validated quantitative analytical methods that can detect the changes with time in the chemical, physical or microbiological properties of the drug substance and drug product, and that are specific so that the contents of the active ingredient, degradation products, and other components of interest can be accurately measured without interference'.*

STABILITY ANALYSIS FOR DRUG SUBSTANCE [8]:

Stability requirements for the worldwide registration of pharmaceutical products have changed dramatically in the past five years. The ICH (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use) process has introduced a standardized approach to the development of stability data for registration purposes. The ICH stability Testing Guideline specifies the storage conditions (temperature and humidity), the number and size of batches, the minimum amount of data at the time of filing, and the testing frequency. The stability of drug substances and drug products has been a concern of both the pharmaceutical industry and regulatory agencies for many years. Along with composition, method of manufacture, and ingredient and product specifications, stability has long been a regulatory requirement in most countries. Both groups want to ensure that the patient receives a safe and effective drug product throughout its claimed shelf life.

STRESS TESTING [3]:

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of stress testing will depend on the individual drug substance and the type of drug product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. It should include the effect of temperatures (in 10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing), humidity (e.g., 75% RH or greater) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH Q1B[9-11].

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long term storage conditions.

Results from these studies will form an integral part of the information provided to regulatory authorities.

A minimal list of stress factors suggested for forced degradation studies must include:

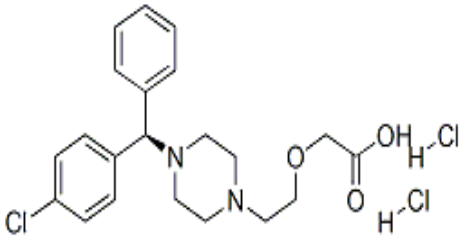
- Acid Hydrolysis
- Base Hydrolysis
- Oxidation
- Thermal Condition
- Photolysis (UV Light)

Levocetirizine dihydrochloride[12]:

Description: A white powder

Chemical Name: *(2-(4-[(R)-(4-Chlorophenyl) (phenyl) methyl] piperazin-1-yl) ethoxy) acetic acid dihydrochloride.*

Chemical Structure:



Molecular formula: $C_{21}H_{27}Cl_3N_2O_3$

Molecular weight: 461.81

Melting point: 215-220^{0}C

Solubility: Soluble in water and methanol.

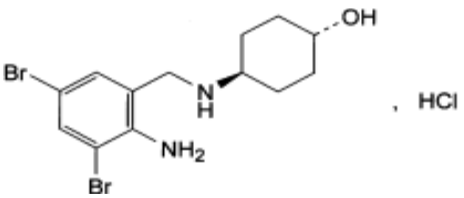
Category: H_1-histamine receptor antagonist

Ambroxol HCl[13]:

Description: White or yellowish crystalline powder.

Chemical Name: *trans-4-[(2-Amino-3,5-dibromobenzyl)amino]cyclohexanol hydrochloride.*

Chemical structure:



Molecular formula: $C_{13}H_{18}Br_2N_2O$, HCl

Molecular weight: 414.6

Melting point: 233-234.5^{0}C

Category: Mucolytic agent and expectorant

Solubility: Sparingly soluble in water, soluble in methanol

MATERIALS AND METHODS

Chemicals and Reagents:

Chemicals and Reagents used: Acetonitrile, HPLC grade (Merck), Methanol, HPLC grade (Merck), Sodium Dihydrogen Ortho Phosphate (Thermo Fisher Scientific India Pvt. Ltd, Mumbai), Millipore water, Ambroxol hydrochloride (Hetero Pharma, Hyderabad), Levocetirizine dihydrochloride (Metro Chem API Pvt. Ltd, Hyderabad) Relent-OD capsules were manufactured by Dr. Reddy's Laboratories, Hyderabad, India purchased from the local market.

HPLC Instrumentation and Conditions:

Instrument	SHIMADZU UFLC-2000 Prominance LC-20AD SPDM 20A Binary Gradient System
Injector	Rheodyne
Column	Enable C-18 G Column 250mm(length) x 4.6mm(I.D) , 5µm (Particle Size)
Detector	PDA Detector
Injection volume	20µl
Flow Rate	1.0 mL/min
Detection Wavelength	236nm

Chromatographic conditions:

The developed HPLC method for simultaneous estimation of Ambroxol hydrochloride and Levocetirizine dihydrochloride using C18 column Enable 250mm x 4.6mm, 5µm, mobile phase 0.1M Phosphate buffer pH(3.0) and Methanol (20:80), detection wavelength at 236nm, at a flow rate of 1.0 mL/min was validated for typical analytical parameters.

Peaks of Ambroxol hydrochloride and Levocetirizine dihydrochloride were well resolved with the solvent system of Methanol and Phosphate buffer (pH 3.0) in the ratio of 80:20 the chromatograms are presented.

Preparation of Mobile Phase:

Sodium dihydrogen orthophosphate buffer (NaH2PO4) pH 3.0 was prepared by dissolving 15.61 gm of Sodium dihydrogen orthophosphate (KH2PO4) in 1000 mL of water to get a concentration of 0.1M. Then it was adjusted to pH 3 with orthophosphoric acid. The mobile phase was prepared in the ratio of 20:80 (Sodium dihydrogen orthophosphate buffer pH 3.0: Methanol) filtered, degassed and sonicated for 10 min.

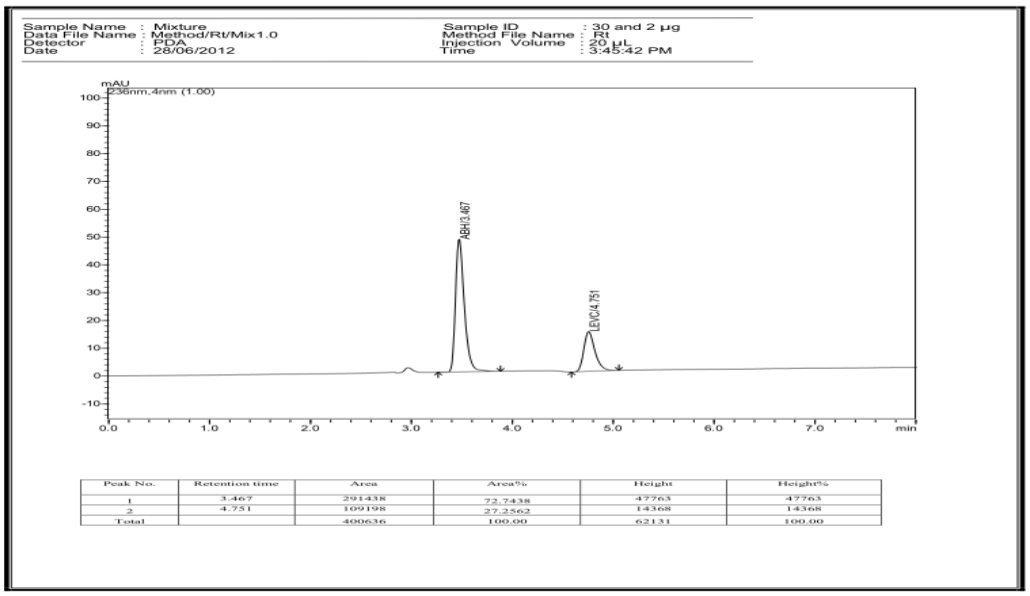
A standard stock solution of Ambroxol Hydrochloride:

Accurately, 75 mg of Ambroxol hydrochloride was weighed into a clean and dry 100 mL volumetric flask, dissolved with a sufficient volume of the mobile phase. The volume was then made up to 100 mL with mobile phase to get the concentration of 750µg/mL (Stock I).

Working standard solution: 4mL of the stock solution was further diluted to 100 mL with mobile phase to get a concentration of 30µg/mL (Stock II).

The developed HPLC method for simultaneous estimation of Ambroxol hydrochloride and Levocetirizine dihydrochloride using C18 column Enable 250mm x 4.6mm, 5µm, mobile phase 0.1M Phosphate buffer pH(3.0) and Methanol (20:80), detection wavelength at 236nm, at a flow rate of 1.0 mL/min was validated for typical analytical parameters like, Accuracy, Precision, System precision, Method precision, Intermediate precision (Ruggedness), Specificity, Detection Limit, Quantitation Limit, Linearity, Range Robustness.

Overlay Spectrum of Ambroxol hydrochloride and Levocetirizine dihydrochloride



Peak No.	Retention time	Area	Area%	Height	Height%
1	3.467	291438	72.7438	47763	47763
2	4.751	109198	27.2562	14368	14368
Total		400636	100.00	62131	100.00

Figure No. 1: Chromatogram of Ambroxol hydrochloride and Levocetirizine dihydrochloride peaks showing good resolution with mobile phase Phosphate buffer (pH 3.0) and Methanol (20:80)

RESULTS AND DISCUSSION

The objective of the proposed project was to develop and validate a stability-indicating HPLC method for simultaneous estimation of Ambroxol hydrochloride and Levocetirizine dihydrochloride in marketed dosage forms and to carry out the forced degradation of drugs and study the effect of degraded products on the developed method.

Various combinations of the solvent system in different ratios of the mobile phase were tried and the mobile phase of Methanol and Phosphate buffer (pH: 3.0) in the ratio of 80:20 v/v was selected and standardized as it evoked satisfactory resolution. The overlay spectra of standard drugs of Ambroxol hydrochloride and Levocetirizine dihydrochloride showed isosbestic point at 236 nm, which was selected, standardized and was used as optimum wavelength. The peaks with good resolution were observed for Ambroxol hydrochloride and Levocetirizine dihydrochloride at the optimum flow rate of 1.0 mL/min which was used for our further study.

Stability indicating HPLC method was developed for the simultaneous estimation of Ambroxol hydrochloride and Levocetirizine dihydrochloride using a C18 column (Enable C-

18 G, 250 mm x 4.6 mm, 5 µm) mobile phase consisting of Phosphate Buffer, pH 3.0: Methanol in the ratio of 20:80 v/v, with a flow rate of 1.0 mL/ min, PDA detection at a wavelength of 236 nm. The retention time of Ambroxol hydrochloride and Levocetirizine dihydrochloride was observed at 3.4 and 4.7 min respectively.

The developed method was then validated by using various parameters like accuracy, precision, linearity, specificity, ruggedness, and robustness, etc., as per ICH guidelines.

System suitability:

Table No. 1: System suitability data for Ambroxol hydrochloride and Levocetirizine dihydrochloride

System Suitability Factor	Ambroxol Hydrochloride	Levocetirizine dihydrochloride	Acceptance Criteria
Tailing factor	1.494	1.388	2
HETP(mm)	23.392	19.148	-
Resolution	6.617		-
Theoretical plates	6412.446	7833.830	>6000
Asymmetry	0.75	1	1

The system suitability parameters were obtained to ascertain the suitability of the proposed method in the mobile phase of Methanol and Phosphate buffer (pH: 3.0) in the ratio of 80:20 Flow rate of 1.0 mL/ min, PDA detection at a wavelength of 236 nm was injected into the chromatograph.

The number of plates was found to be 6412.446 and 7833.830 for Ambroxol hydrochloride and Levocetirizine dihydrochloride respectively. The HETP was found to be 23.392 and 19.148 for Ambroxol hydrochloride and Levocetirizine dihydrochloride respectively, indicating the system suitability of the method. The asymmetry factor was found to be 0.75 and 1 for Ambroxol hydrochloride and Levocetirizine dihydrochloride respectively. The resolution of the method was good as found from the value of 6.617 indicating good and complete separation of the two components from each other with the well-defined baseline.

The developed HPLC method was applied for the simultaneous estimation of Ambroxol hydrochloride and Levocetirizine dihydrochloride in the marketed formulation (Relent-OD

capsules). The % assay of Ambroxol hydrochloride and Levocetirizine dihydrochloride was found in the range of 100.86 to 102.18% and 99.38to 104.22 % respectively. As assay ranges in the acceptable limits, indicating that the method can be applied for simultaneous determination of Ambroxol hydrochloride and Levocetirizine dihydrochloride in marketed formulations (capsules).

Validation parameters:

Table No. 2: Validation parameters for the proposed HPLC method

Parameters		Ambroxol Hydrochloride	Levocetirizine dihydrochloride	Acceptance criteria
Accuracy (% Recovery)		102.14-103.93%	99.19 - 104 %	90-110 %
Precision	System	0.22 %	0.33 %	NMT 2%
	Method	0.2%	0.33%	
	Inter day	0.44 %	0.44%	
	Intra day	0.29 %	0.36 %	
Specificity		No Interference by degraded components		No Interference by degraded components
LOD (mcg/mL)		3(ng/mL)	0.05(ng/mL)	-
LOQ (mcg/mL)		9(ng/mL)	0.15(ng/mL)	-
Linearity range		15-45 µg/mL	1-3 µg/mL	-
Robustnes	0.9 mL/min	102.37 %	104.56 %	90-110 %
	1.1 mL/min	107.63 %	104.25 %	
	231 nm	103.44 %	98.7 %	90-110 %
	241 nm	102.32 %	98.36 %	

Accuracy:

- The accuracy was determined through the recovery study of the drugs by spiking the standard drug of Ambroxol hydrochloride and Levocetirizine dihydrochloride at three different levels 50%, 100% and 150% with the previously assayed samples of known fixed concentration.

- The percentage recovery was found to be 102.14% to 103.93% for Ambroxol hydrochloride and 99.19% to 104% for Levocetirizine dihydrochloride indicating no

interference of Ambroxol hydrochloride and Levocetirizine dihydrochloride, the percentage recovery was in total agreement with acceptance criteria of 90- 110%.

Precision:

- The precision of the method and system was determined to study the concordance of data between the series of measurements.

- In system precision, the % RSD value of peak area was found to be 0.22% for Ambroxol hydrochloride and 0.33% for Levocetirizine dihydrochloride.

- In method precision, the % RSD value of concentration was found to be 0.2% for Ambroxol hydrochloride and 0.33% for Levocetirizine dihydrochloride.

- The intermediate precision of the method was determined by performing the assay at two different days (inter-day and intraday) to check the reproducibility. On intraday % RSD value of peak area was found to be 0.29% for Ambroxol hydrochloride and 0.36% for Levocetirizine dihydrochloride. On inter-day % RSD value of peak area was found to be 0.44% for Ambroxol hydrochloride and 0.44% for Levocetirizine dihydrochloride.

- All the values of % RSD for precision study obtained were well within the acceptance criteria of NMT 2%. Thus the proposed method was found to be providing a high degree of precision and reproducibility.

Specificity:

- The specificity of the proposed method was determined by studying the effect of impurities etc at the retention time of Ambroxol hydrochloride and Levocetirizine dihydrochloride. Hence there was no interference from impurities with the peaks of Ambroxol hydrochloride and Levocetirizine dihydrochloride, indicating a high degree of specificity for the proposed method.

LOD and LOQ:

- The LOD and LOQ were determined by the visualization method. The LOD was determined to find out the lowest amount of Ambroxol hydrochloride and Levocetirizine dihydrochloride that can be detected and it was found to be 2.9ng/mL and 0.05ng/mL

respectively. The LOQ was determined to find out the lowest amount of Ambroxol hydrochloride and Levocetirizine dihydrochloride that can be quantified and it was found to be 9ng/mL and 0.15ng/mL for Ambroxol hydrochloride and Levocetirizine dihydrochloride respectively, indicating that the small concentration in micrograms level can be determined with acceptable accuracy and precision.

Linearity and Range:

- The linearity for the drugs by the proposed method was determined to study its ability to elicit test results which are directly proportional to the concentration of the analyte in the sample.

- Standard solutions in the concentration range of 15 to 45µg/mL of Ambroxol hydrochloride and Levocetirizine dihydrochloride in the mobile phase of Phosphate Buffer and Methanol in the ratio of 20:80 v/v, the flow rate of 1.0 mL/min and PDA detection at 236 nm were injected into the chromatograph. From the peak areas obtained the standard calibration curve was prepared.

- The proposed method is found to be linear at the concentration range of 15 to 45µg/mL for Ambroxol hydrochloride and Levocetirizine dihydrochloride. The percentage curve fittings were found to be 99.8% for Ambroxol hydrochloride and 99.8% for Levocetirizine dihydrochloride.

Robustness:

- The robustness of the method was determined by carrying out the assay after performing deliberate changes in the wavelength and flow rate.

- The flow rate was slightly altered from 1.0mL/min to 1.1mL/min and 0.9mL/min the % assay for Ambroxol hydrochloride was found to be 102.37% and 107.63% and for Levocetirizine dihydrochloride was found to be 104.56% and 104.25% respectively.

- The detection wavelength was deliberately changed from 236 nm to 231 nm and 241 nm, the % assay of Ambroxol hydrochloride was found to be 103.44 and 102.32% and for Levocetirizine dihydrochloride was found to be 98.7 and 98.36% respectively. All the robustness results indicated that the new method developed was robust and did not show significant variations on deliberate changes in the flow rate and detection wavelength

indicating a lack of influence on the test results by operational variables for the proposed method.

Table No. 3: Data for degradation studies of Ambroxol hydrochloride and Levocetirizine dihydrochloride

Degradation condition	Drug Peak Area at Control		Drug peak area at Stressed Condn.		Rt of degraded Products		% of Degradation	
	ABH	LEVC	ABH	LEVC	ABH	LEVC	ABH	LEVC
Acidic 0.1N HCl	370726	109523	348385	103520	……	……	……	……
Alkaline 0.1N NaOH	352539	106684	344761	83320	……	4.4	……	19.1%
Oxidation 3% v/v H_2O_2	361258	103669	98357	90238	2.8	4.4	64.78%	12.48%
Thermal Condition	375730	108778	369498	106945	……	……	ND	ND
Photo Stability	375730	108778	367310	107687	……	……	ND	ND

- In Acidic Condition standard drugs of both Ambroxol hydrochloride and Levocetirizine dihydrochloride were found to be stable for 6 hrs with no degradation peaks.

- In Alkaline Condition standard drugs of Ambroxol hydrochloride were found to be stable with no degradation peaks whereas Levocetirizine dihydrochloride showed a peak at Rt of 4.4 which did not interfere with the peaks of drugs under study.

- In Oxidative Condition standard drugs of Ambroxol hydrochloride showed an extra peak at Rt of 2.8 min which did not interfere with the peaks of drugs under study whereas Levocetirizine Dihydrochloride also showed an extra peak at Rt of 4.4 min which did not interfere with the peaks of drugs under study.

- In Thermal Studies standard drugs of Ambroxol hydrochloride and Levocetirizine dihydrochloride were found to be stable at 60^0C for 48 hrs with no degradation peaks.

- In Photostability Studies standard drugs of Ambroxol hydrochloride and Levocetirizine dihydrochloride were found to be stable for 48 hrs with no degradation peaks.

- From the degradation studies data, it was found that Ambroxol hydrochloride was found to be stable in acidic, alkali, thermal and photostability conditions and showed degradation in oxidative conditions whereas Levocetirizine dihydrochloride was found to be stable in acidic, thermal and photostability conditions and showed degradation in alkaline and oxidative conditions. It was also found that the degraded products did not interfere with the peaks of Ambroxol hydrochloride and Levocetirizine dihydrochloride.

- Hence stress testing should be given importance for such a combination of drugs and quantification of degraded products of such drugs helps us to maintain the quality, safety, and efficacy of drugs in formulations.

CONCLUSION

Stability indicating HPLC and UV methods were developed for the simultaneous estimation of Ambroxol hydrochloride and Levocetirizine dihydrochloride in marketed formulation. The HPLC system used was SHIMADZU UFLC-2000 Prominence LC-20AD SPDM 20A Binary Gradient System with Rheodyne injector 20 µL and the column Enable C18 250 x 4.6 mm, 5 µm. The mobile phase comprised of Phosphate buffer (pH 3.0): Methanol in the ratio of 20:80 v/v and flow rate of 1.0 mL/min with PDA detection at 236 nm produced peaks of Ambroxol hydrochloride and Levocetirizine dihydrochloride in the chromatogram which was well resolved with a retention time of 3.4 min and 4.7 min respectively.

The developed HPLC method was validated for various parameters like accuracy, precision, specificity, LOD, LOQ, linearity, range, and robustness as per ICH guidelines. The results obtained were well within the acceptance criteria for all the parameters. The proposed method was applied for the simultaneous estimation of Ambroxol hydrochloride and Levocetirizine dihydrochloride in marketed formulations (capsule). The assay results conformed to the label claim of the formulation. Hence the proposed method can be used for the routine analysis of Ambroxol hydrochloride and Levocetirizine dihydrochloride in their marketed capsule dosage formulations.

Forced degradation studies were carried out in Acidic medium, Alkaline medium, Oxidation condition, Thermal condition, and Photostability condition and it was found that the degradation and the peaks of degraded products did not interfere with the method. Hence the developed and validated HPLC method can be employed for routine analysis of Ambroxol hydrochloride and Levocetirizine dihydrochloride in marketed formulations.

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