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Research Article

Identification of Degradation Pathway of Bilastine and Montelukast by LC/MS

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ABSTRACT

It is necessary for a dosage form to maintain its chemical, physical, microbiological and toxicological stability during its entire shelf life. Knowing the intrinsic stability of the chemical and the breakdown pathway of the dosage form is crucial for this reason. We have developed a straightforward analytical approach using HPLC-UV/MS for the simultaneous measurement of bilastine and montelukast, as well as the identification of their degradants in tablet formulation. This method is specific, linear, accurate, and robust. The narcotic compounds were broken down one by one. The Zorbax XDB C-18 column (150*4.6) mm, 5 µ, with a mobile phase of Water:Acetonitrile:Formic acid (50:50:1), was used to achieve the separation. A flow rate of 1-mL/min was used with an injection volume of 20 µL. A UV-vis spectrophotometer was used for peak detection, while a mass spectrophotometer was employed for identification. Bilastine had a retention time of 3.22 minutes and montelukast of 4.80 minutes. The proposed method was stability indicating, specific, linear, accurate and robust. The degradation pathway was established for bilastine and montelukast by studying their degradation under various stress conditions. The bilastine was found stable in photolytic and thermal degradation while there was degradation observed in montelukast in all stress conditions.

INTRODUCTION

The stability of the pharmaceutical dosage form is the main concern, which affects the efficacy and potency along with the physical appearance of the dosage form and finally determines shelf life and decides the expiry date.[1,2] As a means of testing the drug's stability, ICH guideline Q1A(R2) provides information about the stability parameters according to which the data needs to be generated to establish the storage conditions, packing details, shipment details and shelf life of drug product.

Forced degradation is an effective technique that generates preliminary data that would be helpful in finalizing tentative storage conditions and the creation of a technique that indicates stability.[3,4] In forced degradation, the drug product is subjected to extreme circumstances in order to hasten its deterioration, which generates the degradation products that can be identified and thus helps in establishing the ambient storage and shipment conditions for the drug product. ICH Q1A (R2) guideline basically suggests stress testing, in which the drug product is exposed to slightly harsher circumstances than accelerated stability conditions (40°C/75% RH), which further helps in establishing the inherent stability of the molecule. To validate analytical processes' stability representing power and to discover degradation pathways, it is helpful to conduct stress tests on drug ingredients. These tests can assist in identifying the likely degradation products. The medicine and its product type will determine the specifics of the stress tests. Effects of oxidation, photolysis, humidity (e.g., ≥75%

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RH), and temperatures (i.e., 50, 60°C, etc.) beyond those for accelerated testing must be involved. Additionally, the assay needs to check how the medicinal component reacts to hydrolysis in different solutions or suspensions across a broad pH range. An essential aspect of stress testing ought to be photostability testing. In order to determine degradation pathways and create and validate appropriate analytical methods, it is helpful to examine degradation products under stress circumstances. There may be no need to look for particular degradation products if it has been proven that they don't occur in accelerated or long-term storage. Data supplied to regulatory agencies during submission will include the results of this research.[5-9]

Materials And Methods

Chemical and Reagents

Samples of bilastine API were received from Montage Laboratories Pvt Ltd, and montelukast API was received from Mediwin Pharmaceuticals. The marketed sample Bilzest M was used for the study procured from the market. The LC-MS grade methanol and acetonitrile were purchased from JT-Baker. LC-MS grade H_2O from Aquarch. LC-MS grade formic acid was purchased from Merck.

Instrumentation

An Agilent Zorbax XDB C-18, (150*4.6) mm, 5 µ column was used. The Zorbax XDB (eXtra Dense Bonding) column offers great performance at lower and mid pH. The dense layer of C-18 attached to the surface of Silica, followed by the end-capping process, offers a good peak shape and minimal secondary interaction with the analyte. The HPLC used was Shimadzu LC-20 AT connected with a UV detector and MS/MS was ABScix API 200. The instrument provides UV chromatogram and MS spectra in a single run. The photostability and thermal stability were carried out in the hot air oven and photostability chamber of make Kesar control system, respectively. The analytical balance capable of weighing up to 4 decimal places of Shimadzu ATX-224 make was used. The sonicator used was Frontline 1870 make and pH meter of Analab Scientific Private Ltd (Table 1).

Chromatographic Conditions

A column with dimensions of 150 × 4.6 mm and a height of 5 µ is utilized, which is manufactured by Agilent. A mobile phase A, consisting of 0.1% formic acid in H_2O (made by mixing 1-mL of formic acid with 1000 mL of water), and a binary mobile phase B, comprising acetonitrile, are utilized. To make the mobile phase, we combine mobile phases A and B in a 50:50 ratio. A 10-minute isocratic program with a flow rate of 1.0 mL/min operates a mobile phase. Constantly kept at 35°C is the temperature of the column. The volume of the injection is 20 µL. The diluent was a mixture of 50 parts water and 50 parts acetonitrile by volume. The sample compartment temperature is kept at room temperature.[20-23] The UV detection wavelength selected is 280 nm (Fig. 1).

MS Conditions

The MS system of ABScix API200 equipped with the autosampler, autoinjector, and ion-source-ESI was used.[10-34]

Preparation of Sample and Standard Solutions

To make a 20 µg/mL stock solution of bilastine, 20 mg of the drug was shifted to a 100 mL volumetric flask and the diluent was dissolved. To make the montelukast stock solution (10 µg/mL), 10 mg of montelukast was dissolved in 100 mL of a volumetric flask and then mixed with a diluent. All things considered. A 2 and 1 µg/mL stock solution of bilastine and montelukast, respectively, was used to prepare a working standard solution.[35-36]

Forced Degradation Solution

Forced degradation of the APIs was done to identify the degradants and to establish the degradation pathway of the bilastine and montelukast.[37-38]

Bilastine Degradation Procedure

Acid degradation

A 1-mL of the standard solution was added to a 100 mL volumetric flask along with 1-mL of 1N HCl, and the combination was allowed to settle for 5 hours at room temperature. To neutralize sample after 5 hours, 1.0 mL of 1N NaOH was added. Then, diluent (2 µg/mL) was added till the volume was reached.

Base degradation

About 1-mL of standard solution was put to a 100 mL volumetric flask along with 1-mL of 1N NaOH. The mixture was then let to sit at room temperature for 5 hours. Dilute the sample to volume with diluent (2 µg/mL) and neutralize it with 1.0 mL of 1N HCl after 5 hours.

Table 1: MS parameters

Instrument	Automated sample and injector systems, a collision energy spectrometer, a Q1 ion source, a column oven, and an ESI electron spray ionizer are all standard features of the API-2000 liquid chromatography-mass spectrometer.		
Ion source setting		*Scan setting*	
Ion source	ESI	Positive ion	Polarity
Temperature	400°C	40	Declustering potential
Ion spray voltage	5000	1–10 min	Scan time
Curtain gas	20 psi	MRM	Scan type
Ion source gas (GS1)	50 psi	400	Focusing potential
Ion source gas (GS2)	60 psi	10	Entrance potential

Oxidative degradation

About 1-mL of standard stock solution was added to a 100 mL volumetric flask along with 1-mL of 30% H_2O_2, and this combination was allowed to settle for 3 hours at room temperature. Diluted to volume with a solution containing 2 µg/mL after three hours.

Thermal degradation

About 50 mg of bilastine was measured and then stored in a petri dish in a hot air oven set at 1000°C for a duration of 72 hours. Following a 72-hour period, 20 mg of bilastine was measured, moved to a 100 mL volumetric flask, and mixed with a diluent. 1.5 mL of solution was added to a 100 mL volumetric flask with diluent (2 µg/mL) until the volume was reached.

Photodegradation

About 50 mg of bilastine was measured and then exposed to light for 1.6 lux hours in a photostability chamber. About 20 mg of bilastine was weighed when the cycle ended and then dissolved in 100 mL of a volumetric flask with diluent. 1.5 mL of solution was added to a 100 mL volumetric flask with diluent (2 µg/mL) until the volume was reached. [39]

Montelukast Degradation Procedure

Acid degradation

A 1-mL of the standard solution was put into a 100-mL volumetric flask along with 1-mL of 0.1N HCl, and this The combination was allowed to settle for 4 hours at room temperature. A solution of 1N NaOH was added to the sample after 4 hours to neutralize it, then a diluent (1-µg/mL) was added until the volume was reached.

Base degradation

A 1-mL of the standard solution was shifted to a 100 mL volumetric flask, followed by adding 1.0 mL of 0.1N NaOH. The flask was then left at room temperature for 4 hours. Following a 4-hour period, 0.1 mL of 1N HCl was added to the sample to neutralize it, and then diluent (1-µg/mL) was added until up to volume.

Oxidative degradation

A 1-mL of standard stock solution was added to a 100 mL volumetric flask along with 1-mL of 30% H_2O_2, and the combination was allowed to settle for 3 hours at room temperature. After waiting three hours, add diluent (1-µg/mL) until volume is reached.

Thermal degradation

A 50 mg of montelukast was measured and then stored in a petri dish in a hot air oven set at 1000°C for a duration of 72 hours. Following a 72-hour period, 10 mg of montelukast API was measured, transported to a 100 mL volumetric flask, and dissolved in a diluent. A 100 mL volumetric flask was filled to capacity with diluent (1-µg/mL) after 1.0 mL of this solution was added to it.

Photodegradation

About 50 mg of montelukast was measured and then exposed to light for 1.6 lux hours in a photostability chamber. Dissolve 10 mg of montelukast in 100 mL of diluent after the cycle ends. Transfer the mixture to a 100 mL volumetric flask. About 100 mL volumetric flasks were filled to capacity with diluent (1-µg/mL) after 1.0 mL of this solution was added to them.

Chromatographic and LC/MS Interpretation

Standard solution

Standard solution of 2 µg/mL of bilastine and 1-µg/mL of montelukast was injected as a part of system suitability.

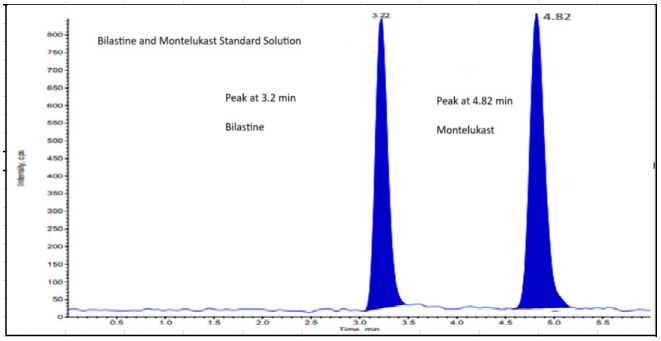


Fig. 1: Representative chromatogram of bilastine and montelukast

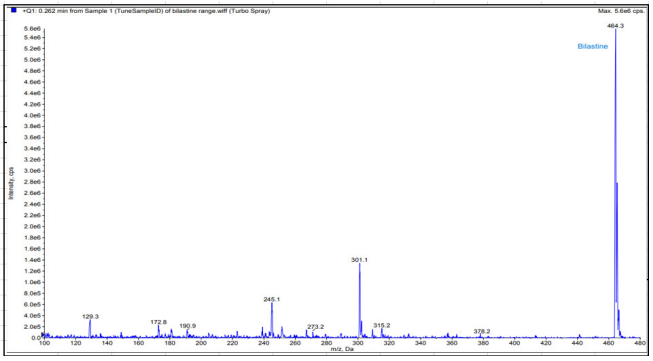


Fig. 2: Extracted mass spectra of bilastine (Molecular weight-463.2 g/mol)

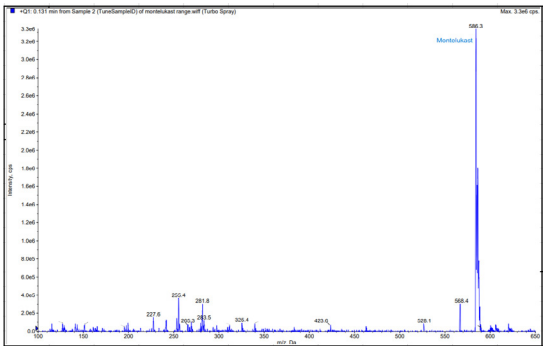


Fig. 3: Extracted mass spectra of bilastine (Molecular weight-586.3 g/mol)

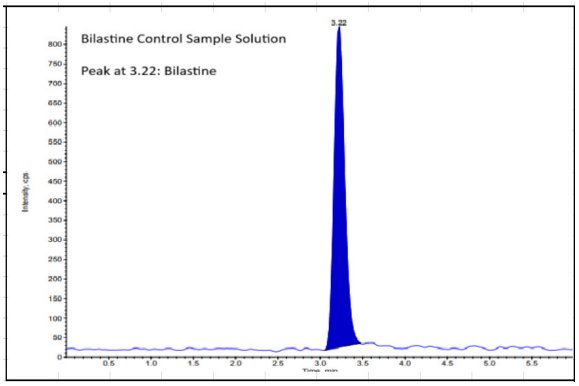


Fig. 4: Representative chromatogram of bilastine control sample

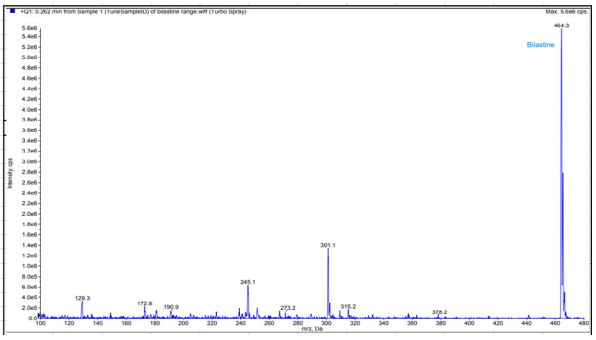


Fig. 5: Extracted mass spectra of bilastine control sample

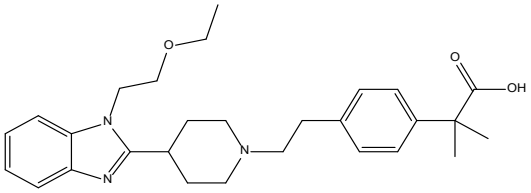


Fig. 6: Structure of bilastine

Bilastine Forced Degradation

The control sample and forced degraded samples of bilastine were injected into the HPLC and following chromatograms and MS spectra were obtained (Figs 2-6 and Table 2).

Bilastine acid degradation

Bilastine on degradation in acidic condition gives bilastine DP-1, which elutes at 2.40 minutes and molecular mass of 279.400 Da (Figs 7-9).

Bilastine base degradation

Bilastine on degradation in acidic condition gives bilastine DP-2, which elutes at 7.09 minutes and molecular mass of 389.200 Da (Figs 10-12).

Bilastine oxidative degradation

Bilastine on Oxidative degradation gives bilastine DP-3, which elutes at 5.60 minutes and molecular mass of 394.500 Da (Figs 13-15).

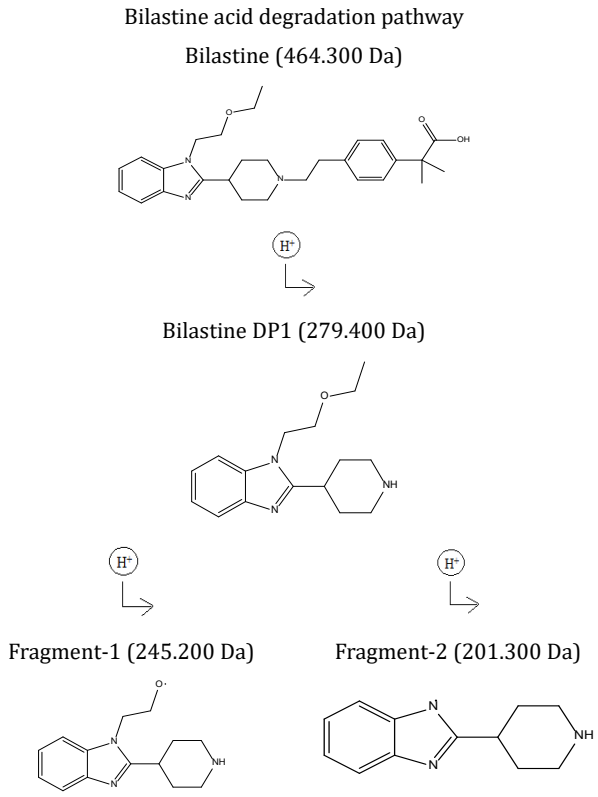


Fig. 7: Acid degradation pathway of bilastine

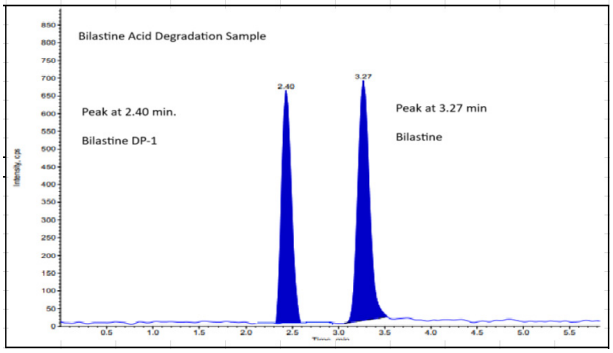


Fig. 8: Representative chromatogram of acid degradation sample of bilastine

Bilastine thermal and photodegradation

Bilastine is stable in thermal and photolytic conditions as no degradation observed (Fig. 16).

Degradation summary of bilastine

Degradation product-1 formed by acid hydrolysis, degradation product-2 formed by base hydrolysis and degradation product-3 formed by oxidative hydrolysis, while there was no degradation observed in the thermal and photolysis. This study shows that bilastine is prone to hydrolysis and remains stable when exposed to thermal and photolytic stress conditions (Figs 17 and 18).

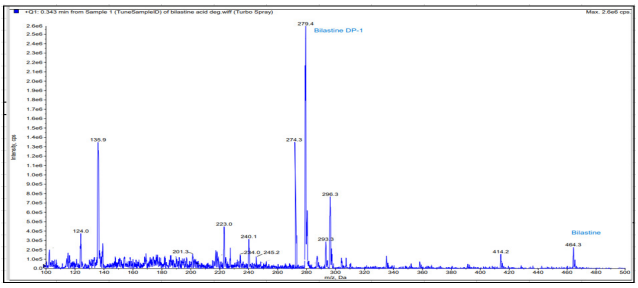


Fig. 9: Mass spectra of bilastine acid degradation

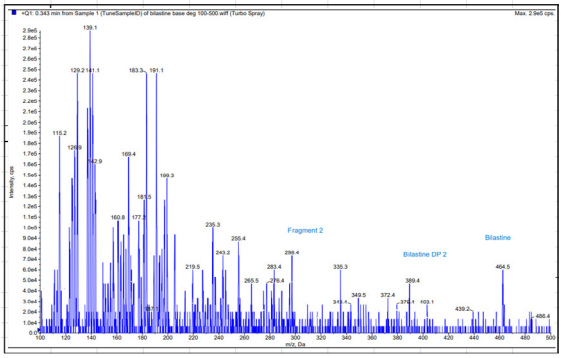


Fig. 12: MS spectra of base degradation of bilastine

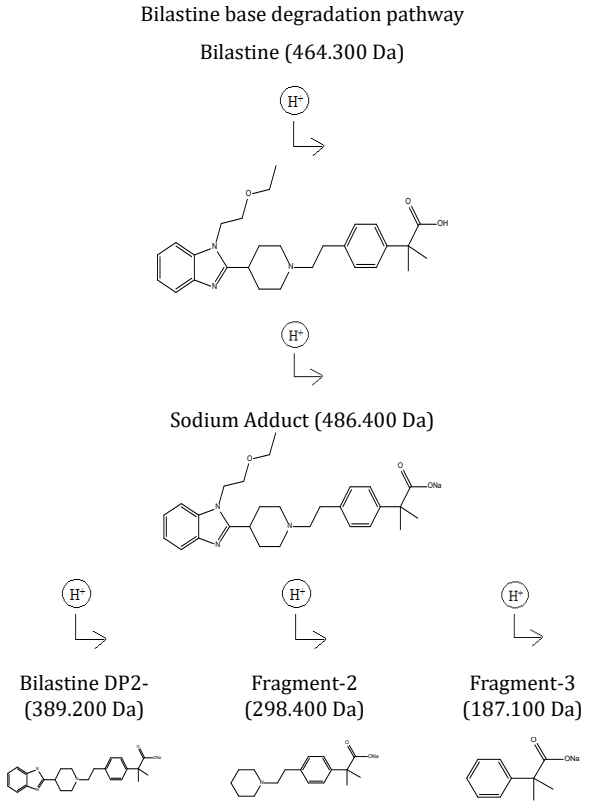


Fig. 10: Base degradation pathway of bilastine

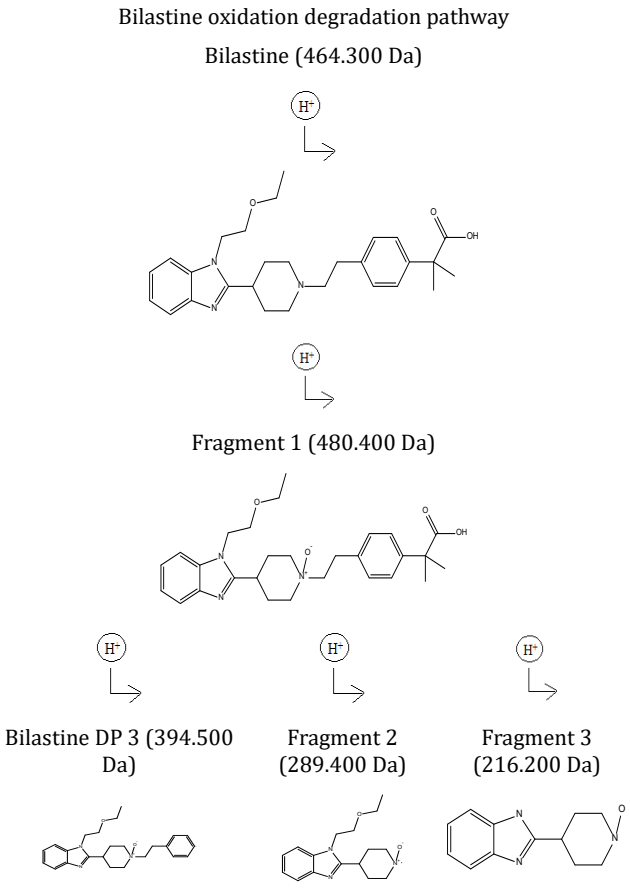


Fig. 13: Oxidative degradation pathway of bilastine

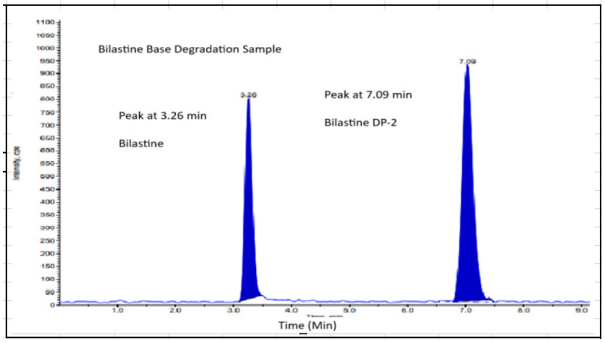


Fig. 11: Representative chromatogram of base degradation sample of bilastine

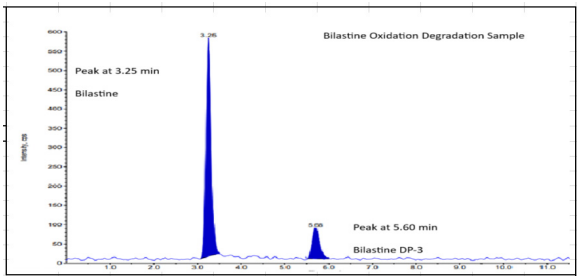


Fig. 14: Representative chromatogram of oxidative degradation of bilastine

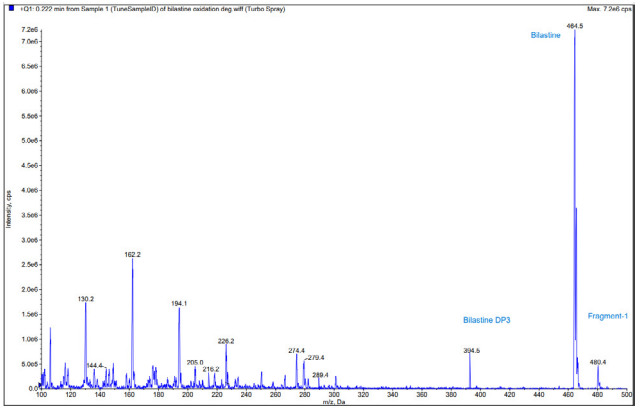


Fig. 15: Mass spectra of oxidative degradation of bilastine

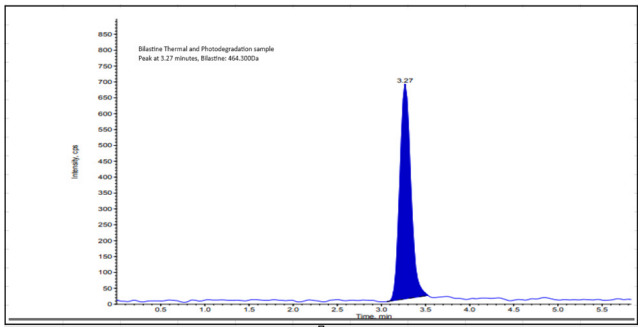


Fig. 16: Representative chromatogram of bilastine thermal and photodegradation sample.

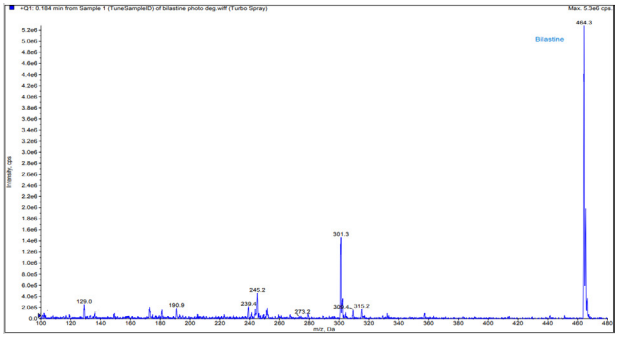


Fig. 17: Mass spectra of bilastine photodegradation

Table 2: Degradation of bilastine

API/Degradant	*Degradation*	*Retention time (min)*	*m/z Ratio (Da)*	
			MRM Q1	*MRM Q3*
Bilastine	NA	3.27	464.3	190.9
Bilastine DP-1	Acid	2.40	274.3	201.3
Bilastine DP-2	Base	7.09	389.2	298.4
Bilastine DP-3	Oxidative	5.60	394.5	289.4
	Thermal	No Degradation Observed		
	Photo			

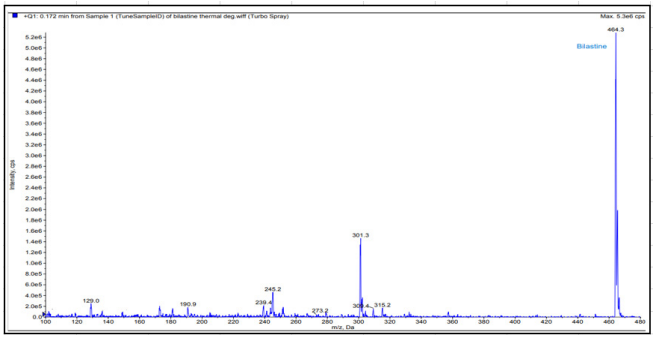


Fig. 18: Mass spectra of bilastine thermal degradation

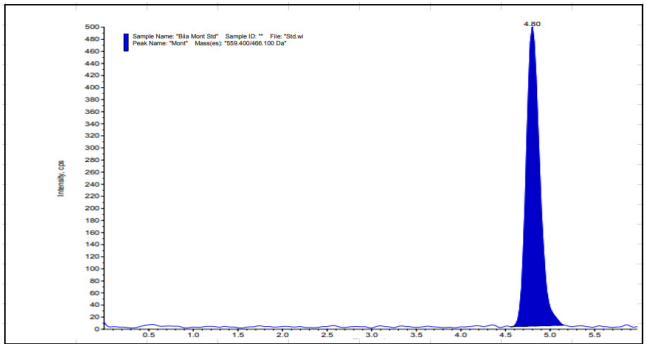
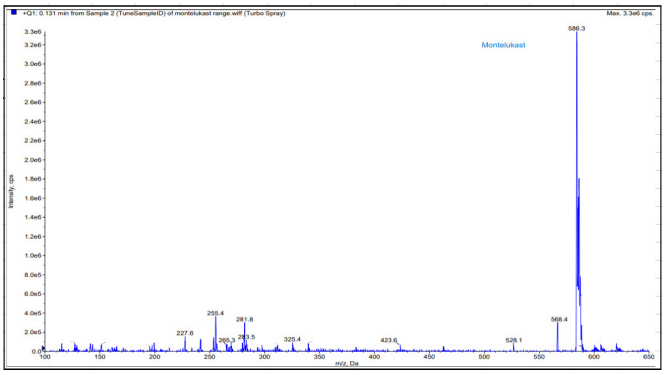


Fig. 19: Representative chromatrogram of montelukast control sample



Note: The spectra of thermal and photo degradation were same to bilastine API. This shows that there is no degradation.

Fig. 20: Mass spectra of montelukast control sample

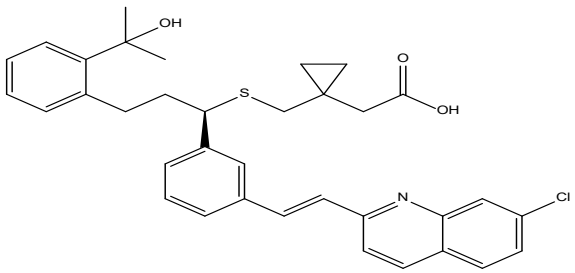


Fig. 21: Montelukast structure

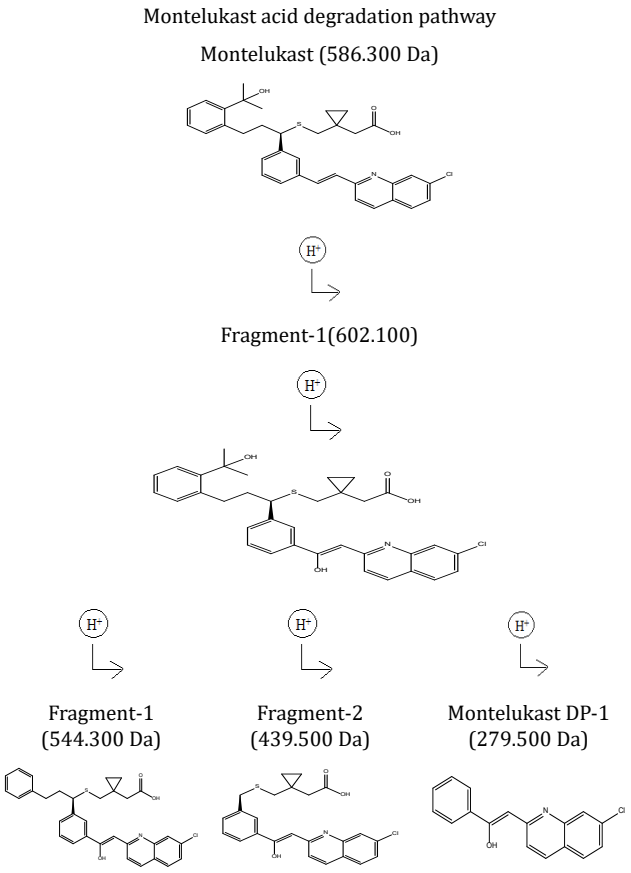


Fig. 22: Acid degradation pathway of montelukast

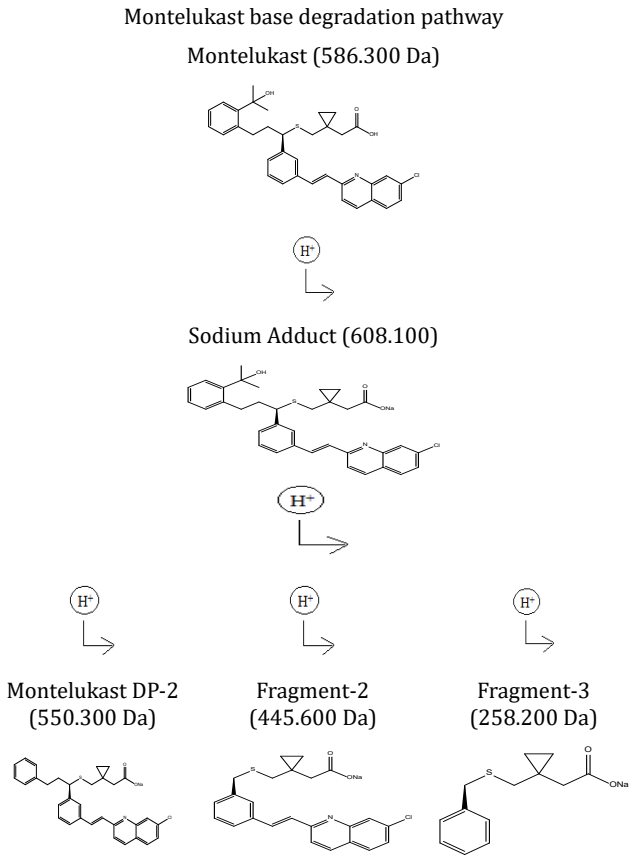


Fig. 25: Base degradation pathway of montelukast

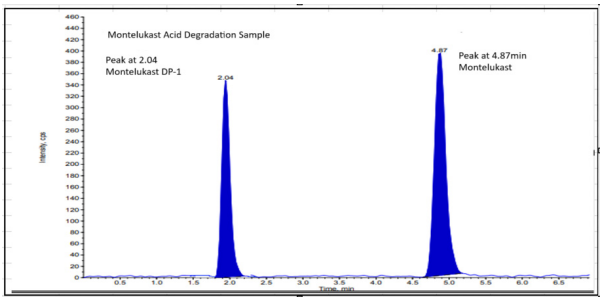


Fig. 23: Representative chromatogram of acid degradation sample of montelukast

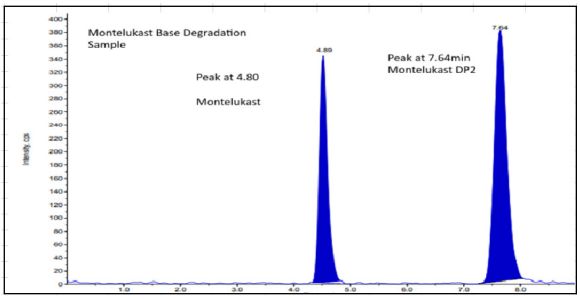


Fig. 26: Representative chromatogram of base degradation sample of montelukast

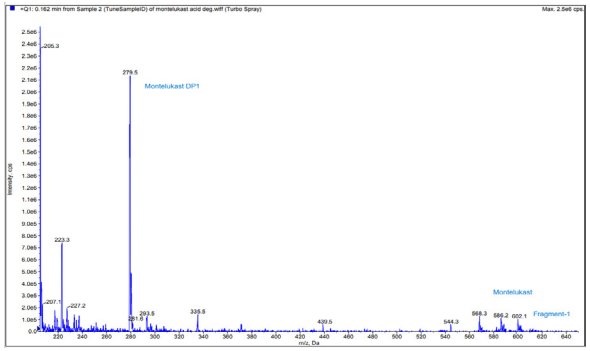


Fig. 24: Mass spectra of acid degradation of montelukast

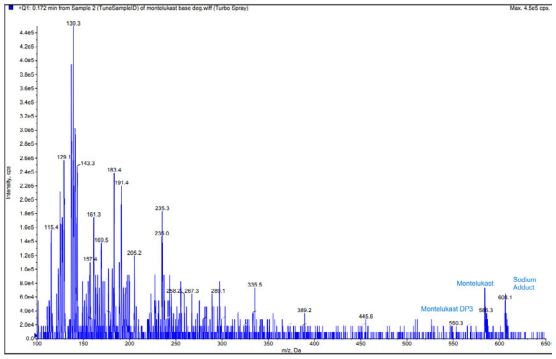


Fig. 27: Mass spectra of base degradation of montelukast

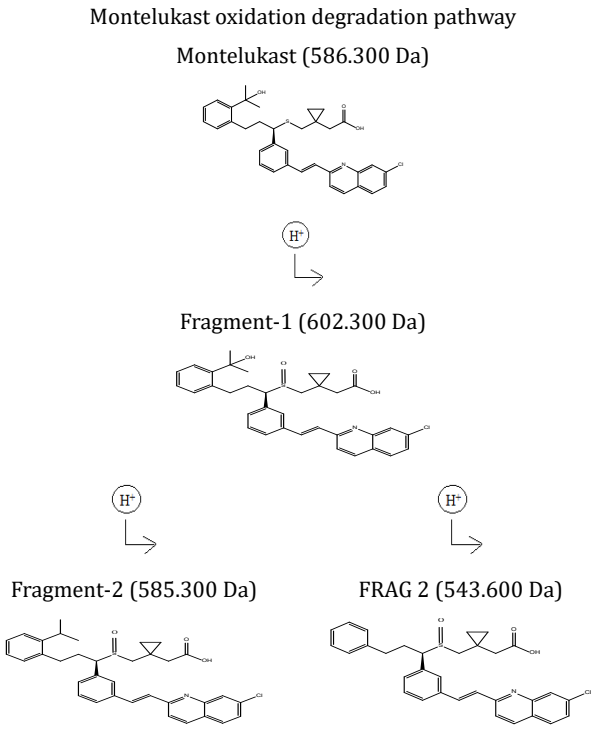


Fig. 28: Oxidative degradation pathway of bilastine acid degradation

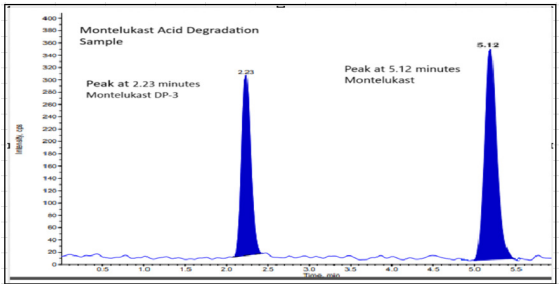


Fig. 29: Representative chromatogram of oxidative degradation of montelukast

Montelukast degradation

The control sample and forced degraded samples of montelukast are injected into the HPLC and following chromatograms and MS spectra obtained (Figs 19-21).

Montelukast acid degradation

Montelukast on degradation in acidic condition gives montelukast DP-1, which elutes at 2.04 minutes and molecular mass of 279.500 Da (Figs 22-24).

Montelukast base degradation

Montelukast on degradation in Basic condition gives montelukast DP-2, which elutes at 7.04 minutes and molecular mass of 550.300 Da (Figs 25-27).

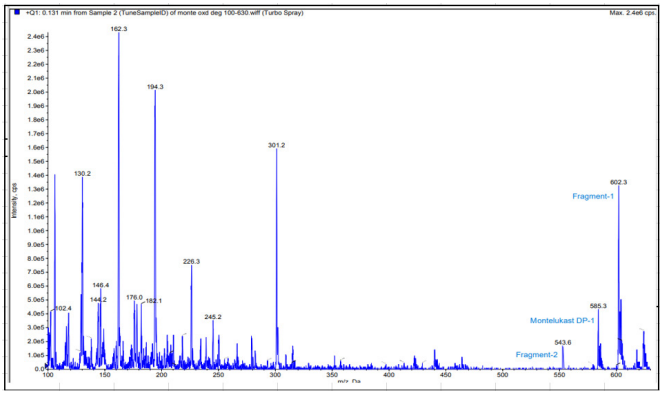


Fig. 30: Mass spectra of oxidation degradation of montelukast

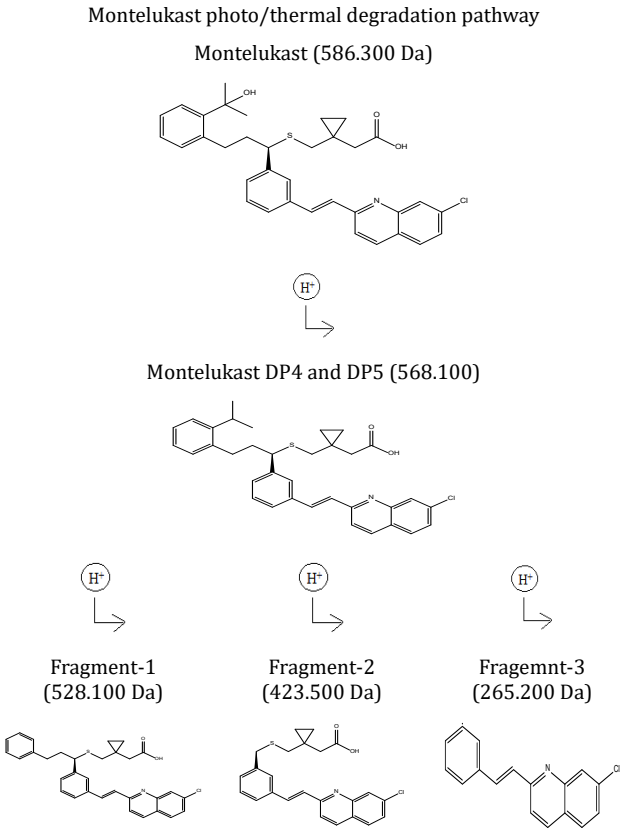


Fig. 31: Thermal/photo degradation pathway of bilastine acid degradation

Montelukast oxidative degradation

Montelukast on degradation in basic condition gives montelukast DP-2, which elutes at 7.04 minutes and molecular mass of 550.300 Da (Figs 28-30).

Montelukast Thermal/Photo Degradation

Montelukast degrades to Montelukast DP4 and DP5 in thermal and photolytic degradation. The degradant was same, which elutes at 8.14 minutes with molecular mass of 568.100 Da (Figs 31 and 32).

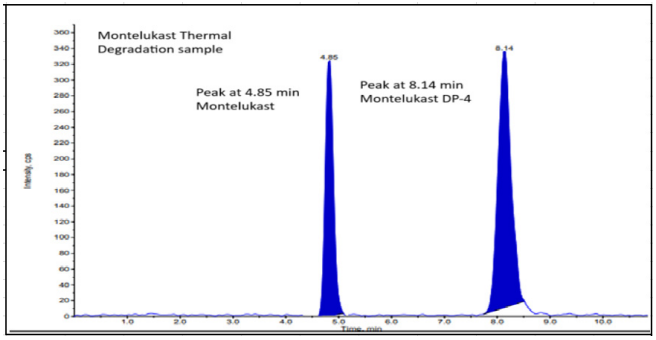


Fig. 32: Representative chromatogram of thermal degradation of montelukast

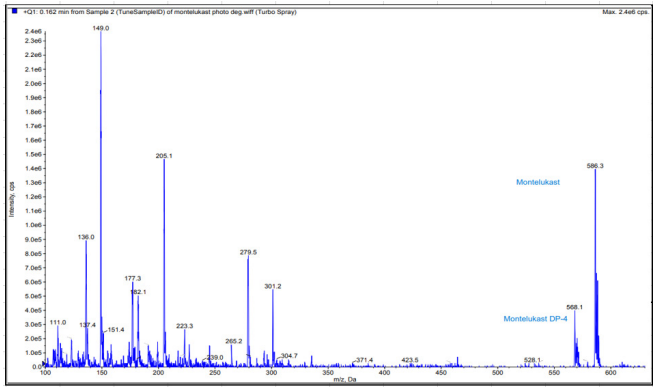


Fig. 33: Mass spectra of thermal degradation of montelukast

Summary of Montelukast Degradation

Montelukast degradation product-1 formed by acid hydrolysis, degradation product-2 formed by base hydrolysis and degradation product-3 was formed by oxidative hydrolysis, while the degradation products 4 and 5 have the same retention time and same molecular mass, which predicted the same structure in the thermal and photolysis, respectively, which means degradation product of thermal and photolytic degradation is same for montelukast. This study shows that montelukast gets degraded when exposed to the acid, base, oxidation, photo and thermal degradation (Fig. 33 and Table 3).

Method Validation

According to ICH Q2 (R1) standards, the procedure underwent thorough validation. Specificity was tested by injecting the blank, standard, and marketed samples. Linearity and accuracy was proved from LoQ to 125% level (For bilastine 0.1–2.5 µg/mL and for montelukast 0.05–12.5 µg/mL). The method was precise at LoQ level for montelukast with s/n ratio of 11 and for bilastine s/n ratio was 12. LoD of the method was established at 0.05 µg/mL for bilastine and 0.025 µg/mL for montelukast. The method was found robust for flow rate variation (1.2 and 0.8 mL/min) and for mobile phase composition variation (40:60- Mobile Phase A: Mobile Phase B and 60:40- Mobile Phase A: Mobile Phase B). All system suitability parameters were passing for robustness conditions.

Results And Discussion

Method Development and Optimization

Separation of peaks (primary peak, impurities, and others) is the fundamental goal of chromatographic methods. Various trials were taken to optimize the method using different columns and mobile phase combinations. Method development was initiated with mobile phase A as water and mobile phase B as acetonitrile in 70:30 ratio, with flow rate of 0.8 mL/min, column as Phenomenex Luna C-18 (250*4.6) mm, 5 µm. Bilastine was observed at 6 minutes, while montelukast peak was not observed. Further flow rate was increased to 1.0 mL/minute and mobile phase composition was changed to 60:40. Montelukast peak was not eluted in this trial. The mobile phase A was replaced by 0.1% CH_2O_2 in H_2O and the flow rate was changed to 0.8 mL/min and column as Zorbax XDB C-18 (150*4.6) mm, 5 µm and in this trial Bilastine and Montelukast was observed. During forced degradation few changes in the method were made to elute the degradation peaks within 10 minutes of run time. The chromatographic condition was finalized with column Agilent, Zorbax XDB C-18 (150*4.6) mm, 5 µm, and mobile phase as 0.1% CH_2O_2 in H_2O and acetonitrile (50:50) as mobile phase, with mode of elution as isocratic and column temperature of 35°C with flow rate of 1.0 mL/minute, injection volume of 20 µL and run time of 10 minutes (Figs 34 and 35).

Table 3: Degradation of montelukast

API/Degradant	*Degradation*	*Retention time (min)*	*m/z Ratio (Da)*	
			MRM Q1	*MRM Q3*
Montelukast	NA	4.8	586.3	568.4
Montelukast DP-1	Acid	2.0	279.5	281.6
Montelukast DP-2	Base	7.6	550.3	258.2
Montelukast DP-3	Oxidative	2.2	585.3	543.6
Montelukast DP-4	Thermal	8.1	568.1	265.2
Montelukast DP-5	Photo	8.1	568.1	265.2

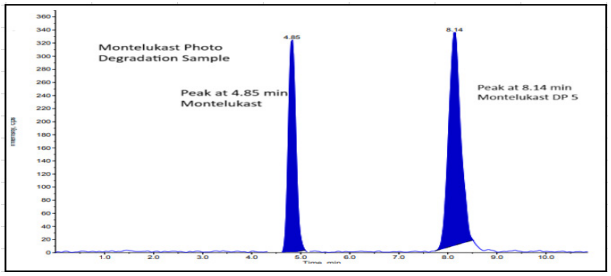


Fig. 34: Representative chromatogram of photodegradation of montelukast

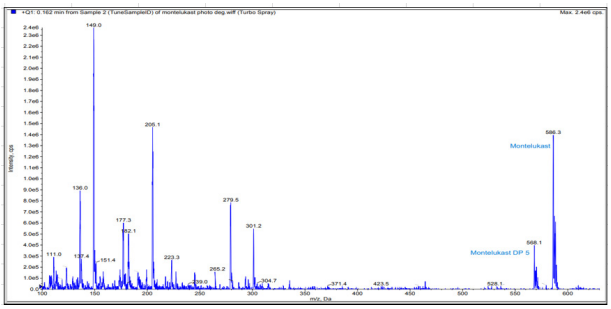


Fig. 35: Mass spectra of photodegradation of montelukast

Forced Degradation Studies

Bilastine

Degradation was observed in bilastine in acid, base and oxidation condition. The major acid degradant (Bilastine DP1) was witnessed with m/z ratio of 274.300 Da, for base degradation (Bilastine DP2) major degradant was witnessed with m/z ratio of 389.200 Da, for oxidative degradation (Bilastine DP3) major degradant was witnessed with m/z ratio of 394.500 Da. No degradation was observed in thermal and photodegradation.

Montelukast

Degradation was observed in montelukast in acid, base, oxidation, photo and thermal condition. The major acid degradant (Montelukast DP1) was witnessed with m/z ratio of 279.500 Da, for base degradation (Montelukast DP2) major degradant was witnessed with m/z ratio of 550.300 Da, for oxidative degradation (Montelukast DP3) major degradant was witnessed with m/z ratio of 585.300 Da. For thermal and photodegradation, the same profile was observed, with major degradants (Montelukast DP4 & DP5) with m/z ratio of 568.100 Da.

Conclusion

A short, mass-compatible method is developed for simultaneous quantification of degradation products of montelukast and bilastine. Degradation pathways of montelukast and bilastine are established and structures of degradation products are identified. The bilastine is stable under thermal and photolytic degradation, while the montelukast shows degradation in all stress conditions. The results obtained indicate that the process is stability-indicating, specific, accurate, linear and specific. The commercialized preparation has been successfully prepared using the procedure. The aforementioned medicinal goods, or a mix of the two, can be effectively subjected to the method's routine and stability analyses. The method's key selling point is that it can be utilized to detect any unknown peak-generating during stability investigations without requiring any additional adjustments, and it is also mass-compatible.

References

1. Narang AS, Desai D, Badawy S. Impact of excipient interactions on solid dosage form stability. Pharm Res. 2012 Oct;29(10):2660-83. Available from doi: 10.1007/s11095-012-0782-9.
2. Murthy KS, Ghebre-Sellassie I. Current perspectives on the dissolution stability of solid oral dosage forms. Journal of pharmaceutical sciences. 1993 Feb;82(2):113-26. Available from doi: 10.1002/jps.2600820202.
3. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. European Journal of Pharmaceutics and Biopharmaceutics. 2004 Sep 1;58(2):265-78. Available from doi:10.1016/j.ejpb.2004.03.001.
4. Siepmann J, Siepmann F. Mathematical modeling of drug delivery. International journal of pharmaceutics. 2008 Dec 8;364(2):328-43. Available from doi: 10.1016/j.ijpharm.2008.09.004.
5. Tamizi E, Jouyban A. Forced degradation studies of biopharmaceuticals: Selection of stress conditions. European Journal of Pharmaceutics and Biopharmaceutics. 2016 Jan 1;98:26-46. Available from doi: 10.1016/j.ejpb.2015.10.016.
6. Sharma MK, Murugesan M. Forced degradation study an essential approach to develop stability indicating method. J Chromatogr Sep Tech. 2017;8(1):349. Available from doi: 10.4172/2157-7064.1000349
7. Rawat, T., & Pandey, I. P. (2015). Forced degradation studies for drug substances and drug products-scientific and regulatory considerations. Journal of pharmaceutical Sciences and research, 7(5), 238-41. Available from doi: https://doi.org/10.22270/ajprd.v10i2.1104
8. Ridolo E, Montagni M, Bonzano L, Incorvaia C, Canonica GW. Bilastine: new insight into antihistamine treatment. Clinical and Molecular Allergy. 2015 Dec;13:1-6. Available from doi: 10.1186/s12948-015-0008-x
9. Gandhi J, Godse K, Godse G. Bilastine: A novel antihistamine. Indian Journal of Drugs in Dermatology. 2018 Jan 1;4(1):3-6. Available from doi:10.4103/ijdd.ijdd_12_18
10. Church MK, Tiongco-Recto M, Ridolo E, Novák Z. Bilastine: a lifetime companion for the treatment of allergies. Current Medical Research and Opinion. 2020 Mar 3;36(3):445-54. Available from doi: 10.1080/03007995.2019.1681134.
11. Mittal PA, Godse KV, Patil SP. Second-generation antihistamines. Indian Journal of Drugs in Dermatology. 2016 Jan 1;2(1):3-12. Available from doi: 10.4103/2455-3972.184094
12. Kowal K, DuBuske L. Bilastine as a potential treatment in allergic rhinitis. American Journal of Rhinology & Allergy. 2014 Jul;28(4):312-6. Available from doi: 10.2500/ajra.2014.28.4049.
13. Church, M. K. (2011). Safety and efficacy of bilastine: a new H1-antihistamine for the treatment of allergic rhinoconjunctivitis and urticaria. Expert opinion on drug safety, 10(5), 779-793. Available from doi: 10.1517/14740338.2011.604029.
14. Jáuregui I, Ferrer M, Bartra J, del Cuvillo A, Dávila I, Montoro J, Mullol J, Sastre J, Valero A. Bilastine for the treatment of urticaria. Expert opinion on pharmacotherapy. 2013 Aug 1;14(11):1537-44. Available

from doi: 10.1517/14656566.2013.800044.
15. Gieroń J. Determination of bilastine in biological material–analysis of a fatal case. Problems of Forensic Sciences. 2019;119:225-39. Available from doi: 10.2147/TCRM.S16079
16. Virchow JC, Bachert C. Efficacy and safety of montelukast in adults with asthma and allergic rhinitis. Respiratory medicine. 2006 Nov 1;100(11):1952-9. Available from doi: 10.1016/J.rmed.2006.02.026
17. Lee YJ, Kim CK. Montelukast use over the past 20 years: monitoring of its effects and safety issues. Clinical and Experimental Pediatrics. 2020 Oct;63(10):376. Available from doi: 10.3345/cep.2019.00325.
18. Bjermer L. Montelukast in the treatment of asthma as a systemic disease. Expert Review of Clinical Immunology. 2005 Sep 1;1(3):325-36. Available from doi: 0.1586/1744666X.1.3.325.
19. Benninger MS, Waters H. Montelukast: pharmacology, safety, tolerability and efficacy. Clinical Medicine. Therapeutics. 2009 Jan;1:CMT-S1147. Available from doi: https://doi.org/10.4137/CMT.S1147
20. Esteitie R, deTineo M, Naclerio RM, Baroody FM. Effect of the addition of montelukast to fluticasone propionate for the treatment of perennial allergic rhinitis. Annals of Allergy, Asthma & Immunology. 2010 Aug 1;105(2):155-61. Available from doi: 10.1016/j.anai.2010.05.017.
21. Medić-Šarić M, Jasprica I, Smolčić-Bubalo A, Mornar A. Optimization of chromatographic conditions in thin layer chromatography of flavonoids and phenolic acids. Croatica chemica acta. 2004 May 31;77(1-2):361-6. Available from doi: https://doi.org/10.1186/1475-2891-8-33
22. Guo Y, Srinivasan S, Gaiki S. Investigating the effect of chromatographic conditions on retention of organic acids in hydrophilic interaction chromatography using a design of experiment. Chromatographia. 2007 Aug;66:223-9. Available from doi: 10.1365/s10337-007-0264-0
23. Fujito Y, Hayakawa Y, Izumi Y, Bamba T. Importance of optimizing chromatographic conditions and mass spectrometric parameters for supercritical fluid chromatography/mass spectrometry. Journal of chromatography A. 2017 Jul 28;1508:138-47. Available from doi: 10.1016/j.chroma.2017.05.071.
24. Satapute P, Kamble MV, Adhikari SS, Jogaiah S. Influence of triazole pesticides on tillage soil microbial populations and metabolic changes. Science of the total environment. 2019 Feb 15;651:2334-44. Available from doi: 10.1016/j.scitotenv.2018.10.099.
25. Kolari K, Sahamies J, Kalenius E, Novikov AS, Kukushkin VY, Haukka M. Metallophilic interactions in polymeric group 11 thiols. Solid State Sciences. 2016 Oct 1;60:92-8. Available from doi: https://doi.org/10.1016/j.solidstatesciences.2016.08.005
26. Ghosh BN, Lentz D, Schlecht S. Substituent effects in solution speciation of the mononuclear and dinuclear trimethylplatinum (IV) iodide complexes of pyridines. New Journal of Chemistry. 2015;39(5):3536-42. Available from doi: 10.1039/C7NJ00337D
27. Kawahara K, Ohta K, Miyamoto H, Nakamura S. Preparation and solution properties of pullulan fractions as standard samples for water-soluble polymers. Carbohydrate polymers. 1984 Jan 1;4(5):335-56. Available from doi: 10.22037/afb.v7i4.29747
28. Holechek JL. Sample preparation techniques for microhistological analysis. Rangeland Ecology & Management/Journal of Range Management Archives. 1982 Mar 1;35(2):267-8. Available from doi: 10.2307/3898409
29. Jain D, Basniwal PK. Forced degradation and impurity profiling: recent trends in analytical perspectives. Journal of pharmaceutical and biomedical analysis. 2013 Dec 1;86:11-35. Available from doi: 10.1016/j.jbpa.2013.07.13
30. Blessy MR, Patel RD, Prajapati PN, Agrawal YK. Development of forced degradation and stability indicating studies of drugs—A review. Journal of pharmaceutical analysis. 2014 Jun 1;4(3):159-65. Available from doi: https://doi.org/10.1016/j.jpha.2013.09.003
31. Ouarezki R, Guermouche S, Guermouche MH. Degradation kinetics of Bilastine determined by RP-HPLC method and identification of its degradation product in oxidative condition. Chemical Papers. 2020 Apr;74:1133-42. Available from doi: 10.1007/s11696-019-00956-x
32. Patel DS, Pasha DT. Stability Indicating Isocratic HPLC Method for Bilastine and Characterization of Forced Degradation Products by LC-MS/MS.(2023). Int. J. Life Sci. Pharma Res. 2022;13(1):P83-93. Available from doi: https://doi.org/10.22376/ijlpr.2023.13
33. Patel KK, Patel AM, Patel CN. A new simple RP-HPLC Method development, Validation and Forced degradation studies of Bilastine. Asian Journal of Pharmaceutical Analysis. 2021;11(3):183-7. Available from doi: 10.52711/2231-5675.2021.00031
34. Pasham M, Haridasyam SB, Boppy NP, Venkatanarayana M, Palakurthi AK. Stability-indicating liquid chromatography method development and validation for impurity profiling of montelukast sodium in bulk drug and tablet dosage form. Biomedical Chromatography. 2022 Apr;36(4):e5330. Available from doi:10.1002/bmc.5330
35. Sunkara R, Ajitha M. Stability Indicating RP-HPLC Method Development and Validation for Simultaneous Estimation of Montelukast and Bilastine in Bulk and Pharmaceutical Dosage Form: https://doi. org/10.54037/WJPS. 2022.100109. World Journal of Pharmaceutical Sciences. 2022 Jan 2:90-7. Available from doi: https://doi.org/10.54037/WJPS.2022.100109
36. Andhale SM, Nikalje AP. G. Simultaneous estimation of Bilastine and montelukast in bulk by RP-HPLC and assessment of its applicability in the marketed tablet dosage form. J Pharm Res Int. 2022;34(3B):8-25. Available from doi: 10.9734/jpri/2022/v34i3B35388
37. Ali S, Gupta M. Method development and validation for the simultaneous estimation of montelukast sodium and levocetirizine hydrochloride tablet using RP-HPLC. Journal of Pharmaceutical Sciences and Research. 2019 Aug 1;11(8):2998-3000. Available from doi: https://doi.org/10.24092/CRPS.2022.120110

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