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Development and validation of stability-indicating UPLC method for the determination of lafutidine and its impurities in bulk and pharmaceutical dosage form

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Abstract

Background: A simple and rapid stability-indicating, reversed phase ultra-performance liquid chromatography (UPLC) method was developed for the quantitative determination of lafutidine and its four potential impurities.

Results: Separation was achieved on Acquity BEH-shield RP18 UPLC column (3.0 mm × 100 mm, 1.7 μm) under the gradient mode of elution by using mobile phase A (0.02M diammonium hydrogen phosphate/acetonitrile, 80:20 v/v) and mobile phase B (0.02M diammonium hydrogen phosphate/acetonitrile, 30:70 v/v). The flow rate was maintained at 0.5 mL min⁻¹. UV detection was carried out at 276 nm.

Conclusions: Stability-indicating capability of the developed method is established by analyzing forced degradation samples in which the spectral purity of lafutidine is ascertained along with the separation of degradation products from analyte peak. The developed UPLC method is validated as per International Conference on Harmonization guidelines with respect to system suitability, specificity, precision, sensitivity, accuracy, linearity, and robustness.

Keywords: Lafutidine, UPLC, Degradation, RSD and validation, Stability indicating

Background

Lafutidine belongs to the class of H₂-receptor antagonists and is used in the treatment of peptic ulcer and gastro-esophageal reflux disease or GERD [1]. It is available in the market under the brand name Lafaxid[®] in the form of tablets for oral administration containing 5 or 10 mg of lafutidine with daily dose of 5 to 10 mg twice daily [2]. Being a histamine H₂-receptor antagonist, it inhibits daytime (i.e., postprandial) as well as night time gastric acid secretion. It also has gastroprotective activity that particularly affects the mucosal blood flow. It elevates the postprandial intragastric pH and increases plasma calcitonin gene-related peptide and somatostatin concentrations in humans. From the clinical studies, it is proven that lafutidine is equal or superior to conventional H₂ antagonists in antiulcer potency and it is

useful for the prevention of ulcer relapse and or treatment of NSAID-induced gastroduodenal damage [3].

The analytical method for determination of lafutidine and its impurities in bulk and pharmaceutical dosage form is highly essential to monitor and control the impurities in the drug substances. Although many analytical techniques like gas chromatography (GC), capillary electrophoresis (CE), and liquid chromatography (LC) can be employed for the analysis, the most widely used technique is the reversed-phase liquid chromatography employing a non-polar stationary phase [4,5]. An extensive literature survey revealed that there are several bioanalytical high performance liquid chromatography (HPLC) methods reported in the literature for the analysis of lafutidine in human plasma using HPLC-ESI-MS [6,7], in tablet dosage form by reversed-phase high performance liquid chromatography [8] and in human serum by HPLC with fluorescence detection [9]. To the best of our knowledge, none of the currently available

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analytical methods can separate all the known related compounds and degradation impurities of lafutidine drug substance. There is no pharmacopoeial reference available for analysis of bulk API or solid dosage form of lafutidine. Furthermore, there is no cost- and time-effective method reported in the literature that can adequately separate lafutidine from its impurities and degradants in bulk and pharmaceutical dosage form. Moreover, the analysis using LCMS, GC/MSD, and LC-MS is very expensive and delicate as compared to ultra-performance liquid chromatography (UPLC) for routine quality control analysis. Hence, we focused on developing a selective, fast, cost-effective, and stability-indicating method using this advanced technique (UPLC) for the determination of lafutidine and its impurities in bulk and pharmaceutical dosage form. Hence, a reproducible stability-indicating UPLC method was developed which is time- and cost-effective as compared to the reported methods. The method was successfully validated according to the USP<1225> Validation of Compendial Procedures and International Conference on Harmonization (ICH) guidelines Q2 (R1) for validation of analytical procedures: text and methodology [10,11].

Methods

Materials and reagents

The samples of lafutidine and its four impurities viz., Imp A, Imp B, Imp C, and Imp D as shown in Figure 1 were received from synthetic laboratory, Emcure Pharmaceutical Ltd, Pune, India. Diammonium hydro-

gen orthophosphate of HPLC grade and liquid ammonia of AR grade were purchased from Merck, Mumbai, India. Acetonitrile of gradient grade was purchased from J.T. Baker, Mumbai, India. De-ionized water of high purity was obtained from Millipore, Milli-Q (Bedford, MA, USA) purification system.

Instrumentation and operating conditions

Waters' Acquity UPLC system (Waters, Milford, MA, USA) equipped with quaternary gradient pump, auto sampler, column oven, and photodiode array detector was used for method development and method validation. The output signal was monitored and processed using Empower software version 3. The UPLC columns used during method development were Acquity UPLC BEH-C18 (2.1 mm × 50 mm, 1.7 μm), Acquity CSH phenyl-hexyl (2.1 mm × 100 mm, 1.7 μm), and Acquity UPLC BEH-shield RP18 (3.0 mm × 100 mm, 1.7 μm).

Acquity UPLC BEH-shield RP18 (3.0 mm × 100 mm, 1.7 μm) column thermostated at 35°C was used for the separation. Mobile phase A was prepared by mixing the phosphate buffer (aqueous solution of 0.02 M diammonium hydrogen phosphate, adjusted the pH to 9 with liquid ammonia) and acetonitrile in the ratio of 80:20 v/v, whereas mobile phase B was prepared by mixing the phosphate buffer and acetonitrile in the ratio of 30:70 v/v. The flow rate and injection volume was 0.5 mL min⁻¹ and 4 μL, respectively. The analysis was carried out under the gradient conditions as time (min)/A (v/v)/B (v/v); $T_{0.01}/100:0$, $T_{2.0}/75:25$, $T_{3.0}/60:40$, $T_{10}/30:70$, $T_{12}/30:70$, $T_{12.5}/100:0$, and $T_{16}/100:0$. The data

Figure 1 Process-related impurities and degradation-related impurities of lafutidine. (a) Blank preparation. (b) Standard preparation.

were acquired at 276 nm for 16 min and processed by using Empower software version 3.0. For the analysis of forced degradation study, the photo diode array detector was set to scan from 200 to 400 nm. The peak homogeneity was calculated in terms of peak purity.

Preparation of solutions

The diluent used for the analysis was prepared by preparing homogenous mixture of 700 ml of water and 300 ml acetonitrile. A solution of lafutidine was prepared at concentration of $1,000\ \mu\text{g mL}^{-1}$ in diluent. Stock solutions of each impurity (Imp-A, Imp-B, Imp-C, and Imp-D) were prepared at concentration about $150\ \mu\text{g mL}^{-1}$ in diluent. These solutions were further diluted to prepare the standard solution for quantification of impurities according to the specification limits (0.15%) of each impurity.

The sample of the formulation drug was prepared by powdering 20 tablets of lafutidine. An accurately weighed quantity of tablet powder was taken to prepare the solution equivalent to $1,000\ \mu\text{g mL}^{-1}$ of lafutidine in diluent. After adding about 50% of the total volume of diluent and ultrasonication for about 15 to 20 min, the solution was made up to the mark with the diluent and filtered through Merck nylon syringe filter (Merck KGaA, Darmstadt, Germany) having pore size $0.45\ \mu\text{m}$. The clear liquid was collected and used for the determination of related substances in the pharmaceutical dosage forms. This solution was diluted further volumetrically to $100\ \mu\text{g mL}^{-1}$ with diluent for assay determination in pharmaceutical dosage forms.

Analytical procedure

Lafutidine with concentration of $1,000\ \mu\text{g mL}^{-1}$ was spiked with Imp-A, Imp-B, Imp-C, and Imp-D at specification level, i.e., of 0.15% and this solution was used as a SSM. Using $4\ \mu\text{L}$ each of blank preparation as SSM, six replicates of standard solution and test solution are injected and separately chromatographed under the given chromatographic conditions. Resolution condition of not less than 2.0 between lafutidine and related compound D was set as system suitability parameter for SSM. The relative standard deviation of not more than 5.0% for areas obtained from six replicate injections of all impurities was used to verify the system precision.

Procedure for forced degradation study

The forced degradation study was planned to investigate specificity and stability-indicating property of the established method. The API was deliberately stressed in a solution state at acidic and alkaline pH and under oxidation conditions, in solid state at thermal and photolytic conditions. Solutions for degradation were prepared by dissolving the API in diluent at specification level,

i.e., $1,000\ \mu\text{g mL}^{-1}$ in diluent and then treating with 0.1 N hydrochloric acid (1 h heating at 90°C), with 0.1 N sodium hydroxide (1 h heating at 90°C), and with 30% aqueous hydrogen peroxide. The solutions after treatment were diluted up to the mark of desired concentration of $1,000\ \mu\text{g mL}^{-1}$ and were injected in the established method. For thermal degradation, the solid API was heated at 60°C for 24 h in calibrated oven. For photolytic degradation, the sample was exposed to UV source as per ICH guidelines for 7 days. The treated samples were diluted with diluent to the desired concentration of $1,000\ \mu\text{g mL}^{-1}$ and injected in the established method. All the stressed samples are quantified for lafutidine and its impurities. A photodiode array detector was used to establish peak purity and thus the homogeneity of lafutidine peaks under every stress condition. Mass balance of the degraded samples was carried out to correlate the loss of a parent drug and the increase in the amount of degradation products.

Results and discussion

Method development

Development and optimization of UPLC chromatographic conditions

Initially, the method was developed on HPLC for determination of lafutidine and its related impurities in bulk and pharmaceutical dosage forms. Due to the longer run time of about 60 min, the HPLC method was not validated but further migrated to UPLC wherein the run time was reduced about four times from 60 to 16 min.

The core objective of developing the UPLC method was to detect and determine the potential impurities present in lafutidine bulk and pharmaceutical dosage form and to achieve the separation of all four impurities (Imp-A, Imp-B, Imp-C, and Imp-D) along with the degradation products generated during stress studies.

UPLC column selection

Various UPLC stationary phases like Acquity UPLC BEH-C18 ($2.1\ \text{mm} \times 50\ \text{mm}$, $1.7\ \mu\text{m}$), Acquity CSH phenyl-hexyl ($2.1\ \text{mm} \times 100\ \text{mm}$, $1.7\ \mu\text{m}$), and Acquity UPLC BEH-shield RP18 ($3.0\ \text{mm} \times 100\ \text{mm}$, $1.7\ \mu\text{m}$) were used during development. Based on parameter-like resolution, tailing factor, and selectivity especially for impurity A which is a phenolic impurity, Acquity UPLC BEH-shield RP18 ($3.0\ \text{mm} \times 100\ \text{mm}$, $1.7\ \mu\text{m}$) was finalized for analysis.

Buffer selection

Various buffers like phosphate, sulfate, and acetate with pH ranging from 3.0 to 10.0 were tried for development. It was observed that at basic pH of about 8.0 which is equivalent to the pKa of the phosphate buffer, the separation and the tailing factors are satisfactory. Therefore,

diammonium hydrogen phosphate buffer was selected for analysis.

Organic modifier selection

Organic modifiers like acetonitrile and methanol were evaluated as mobile phase B. Satisfactory chromatographic separation was achieved when acetonitrile was used as mobile phase B in terms of better resolution and tailing factor. When methanol was tried as an organic modifier, the tailing factor for all the peaks was not within the system suitability criteria. Therefore, acetonitrile was finalized as organic modifier for analysis.

Optimization of chromatographic conditions

Premixed buffer and organic modifier combinations were prepared for mobile phase A and mobile phase B to improve the baseline interference. Various combinations of gradient time programs were tried and then finalized wherein all impurities and degradants are well separated from the main peak due to lafutidine. The

wavelength for analysis was selected as 276 nm which is UV maxima of lafutidine. The temperature selection of 35°C was optimized so as to attain maximum separation between the critical pair which is Imp-D and lafutidine. The rationale for selecting the flow rate of 0.5 ml/min for 3-mm ID column was that the increase in flow rate reduced the resolution between Imp-D and lafutidine to less than 2.0 which was not acceptable. The effect of sub-2 μ m particle size was not considered while calculating the total flow rate because from Van Deemter curve, at around 1.7 μ m particle size, one can attain the lowest height equivalent of theoretical plates (or highest resolution) that is constant over a wide range of flow rates.

The typical retention times of Imp-A, Imp-B, Imp-C, Imp-D, and lafutidine were about 1.37, 1.75, 3.64, 4.79, and 5.04 min, respectively (Figures 2 and 3), and the developed UPLC method was found to be specific for determination of lafutidine and its impurities in bulk and pharmaceutical dosage form.

a Blank preparation:-

b Standard preparation:-

Figure 2 Typical UPLC chromatograms of blank preparation and standard preparation. At specification level (Imp-A, Imp-B, Imp-C, and Imp-D at 0.15% and lafutidine at 0.10% of the test concentration). (a) Unspiked test sample. (b) Spiked test preparation.

a Unspiked test sample:-

b Spiked test preparation:-

Figure 3 Typical UPLC chromatograms of lafutidine unspiked test preparation and lafutidine spiked test preparation with known impurities. Imp-A, Imp-B, Imp-C, and Imp-D. (a) Acid-treated test sample. (b) Alkali-treated test sample. (c) Peroxide-treated test sample.

Identification of impurities

Impurities A, B, C, and D are spiked in lafutidine at desired concentrations of 0.15% with respect to test concentration of 1,000 $\mu\text{g mL}^{-1}$ to confirm the retention times under the chosen chromatographic conditions. All the impurities were well resolved from each other. Among the identified impurities, Imp-A and Imp-B are the process as well as degradation impurities; Imp-C is the key starting material in the process as well as degradation impurity; Imp-D is a process related impurity (Figure 1).

System suitability criteria

A system suitability test was defined based on the results obtained in several representative chromatograms. The

column efficiency determined from the analyte peak $>20,000$, the tailing factor <2.0 , and relative standard deviation (RSD) for impurity areas in six replicate injection of system suitability solution was $<5.0\%$. A resolution between lafutidine and Imp-D was >2.0 in SST solution. All the system suitability criteria during the validation of the study and the batch analysis study were within the acceptance limit. The results of system suitability are depicted in Table 1.

Experimental

Specificity (selectivity)

The data on forced degradation studies revealed that the degradation products were well separated from

Table 1 System suitability test results

Compound	RRT	Theoretical plate	Tailing factor (T)	Resolution (R_s)
Imp-A	0.27	25,721	1.33	-
Imp-B	0.35	35,801	1.10	5.69
Imp-C	0.72	26,913	1.60	21.64
Imp-D	0.95	29,211	1.14	11.12
Lafutidine	1.00	32,469	1.15	2.93

RRT, Relative retention time.

lafutidine and the peak purity data (purity angle less than purity threshold) of lafutidine proved the homogeneity of the peak. Significant degradation was observed in acid, alkali, and peroxide solution as shown in Figure 4. The mass balance is a process of adding together the assay value and the levels of degradation products to see how closely these add up to 100% of the initial value with due consideration of the margin of analytical error [12,13]. The mass balance of stressed samples was close to 100%. Forced degradation study results are given in Table 2.

Linearity

Linearity test solutions for related substance were prepared by diluting the impurity stock solution (as described in the section of 'Analytical procedure') to the required concentrations. The solutions were prepared at six concentration levels from limit of quantitations (LOQ) to 250% (LOQ, 0.75, 1.2, 1.5, 2.25, and 3.75 $\mu\text{g mL}^{-1}$) with respect to the specification level of impurities. The data were subjected to statistical analysis using a linear regression model; the regression equations and correlation coefficients are given in Table 3.

a Acid treated test sample

b Alkali treated test sample

c Peroxide treated test sample

Figure 4 Typical UPLC chromatograms of forced degradation study. (a) Acid-treated test sample, (b) base-treated test sample, and (c) peroxide-treated test sample.

Table 2 Forced degradation study results

Stress condition	Assay of lafutidine (%)	Observation and mass balance	Peak purity angle	Peak purity threshold
Untreated sample	98.74	-	0.205	0.530
Acid degradation	84.29	Unknown degradant of 11.71% and other unknown impurities (Mass balance ^a 99.91%)	0.122	0.391
Alkali degradation	84.65	Imp-B increased to 6.96% and Imp-C increased to 4.06%. Unknown degradant of 3.85% and other unknown impurities (Mass balance 99.4%)	0.165	0.433
Peroxide degradation	85.21	Unknown degradant increased to 8.48% and other unknown impurities (Mass balance 99.78%)	0.072	0.341
Thermal degradation	98.97	No significant change in percentage of known and unknown impurities (Mass balance 98.82%)	0.214	0.505
Photolytic degradation	98.85	No significant change in percentage of known and unknown impurities (Mass balance 99.1%)	0.214	0.505

^a Mass balance =% Assay +% Sum of all impurities +% Sum of all degradants.

Table 3 Validation data results of related substances of lafutidine

Compound	Related substances results			
	IMP-A	IMP-B	IMP-C	IMP-D
Precision (mean results ± % RSD)				
Method precision (n=6)	0.151 ± 0.87	0.155 ± 0.40	0.162 ± 1.22	0.155 ± 0.91
Intermediate precision (n=6)	0.152 ± 0.85	0.158 ± 0.38	0.161 ± 1.30	0.157 ± 0.93
Overall results (n=12)	0.152 ± 0.86	0.156 ± 0.39	0.162 ± 1.26	0.156 ± 0.92
Limit of detection (LOD)				
LOD (% wrt test) ^a	0.008	0.008	0.016	0.016
Limit of quantitations (LOQ)				
LOQ (% wrt test)	0.023	0.024	0.048	0.049
Linearityfor related substances LOQ to 250% of specification level				
Correlation coefficient (r)	0.9991	0.9999	0.9962	0.9995
Slope	55146.15	65742.56	57225.13	40483.59
Intercept	115.8901	74.74945	-685.587	31.96923
Accuracy(mean percentage recovery): LOQ to 150% of specification level				
LOQ	92	86	106	90
20%	103	102	85	99
40%	102	102	92	102
50%	109	101	95	100
80%	101	101	98	101
100%	102	101	98	102
150%	101	100	101	99

^a% wrt test LOD LOQ values are in percent with respect to test concentration of 1,000 µg mL⁻¹.

Limits of detection and quantitation

The limit of detection and limit of quantitation (LOD and LOQ) were determined for lafutidine and for each of the related substances as per ICH Q2R1 guideline from the standard deviation of the peak areas and slope of linearity data. The values of LOD and LOQ for impurities A, B, C, and D were found to be in the range of 0.007% to 0.022% and 0.008% to 0.023%, respectively. The calculated LOQ concentrations of all the components were verified for precision by injecting six individual preparations of Imp-A, Imp-B, Imp-C, Imp-D, and lafutidine. The RSD of LOQ precision was in the range of 1.22% to 9.78%. These limits of quantification levels of the impurities were helpful for the research work in controlling the impurities at the accepted level during the optimization of the process. The results were depicted in Table 3.

Precision

System precision

System precision for related substances determination was verified by system suitability mixture (SSM), which was analyzed for six times and RSD of Lafutidine and all impurities peak areas were evaluated and found to be between 0.36% to 1.30%.

Method precision and Intermediate precision

Precision of the method was studied for method precision and intermediate precision. Related substances method precision was demonstrated by analyzing six separate Lafutidine sample solutions that were prepared by spiking the related substances viz., Imp-A, Imp-B, Imp-C and Imp-D at specification level. The RSD ($n = 6$) for each related substance was evaluated. In the intermediate precision study, the similar procedure of method precision was carried out by a different analyst, using different mobile phase and diluent preparations and instrument on a different day with different lot of same brand column. The percentage relative standard deviation of the results for related substances method was evaluated and found to be 0.4-1.5%. The results were reported in Table 3.

Accuracy (recovery)

Accuracy of the method for all the related substances was determined by analyzing lafutidine sample solutions spiked with all the related substances at seven different concentration levels of LOQ, 20, 40, 50, 80, 100 and 150% of each in triplicate at the specified limit. The recovery of all these related substances were found to be in-between the predefined acceptance criterion of 80.0–120.0% and the data is given in Table 3.

Stability of analytical solution

To determine the stability of sample solution, the sample solutions of lafutidine spiked with related substances at specified level were prepared and analyzed immediately after preparation and after different time intervals up to 48 hrs, while maintaining the sample cooler temperature at about 25°C. The results from these studies indicated that the sample solutions were stable at room temperature up to 48 hrs.

Robustness

To evaluate the robustness of the developed method, the chromatographic conditions were deliberately altered and the resolution between closely eluting peak pair i.e. Imp-D and Lafutidine was evaluated. The flow rate of the mobile phase was 0.5 mL min⁻¹. To study the effect of flow rate on the resolution, the same was altered by 0.1 units i.e. from 0.4 to 0.6 mL min⁻¹. The effect of column temperature on resolution was studied at 32°C and 38°C instead of 35°. All the other mobile phase components were held constant as described above. In all the deliberate varied chromatographic conditions (flow rate and column temperature), the tailing factor of Lafutidine was less than 1.30 and the resolution between any two peaks was greater than 2.0. There was a very minor variation in the resolution and tailing factor results observed in all the robustness conditions illustrating the robustness of the method.

Application of the method

The analysis of commercial formulation sample and bulk drug sample indicated that the method is specific and selective for determination of related substances in the formulation and bulk drug samples (Table 4). The developed method is capable for quantitative analysis of lafutidine in the bulk drug and in a pharmaceutical dosage form.

Conclusions

The method presented in this communication describes the development of a rapid, simple, accurate, and selective

Table 4 Results (%) of formulation tablet analysis and bulk drug batches sample analysis

Sample source	Imp-A	Imp-B	Imp-C	Imp-D
Formulation product analysis results				
Formulation1	ND	ND	ND	0.05
Formulation2	ND	ND	ND	0.04
Batch analysis results (%)				
Bulk drug sample1	ND	ND	BLD	0.04
Bulk drug sample2	ND	BLD	BLD	0.03
Bulk drug sample3	ND	BLD	BLD	0.04

ND, Not detected.

BLD, Below the limit of detection.

gradient UPLC method that separates all related substances of lafutidine with good resolution. The developed method was validated to ensure the compliance in accordance with ICH guidelines. The method was found to be simple, selective, precise, accurate, and robust. Therefore, this method can be used for routine testing as well as stability analysis of lafutidine drug substance and drug products. All statistical results (percentage, mean, RSD, percentage difference, and recovery percentage) were within the acceptance criteria. The method could be of use for routine evaluation of the quality of lafutidine in bulk drug manufacturing unit.

Abbreviations

ICH: International Conference on Harmonization; LC-MS: Liquid chromatography-mass spectrometry; UPLC: Ultra performance liquid chromatography; UV: Ultraviolet-visible.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ASJ carried out designing of analytical method development. NW carried out analytical method development and analytical method validation. SAJ and SRB drafted the manuscript and participated in the design and coordination of manuscript. SD reviewed the manuscript. All authors read and approved the final manuscript.

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