RESEARCH PAPER

Analytical Method Development And Validation Of Lacosamide Using Advanced Analytical Techniques

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Abstract

Objective: The current work intended to build a robust, precise, accurate, and specific hplc method for the measurement of lacosamide in tablet dosage form and in bulk, using an advanced analytical techniques.

Materials and Methods: Both perception and head part examination were used to control the basic bounds. In this investigation, an enhanced fluid chromatography method that may be used for the evaluation of lacosamide was developed through the use of the quality by design approach. The method was developed using the c18 segment and a portable stage that contained potassium dihydrogen orthophosphate: acetonitrile: methanol at a flow rate of 1.0 ml/min. A pda indicator at 258 nm was used to finish the discovery process.

Results: Under these perfect conditions, the baseline drug separation may be completed in 2.69 minutes with good resolution. The discovery procedure was completed by using a pda indicator at 258 nm. The improved test settings were validated by adhering to ich q2 (r1) guidelines.

Conclusion: The methods that were suggested have been found to be effective and explicit, making them suitable for regular examination of the structure of tablets containing lacosamide.

Keywords: Lacosamide, Hplc, Method Development, Qbd, Quality By Design, Ich.

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Introduction:

A novel antiepileptic drug, Lacosamide, is primarily prescribed for the management of partial-onset seizures in patients with epilepsy. It exerts its pharmacological action by selectively enhancing the slow inactivation of voltage-gated sodium channels without affecting fast inactivation[1–4]. This unique mechanism stabilizes hyperexcitable neuronal membranes and inhibits repetitive neuronal firing, thereby reducing seizure activity[5–7].

A review of the literature indicates that several analytical methods have been reported for the estimation of lacosamide in bulk drug, pharmaceutical dosage forms, and biological matrices. These include high-performance liquid chromatography (HPLC), liquid chromatography–mass spectrometry (LC-MS), and spectrophotometric techniques, which provide reliable sensitivity, accuracy, and precision for quantitative analysis[8–12].

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use has established guidelines such as Q8, Q9, and Q10 with emphasis on pharmaceutical development, quality risk management, and quality systems for ensuring product quality[13–15]. Quality by Design (QbD) is a systematic and science-based approach that begins with predefined objectives and focuses on process understanding and control. In contemporary pharmaceutical development, QbD plays a crucial role in achieving consistent product quality. However, its industrial implementation can be challenging due to complexities in identifying critical process parameters and establishing a robust design space. The development of a design space and control strategy is fundamental to QbD, allowing identification of optimal conditions that ensure reproducibility, robustness, and accuracy. Various statistical and mathematical tools are applied to evaluate experimental data and generate the design space[16–17].

Therefore, the aim of the present study was to develop a simple, economical, and time-efficient analytical method for the determination of lacosamide using the QbD approach. High-Performance Liquid Chromatography (HPLC) is widely employed due to its specificity, sensitivity, and reproducibility. Application of QbD principles in analytical method development enhances

robustness and ensures consistent performance across the method lifecycle. This approach minimizes variability, reduces the occurrence of method failures during routine analysis, and ultimately saves time and cost by decreasing the need for repeated investigations[18].

Method Development for Lacosamide

Chemicals: Lacosamide received as gift sample from Lupin Ltd., Pune and other chemicals used were HPLC grade (Merck).

Chromatographic Conditions: Agilent 1260 Infinity with Autosampler (AS-4050), PDA locator, and implicit degasser was the HPLC framework used. The framework made use of EZ Chrome programming from Open Lab. Following various preliminary steps, the C18 column was selected using a portable stage composed of 0.1 M acetonitrile and potassium dihydrogen orthophosphate. The finder was calibrated to 215 nm, and the stream rate was maintained at 1.0 ml/min. Using an autosampler with a variable circle volume of 70-130 µl, 20 µl was infused in this method. Because of the framework's segment stove, section temperatures could be programmed throughout the run. It was decided to keep the segment temperature at 40 °C throughout the procedure following an initial run at various temperatures.

Preparation of stock solution:

10 milligrammes of Lacosamide, precisely weighed, were added to a 10-milliliter volumetric flask along with a small quantity of 0.1 M potassium dihydrogen orthophosphate and acetonitrile in a 40:60 ratio. Using the same mobile phase mixture, the volume was increased to the required level to achieve a 1000 ppm concentration.

Preparation of working solution:

Remove 1 millilitre (ml) from the stock solution, transfer it to a volumetric flask, and dilute it with the mobile phase to a level of 10 millilitres (100 ppm). After that, the mixture is sonicated for ten minutes.

Table 1: Optimized Chromatographic Conditions

Sr. No.	Parameters	Values
1	Stationary phase	C18
2	Mobile phase	0.1 M Potassium Dihydrogen Orthophosphate and Acetonitrile
3	Flow rate (mL/min)	1.0 ml/min
4	Run time (min)	2.69 min
5	Column Temperature	40 °C
6	Injection Volume (µl)	20 µl
7	Detection Wavelength (nm)	215 nm

Selection and Preparation of Mobile Phase: Different amounts and stream rates of mobile phases comprising methanol, water, acetonitrile, and cradles at different pH values were tried. With a flexible stage consisting of 40 sections of potassium dihydrogen orthophosphate and 60 pieces of acetonitrile, good pinnacles were obtained at a stream speed of 1.0 ml/min. Before being inserted into the framework, the two components of the portable stage were vacuum-separated through 0.45µm film channels and sonicated for 15 minutes.

Preparation of Standard Stock Solutions:

Acetonitrile was used to prepare the drug standard solutions. To create standard stock solutions containing 1000 µg/mL of each drug, 10 mg of each drug was weighed and dissolved in acetonitrile in 10 ml volumetric flasks. To get the necessary concentrations of each medication, acetonitrile was added to the standard stock solutions. Every day, all solutions—including the stock solution—were made from scratch.

Preparation of Calibration Curve: Each medication's typical stock arrangements were transferred to a 10 mL volumetric flagon and sufficiently diluted with acetonitrile. Aliquots were taken with the intention of obtaining final fixations for each medicine within the range of 70-130 µg/mL. Plotting the top regions recorded for each fixation on the y-pivot and the medicine's centralisation on the x-hub allowed calibration curves to be created for each medication. Each medication's alignment bend was measured to estimate its coefficient of assurance (R2).

Experimental Design

Factorial Design

A 2-factor, 3-level design used is suitable for exploring quadratic response surfaces and constructing second order polynomial models with Design Expert®

Table 2: Coded Values for Independent Variables

Name of Factor	Code Values	Levels		
		Small	Medium	High
Mobile Phase Ratio	A	20:80	40:60	60:40

Flow rate	B	0.8	1	1.2

Table 3: Different Batches with their Respective Composition

Batch Code	Mobile Phase Ratio	Flow rate
M1	20:80	0.8
M2	20:80	1
M3	20:80	1.2
M4	40:60	0.8
M5	40:60	1
M6	40:60	1.2
M7	60:40	0.8
M8	60:40	1
M9	60:40	1.2

Method Validation: By evaluating criteria such as exactness, precision, linearity, heartiness, roughness, recognition, and measurement limits, the developed technique was authorised in compliance with ICH regulations. Relative Standard Deviation (RSD) of less than 2% was used as a reasonable cutoff threshold when evaluating the results.

Precision: For each of the drugs, the developed method's accuracy was confirmed. The peak areas observed through actual research of six simulated infusions of a typical centralisation of every drug. Calculating the RSD allowed for an extra check on the accuracy of the method with regard to intra- and between-day variation in the pinnacle zones.

Accuracy: Each drug's known concentration was spiked at three distinct concentration levels—50%, 100%, and 150%—in order to assess the accuracy of the approach. The difference between the theoretical and predicted values was then compared to the concentration found by the procedure.

Linearity: For Lacosamide, a stock solution containing 1000 µg/mL in methanol was created. Working standard solutions ranging from 70 to 130 µg/mL were created from this stock for every medication, and they were then injected into the HPLC apparatus. Every medication has been demonstrated to exhibit linearity within the 10-100 µg/mL range. Plotting the peak regions of the medication under study against its concentration produced the calibration graph, which was produced by repeat analysis at all concentration levels. The Microsoft Excel® tool was then used to determine the linearity of the relationship.

RESULTS AND DISCUSSION:

Chromatographic Separation: Chromatographic conditions were refined and chosen based on System Suitability factors following several experiments.

The optimized chromatographic conditions are reported in **Table 1**.

Representative HPLC Chromatogram are shown in **Figure 2**.

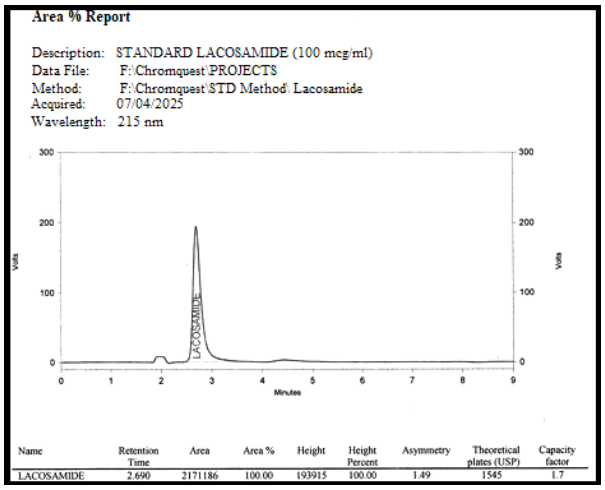


Figure 2: Chromatogram of Lacosamide

System Suitability parameters for each drug were checked and are tabulated in **Table 2**.

Table 4: System Suitability Parameters

Sr. No.	Parameters	Acceptance Criteria	Lacosamide
1	Theoretical Plates	>1000	**1545**
2	Tailing factor	<2	**1.49**
3	RSD of area	<2%	**0.4303**
4	RSD of Ret.Time	<1%	**0.4262**

Calibration Curve: The correlation coefficients (R^2) for each of Lacosamide under consideration and also the linearity equations are displayed in **Table**.

Table 5: Correlation Coefficients and Linearity Equations

Sr. No.	Drug	Regression Value	Equation
1	Lacosamide	0.9911	y = 16.664x – 262.71

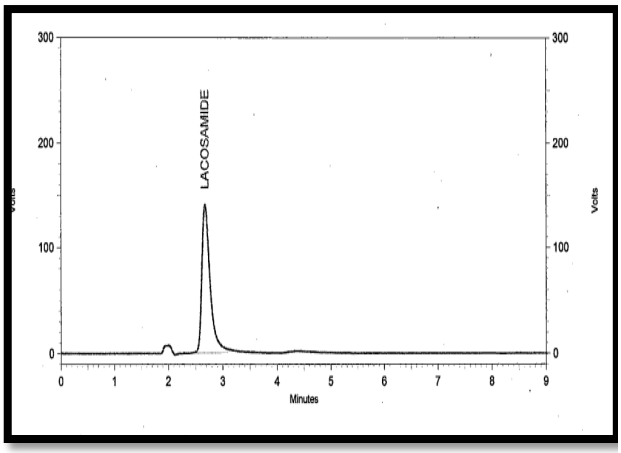
Method Validation: The method was validated

Accuracy

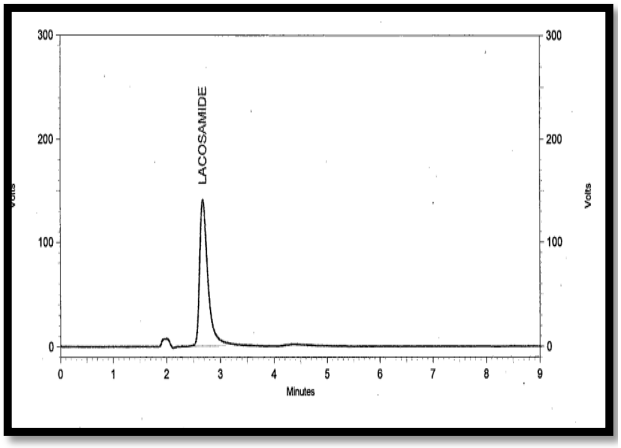
The percentage recovery of Lacosamide

Table 6: Result of Accuracy (%Recovery)

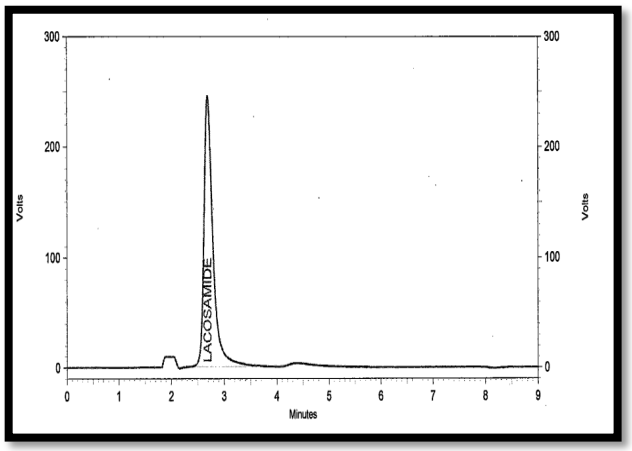
Sr. No.	Assay Level	% Recovery
1	50	99.6
2	100	99.5
3	150	99.5



A) Chromatogram of 50% of Lacosamide



B) Chromatogram of 100% of Lacosamide



C) Chromatogram of 150% of Lacosamide

Linearity

The linearity response was determined by analyzing independent levels of Calibration curve in the range of 70-130 µg/ml for Lacosamide

% Conc. wrt working conc.	Average Area
70	873
80	1055
90	1264
100	1432
110	1605
130	1860

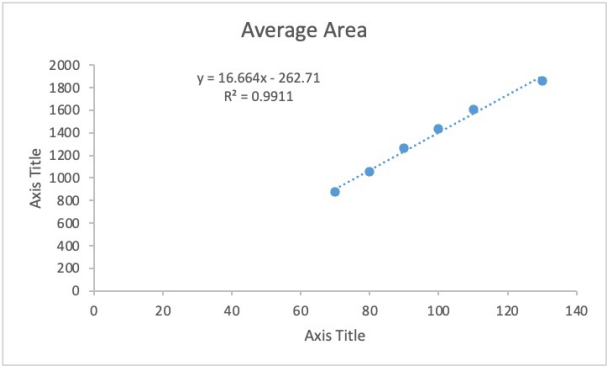
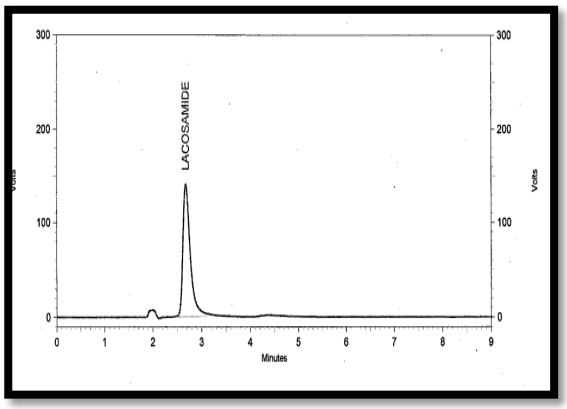
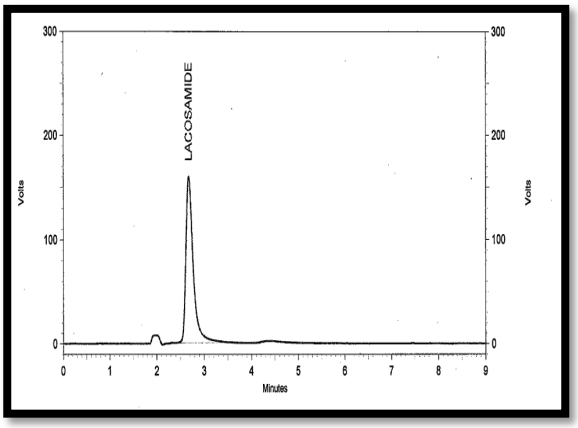


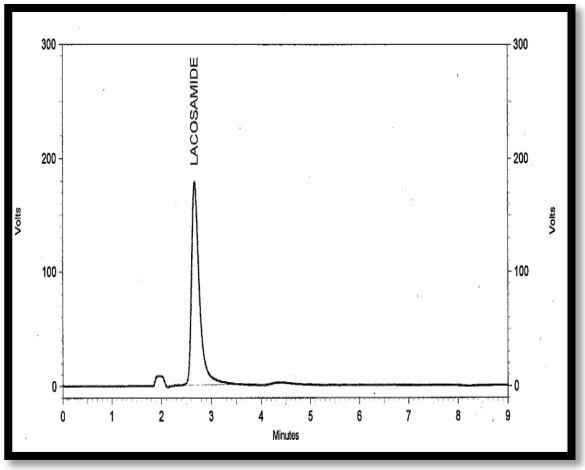
Figure 2: Calibration curve of Lacosamide



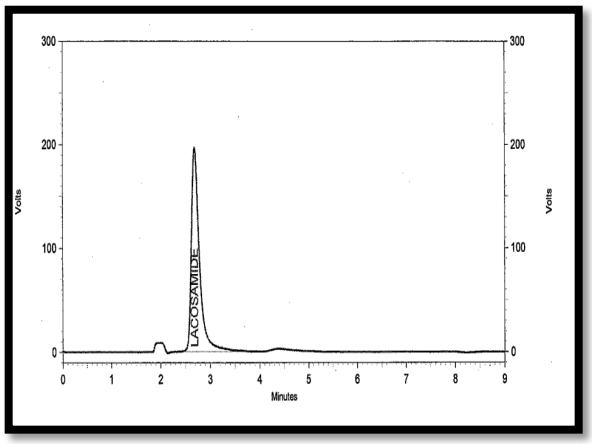
A: Linearity Chromatogram of Lacosamide (70 µg/ mL)



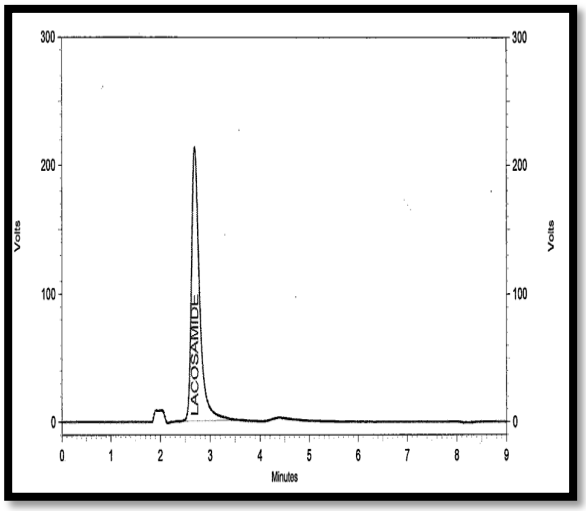
B: Linearity Chromatogram of Lacosamide (80 µg/ mL)



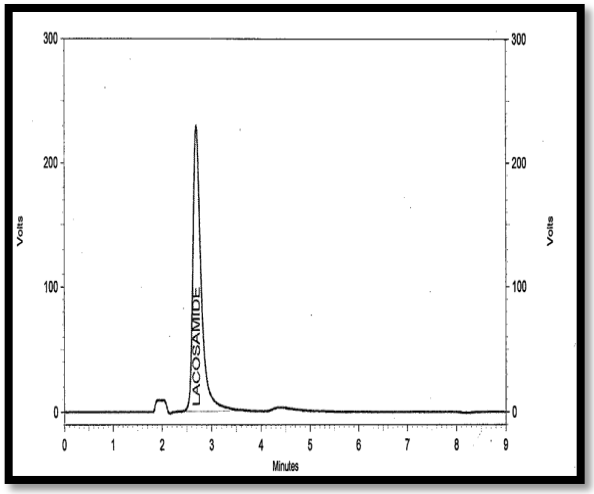
C: Linearity Chromatogram of Lacosamide (90 µg/ mL)



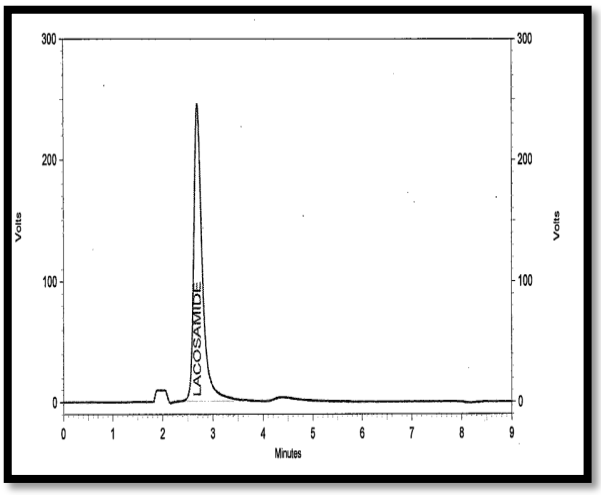
D: Linearity Chromatogram of Lacosamide (100 µg/ mL)



E: Linearity Chromatogram of Lacosamide (110 µg/ mL)



F: Linearity Chromatogram of Lacosamide (120 µg/ mL)



G: Linearity Chromatogram of Lacosamide (130 µg/ mL)

Precision

The value of Lacosamide were found within Limit, which indicates that the developed method is precise.

Table 7: Result of Precision (%Recovery)

Sr. No.	Evaluation Parameter	Results	Acceptance Criteria
1	% Assay values obtained by six test solutions (Average)	99.6	NLT 98% and NMT 102 %
2	% RSD for Assay values obtained by six test solutions	1.0	NMT 2.0 %

Specificity:

The value of Lacosamide were found within Limit, which indicates that the developed method is specific.

Table 8: Result of Specificity

Sr. No.	Results	Acceptance Criteria
1	Retention time of Lacosamide peak in test solution is comparable to that in standard solution.	Retention time of Lacosamide peak in test solution should be comparable to that in standard solution.
2	peak purity of standard and test solution is within acceptance criteria	NLT 98.0

Conclusion:

The QbD approach for logical strategy improvement has been introduced. It consists of the following steps: (i) developing a thorough understanding of the expected reason; (ii) making prescient arrangements; (iii) planning a significant framework reasonableness arrangement that aids in the identification of disappointment modes; and (iv) adhering to a test plan in order to address the technique advancement. These concepts were successfully used to improve the HPLC procedure for drugs and the course of events. A thorough understanding of the item was gathered in order to develop technique execution assumptions, which included remembering fundamental settings for the chromatographic partition in addition to developing future test plans. The framework's reasonableness organisation was important since it ensured the chromatographic separation of the peaks in samples based on steadiness considerations. The HPLC technique was successfully developed using the QbD approach and was found to be straightforward, fast, sensitive, affordable, precise, and dependable.

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