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Research article

Analytical quality-by-design (AQBD) approach for the development and validation of RP-HPLC method for the estimation of lamotrigine in bulk and tablet formulation

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ABSTRACT

The current analytical exploration illustrated developing a reversed-phase high-performance liquid chromatography (RP-HPLC) technique and consequent substantiation for analyzing lamotrigine (LAM) active pharmaceutical ingredient (API) using a Quality-by-design (QbD) approach (Central Composite Design), in bulk product as well as in the tablet formulations. In this experiment, based on systematic scouting, four key components (*viz*., mobile phase, column, flow-rate, and wavelength) were studied by the RP-HPLC method. 13 experimental runs were done with acetonitrile (ACN) (40-60% v/v) having flow-rate in the range 0.8 mL/min to 1.2 mL/min. The proposed analytical method was thoroughly corroborated in terms of ruggedness linearity, robustness, accuracy, and precision in accordance with ICH guideline Q2A and ICH guideline Q2B. Under the optimum chromatographic environment; Intersil C_8 column of 250 mm length, 4.6 mm (i.d.); 20 µL injection volume; and mobile phase ACN: Methanol (60:40 v/v), a retention time of 2.542 min was noticed at 220 nm detection wavelength. The method was found to be extremely reproducible, accurate, linear, precise, robust, and economically adequate to execute the estimation. The intended analytical technique was thoroughly assessed through statistical tools and could be an imperative concern for the habitual scrutiny of LAM in bulk products and its formulation.

Keywords: Quality by Design, RP-HPLC, Lamotrigine, Central Composite Design, Estimation, Validation

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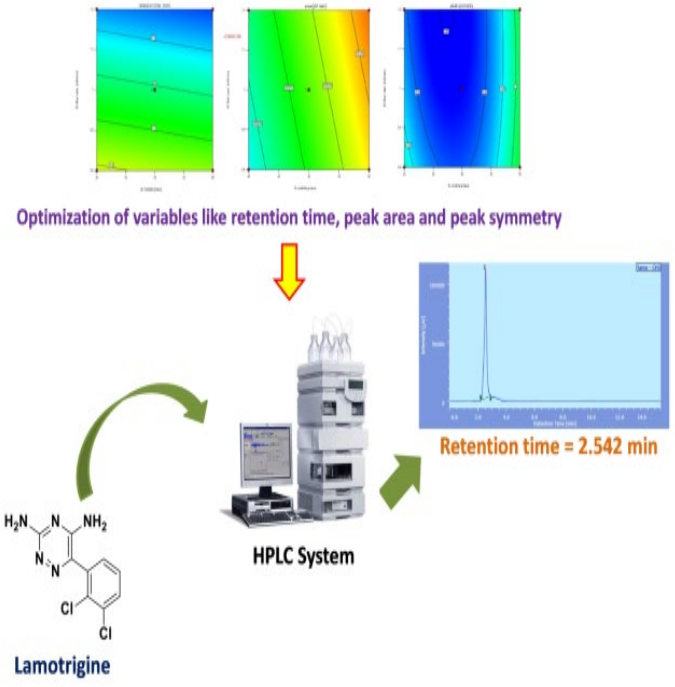
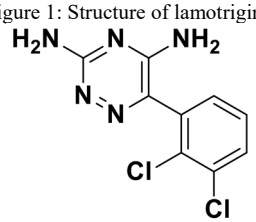
GRAPHICAL ABSTRACT



INTRODUCTION

Lamotrigine (LAM), 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine (Figure 1) is a sodium channel blocking phenyltriazine class of anti-epileptic drug recommended along with phenytoin, carbamazepine, etc. for treating the tonic-clonic seizures conditions as well as for generalized seizures.[1] It is also employed as a mood stabilizer in treating the bipolar disorder type-I and is approved by USFDA for its application in several countries.[2]

Figure 1: Structure of lamotrigine



The analyses of LAM utilizing sophisticated instrumental methods such as derivative spectrophotometric,[3] Gas Chromatography (GC),[4] High Performance-Thin Layer Chromatography (HPTLC),[5] Capillary Electrophoresis,[6] Liquid

Chromatography-Mass Spectroscopy (LC-MS),[7] Gas Chromatography-Mass Spectroscopy (GC-MS),[8] and other simple methods like Thin Layer Chromatography (TLC) have been perceived in literature.[9] The enthusiastic researchers have reported for analysing LAM through Reverse-Phase High Performance-Liquid Chromatography (RP-HPLC) method in tablet formulations,[10-13] saliva,[14] cultured cells,[15] and human plasma.[16-21] Even, simultaneously assessing LAM with other anti-epileptic drugs in formulations[22,23] and human plasma[24,25] using RP-HPLC has been reported so far.

While going through literature from pharmaceutical and analytical databases, it was stringently observed that the concept of Analytical Quality-by-Design (AQbD), a recent trending built-in science-based risk assessment approach for enhancing the quality attributes of analytical process design during the developmental stage, was never ever applied and reported for developing any RP-HPLC method for LAM analysis in bulk product and formulations. Therefore, moving in a similar direction, the present analytical study was planned for exploring the plausible applications of AQbD in optimizing several variables (retention time, peak area, and peak symmetry) for developing a method for estimating the quantity of LAM in bulk components and tablet formulations.

MATERIALS AND METHODS

Materials

Pharmaceutical grade (99.1% purity) LAM was obtained as a generous gift sample by CTX Life Sciences Pvt. Ltd., Surat, India. Loba Chemie Pvt. Ltd., Mumbai, India provided the HPLC grade ACN, Water, and Methanol. Lamosyn® (100 mg LAM Tablet, Sun Pharma Laboratories Ltd.) was obtained from a local Pharmacy shop and utilized for the formulation analysis.

Instrumentations

The RP-HPLC analysis was carried out employing the Jasco PU-2089+ Intelligent HPLC on a reverse-phase C_8 Intersil column having the dimensions 250 mm × 4.6 mm with 5 µm particle size, having changeable wavelength UV/Vis detector system. The system was equipped with Total Chrom Navigator v.6.3 software with a manual injection facility (20 µL fixed loop). The pH measurement was performed through Lovibond® SensoDirect pH110 system. The sonication process was conducted employing the ultrasonicator 3.5 L100 system. Weighing operations were performed utilizing the Shimadzu® electronic balance AW220 system. UV Spectrophotometer (Shimadzu® UV-2401 PC S220V) and hot air oven (Bionics® BST/HAO-1122) were also taken into the application for this study.

Preparation of Solutions

Mobile Phase Preparation

While preparing the mobile phase, 600 mL acetonitrile (ACN) and 400 mL methanol were mixed. This prepared above mixture was thoroughly sonicated for the duration of 10 min and further 0.22 µm membrane filter was employed for filtering the mobile phase.

Stock Solutions Preparation

For preparing the stock solution, initially weighing 10 mg LAM and transferred into volumetric flasks of 10 mL volume. Further, ACN was added to have the desired LAM concentration of 1000 µg/mL. Then, the above solution was consequently diluted with ACN to attain the preferred strength of 100 µg/mL concentration of LAM. Further, by diluting with the mobile phase, the aliquots of LAM stock solutions were organized at 5 working standards of 5 µg/mL, 10 µg/mL, 20 µg/mL, 30 µg/mL, and 50 µg/mL concentrations. The solutions were then injected in the HPLC system using the fixed loop system having 20 µL volume and latterly, the chromatograms were procured.

Sample solution Preparation

100 mg tablet powder containing 25 mg of LAM was weighed accurately and transferred carefully to a volumetric flask of 100 mL volume. 50 mL of ACN was added, further sonicated, and the content was diluted upto the mark to accomplish the preferred strength of 100 µg/mL. The content was filtered employing the Whatman filter paper No. 42 and the volumes of the aliquots were transferred to a volumetric flask of 10 mL volume. Further, dilution was done to produce the desired concentration of 10 µg/mL. The sample solution (20 µL in volume) was then injected in the system and latterly, the peak areas were measured.

Chromatographic condition

The RP-HPLC analysis was performed utilizing the C_8 Intertsil column, employing the mobile phase methanol: ACN in the ratio 60:40 v/v under isocratic elution mode at flow-rate of 1.2 mL/min and analyzed through UV-detector at 220 nm.

Experimental design

The present QbD work was performed to examine the role(s) of diverse changeable factors on retention time and to authenticate the performances of the proposed method. The variable levels were: mobile phase (X1) of aqueous phase used in the proportion of 40% and 60%, and the flow rate (X2) of mobile phase (0.8 mL/min and 1.2 mL/min) (Table 1).

Table 1: Coded Value for Independent Variables.

Name of the factor	Coded values	Level		
		-1	0	1
Mobile phase composition	A	40	50	60
Flow rate	B	0.8	1.0	1.2

The critical responses monitored were retention time (y1), peak area (y2), and symmetry factor (y3), which is expected to affect and control method responses. A 13-factorial design consisting of 2 factors at 3-levels were initially taken for the experimental preparation and after verifying, non-linear central composite design (CCD) was employed (Table 2).

Table 2: Different Batches with their Respective Compositions.

Batch Code	Mobile phase composition (A)	Flow rate (B)
1	0	0
2	1	0
3	0	-1
4	-1	-1
5	1	-1
6	-1	0
7	0	0
8	-1	1
9	0	0
10	0	0
11	0	0
12	1	1
13	0	1

The MODR was characterized by employing the all 3 variables (Table 3). From MODR, the appropriate technique were chosen and subjected to substantiation for the method characteristics like superior accuracy, precision (< 2% RSD), and high robustness as a necessitated response.

Table 3: Evaluation Degrees Of Freedom of Design for Optimization of Analytics of Lamotrigine by HPLC approach.

Response	Name	Unit	Analysis	Minimum	Maximum	Ratio	Model
R1	Retention time	min	polynomial	0.71	1.28	1.49	Linear
R2	Area	µV sec	polynomial	431114	164188	741000	Linear
R3	Symmetry factor	-	polynomial	2.54	3.78	1.52	Quadratic

Method validation

The developed chromatography method was suitably validated in agreement with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline Q2A and guideline Q2B, in acquiescence with the United States Food and Drugs Administration (USFDA) guidance and the United States Pharmacopoeia (USP).

Linearity and range

For the valuation of the system linearity, five concentrations; 80% of the necessitated analytical concentration, 90% of the necessitated analytical concentration, 100% of the necessitated analytical concentration, 110% of the necessitated analytical concentration, and 120% of the necessitated analytical concentration were taken. The solutions were carefully prepared in the presence of a diluent and the equivalent volumes were injected under the particular chromatographic condition. The linearity equation was derived based on the average areas versus the concentration volume and the regression coefficient value (r^2) was reported. [26]

Accuracy

The accuracy (recovery) of this analytical method was determined by spiking the standard drug concentrations (50% of the necessitated concentration, 100% of the necessitated concentration, and 150% of the necessitated concentration). The procedure was conducted in a triplicate manner and the procured mean data were expressed in the form of % recovery ± confidence interval with calculated % relative error, based on the definite concentrations. [27]

Precision

The precision aspects of the novel analytical method was carefully determined by spiking the standard drug at 50% of the necessitated concentration, 75% of the necessitated concentration, and 150% of the necessitated concentration in 1 day (inter-day variability) and on 3 unlike days (intra-day variability). The degree of precision was estimated through the obtained relative standard deviation (RSD) values. [28]

Robustness

The deliberate discrepancy in the systems suitability parameters such as the flow rate by ±0.1 mL/min (*i.e.*, 1.1 mL/min and 1.3 mL/min), mobile phase concentration by ±5% v/v (*i.e.*, 55:45 % v/v and 65:35 % v/v) and column temperature by ±5°C (*i.e.*, 20°C and 30°C) were methodically studied keeping other factors constant.[29]

Systems suitability parameters

The reproducibility characteristics of the system were estimated by spiking the standard solution five-times and determining the parameters like tailing factor (TF), retention time, theoretical plates, and peak area. [30]

RESULTS

Experimental design

DoE is an approach that enables researchers to assess the consequences of potential interactions of a number of variables on productivity concurrently using a restricted number of experiments. From the data generated in preliminary studies while developing the separation for LAM, limits for experimental levels were eventually recognized.

The experimental design depicted the exploration of the vital HPLC technique constituents including flow rate and mobile phase. Their inter-relationships were cautiously examined and optimized states were acquired for each arrangement of mobile phase and flow rate with the help of design expert 11.0 version. The upper and lower limits for methanol content (X1) were 40 and 60 % v/v and the lower limit and upper limit for flow-rate (X2) were set at 0.8 mL/min and 1.2 mL/min. The critical responses monitored were retention time (y1), peak area (y2), symmetry factor (y3).

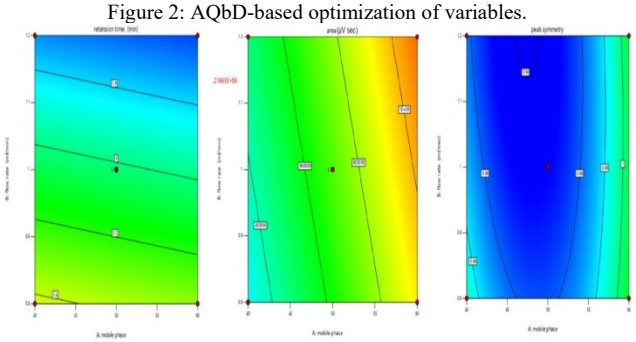
A 2-factor, 3-level design is appropriate for building the second-order polynomial models as well as investigating the quadratic response surfaces with Design Expert Software.

$$Y = \beta_0 + \beta_1 A + \beta_2 B + \beta_{12} AB + \beta_{11} A_2 + \beta_{22} B_2$$

Where Y is the measured response associated with each factor level combination; β_0 is an intercept; β_1 to β_{22} are regression coefficients figured out from scrutinized experimental values of Y from experimental runs; and A and B are the coded levels of the various independent variables. The terms AB, A_2, and B_2 represent the quadratic terms and interaction, respectively. The factors were selected based on preliminary study. The contour plot for LAM

depicted the retention time, peak area, and peak symmetry in Figure 2.

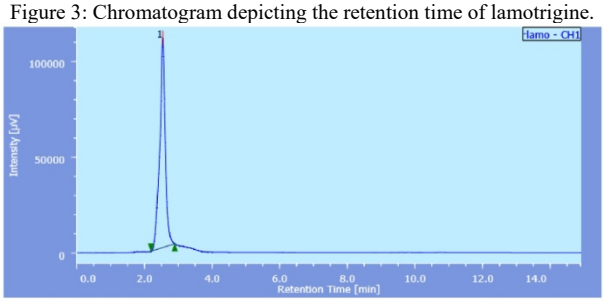
Figure 2: AQbD-based optimization of variables.



Chromatographic features

The best resolution and sharp peak were achieved in the mobile phase consisting of methanol: ACN in the ratio of 60:40 %v/v, flow-rate at 1.2 mL/min on C_8 analytical column, UV visible detection wavelength at 220 nm and 20 µL injection volume, which gave retention time of 2.542 min (Figure 3). These parameters were within the MODR and validated.

Figure 3: Chromatogram depicting the retention time of lamotrigine.



Method validation

Linearity and range

Over the desired range of 80% to 120% of the necessitated analytical concentration, an excellent level of linearity was observed for LAM. The linear regression equation was observed to be y = 26245x + 11890 with a regression coefficient value (r^2) of 0.9905 which signifies a highly acceptable degree of linearity.

Accuracy

The accuracy characteristics of the developed method were computed based on the recovery data by employing the calibration curve where the Y-intercept and the slope play a critical role in estimating the % recovery. The result of the recovery study for LAM was observed to be 98.98% w/w. The % RSD values were observed to be 1.31%, 0.84%, and 0.44%, respectively at three different concentrations; 50% of the necessitated concentration, 100% of the necessitated concentration, and 150% of the necessitated concentration. The % RSD values laid within the pharmacopeia acceptance limit of ±2% that point towards a good accuracy feature of the developed analytical method.

Precision

Over the 50%, 75%, and 150% of the necessitated concentration, observed % RSD values were observed to be 0.72%, 0.23%, and 0.17%, respectively under intra-day variability whereas 1.13%, 0.91%, and 0.77%, respectively under inter-day variability which represents that the developed chromatographic method has high precision value with reduced variability in the estimation of LAM. The % RSD values lay within ±2%, the pharmacopeia acceptance limit.

Robustness

After intentional alterations in the chromatographic conditions (flow rate at 1.1 mL/min and 1.3 mL/min, column temperature at 20°C and 30°C and mobile phase composition at 55:45 % v/v and 65:35 % v/v), minute changes in the retention time (±0.2) were observed which concluded that the method is robust enough to detect LAM even after modifications in the chromatographic environment.

Systems suitability parameters

This parameter revealed that this original method has reproducible attributes, capability for routine analysis and competent enough to be applied. The average retention time (Rt) of LAM was noticed at 2.5444 min (Table 4). The number of theoretical plates was recognized to be 3850.24 which are above the prescribed USP limit of 2,000 that may be translated into higher column efficacy, better resolution, and superior partitioning potential of the developed technique. The peak area 1216021 µV sec represented a very high value which may be correlated with the theoretical separation ability of the developed method. The tailing factor was perceived to be 0.9768 which represented a good symmetry where the degree of asymmetric factor is also equal to 1, an ideal form of Gaussian peak where both are factors hold equal magnitude. The method has been found to fulfil the lowest essential requirements as prescribed in the monographs of USP and has perspectives to express reproducible results.

Table 4: System Suitability Parameters and Validated Results.

Parameters	Response
Chromatographic column	C_8
Mobile Phase (% v/v)	Methanol: Acetonitrile (60:40)
Flow rate (mL/min)	1.2
Detection wavelength (nm)	220
Peak area (µV sec)	1216021(±815.30)
Retention time (min)	2.5444(±0.0020)
Symmetry	0.9768(±0.000447)
Theoretical plate	3850.24(±6.7195)

DISCUSSION

There were a small number of efforts reported on the accomplishment of QbD in analytical method development at present. A RP-HPLC method development approach for stability study using the QbD approach has been described for LAM. The experimental design illustrated the exploration of the vital HPLC method constituents including the mobile phase (X1) and flow rate (X2) for factorial design. As the curvature consequence was noteworthy, CCD was implemented to attain the response surface to optimize the

design. C_8 column was chosen as the stationary phase owing to superior reproducibility and extensive acceptability. For achieving an absolute scientific consideration between the results (Y; such as peak area, asymmetry factor, and retention time) and input variables, a CCD was designed, applied, and performed. The achieved experimental data were subjected to various statistical parameters for better understanding and established to have non-linear relationship between the input variable and response. The above model was validated by the coefficient of determination (r^2). The process model is valid for forecasting the process attributes and for simulating the process representation. The MODR section for the desired robustness was accomplished from contours. In the optimized model mobile phase was methanol; ACN (60:40 % v/v). The flow rate was optimized at 1.2 mL/min. The obtained results were quite satisfactory. AQbD approach is employed for developing the RP-HPLC method for determining LAM in pharmaceutical products. The prediction form MODR has been confirmed by authentic experimental data which reflected its robustness character. Thus, AQbD based RP-HPLC method was more robust precise, and accurate during the method and also cost-effective. This method assures the designing perception for the proposed analytical technique and appropriate for regulatory compliance under regulatory norms.

CONCLUSION

The study hereby opened a new perspective in rational designing and optimization of numerous variables (peak symmetry, retention time, and peak area) in this RP-HPLC method employing Design Expert Software applications for the chromatographic estimation of USFDA-approved drug LAM in bulk products and tablet formulations. The method was duly validated by the ICH guideline number Q2A and ICH guideline number Q2B, and therefore is perceived to be quite linear, precise, accurate, reproducible, economic, and robust enough to perform daily routine analysis in the pharmaceutical industry scale. The study also opened new possibilities for rational optimization of RP-HPLC-based validated analytical methods for other drugs for the simultaneous analysis of commonly available formulations.

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Conflict of interest

There is no conflict of interest regarding the publication of this article.

Abbreviations

LAM: Lamotrigine; **API**: Active Pharmaceutical Ingredient; **QbD**: Quality-by-design; **RP-HPLC**: Reverse-Phase High-Performance Liquid Chromatography; **MODR**: Method Operable Design Region; **CCD**: Central Composite Design; **ICH**: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; **TLC**: Thin Layer Chromatography; **GC**: Gas Chromatography; **MS**: Mass Spectroscopy; **USFDA**: United States Food and Drugs Administration; **USP**: United States Pharmacopoeia; **AQbD**: Analytical Quality-by-Design.

SUMMARY

- RP-HPLC method employing Design Expert Software applications for the chromatographic estimation of USFDA-approved drug LAM in bulk and tablet formulations.
- Quality-by-design (QbD) Central Composite Design (CCD) approach was employed to optimize the imperative four key components (viz., mobile phase, column, flow-rate, and wavelength).
- Intersil C_8 column of 250 mm length, 4.6 mm (i.d.); 20 µL injection volume; and mobile phase composition ACN: Methanol (60:40 v/v) was employed, a retention time of 2.542 min was noticed at 220 nm detection wavelength.

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