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Research Article

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Understanding Spectral And Pharmacetuical Stablity Lacosamide [(R)-2-acetamido-N-benzyl-3-methoxypropionamide]

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Introduction

Lacosamide is an anticonvulsant used for the adjunctive treatment of partial-onset seizures and diabetic neuropathic pain. It is a functionalized amino acid has activity in the maximal electroshock seizure test.The mechanism of action of Lacosamide has not been fully defined. It works by decreasing abnormal electrical activity in the brain. It is a functionalized amino acid that selectively enhances slow inactivation of voltage-gated sodium channels (VGSCs), increasing the proportion of sodium channels unavailable for depolarization. Lacosamide only affects neurons which are depolarized or active for long periods of time, typical of neurons at the focus of epilepsy [5, 6]. This produces stabilization of neuronal membranes and inhibition of sustained repetitive neuronal firing. It has a dual mechanism of action. It also modulates collapsin response mediator protein 2 (CRMP-2), preventing the formation of abnormal neuronal connections in the brain [7]. Lacosamide is administered orally through film-coated tablets. It can also be administered by injection or by oral solution [8]. The side-effects most commonly leading to discontinuation were dizziness, ataxia, vomiting, diplopia (double vision), nausea, vertigo, and blurred vision. Less common side-effects include forgetfulness, discouragement, feelings of sadness, and lack of appetite. But Lacosamide was generally well tolerated in adult patients with partial-onset seizures [9].

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Materials and Methods

Stock solution of the drug

About 100.21 mg of Lacosamide was weighed accurately and transferred into a 10 mL volumetric flask containing 2mlof methanol. The contents were sonicated for 5 min and then the volume made up with a further quantity of methanol to get an approximate concentration of 10.0mg/ml.The stock is then stored in the refrigerator below 10^0C until further use.

Stock solution of the internal standard

About 20.11mg of Metronidazole was weighed accurately and transferred into a 10ml volumetric flask containing 2mL of methanol. The solution was sonicated for 5 min and then the volume made up with a further quantity of the methanol to get an approximate concentration of 2.0mg/ml. This stock solution was stored below 10^0C in a refrigerator. The calibration curve dilutions were prepared from Lacosamide stock solution as per the table 6.5 in the concentration range of 4.58 to269.21µg/ml.

Data acquisition and processing

The chromatograms were obtained, and data were processed by the peak area ratio method using the LC solution software. The concentrations of the unknown samples were calculated from the following equation

of the regression analysis of the spiked plasma calibration graph using $1/X^2$ as weighting factor.

$$Y = m X + C$$

X = Concentration of Analyte / Concentration of Internal standard
Y = Area of Analyte / Area of Internal standard (area ratio)
m = Slope of the calibration curve
C = Y - intercept value

Results and Discussion

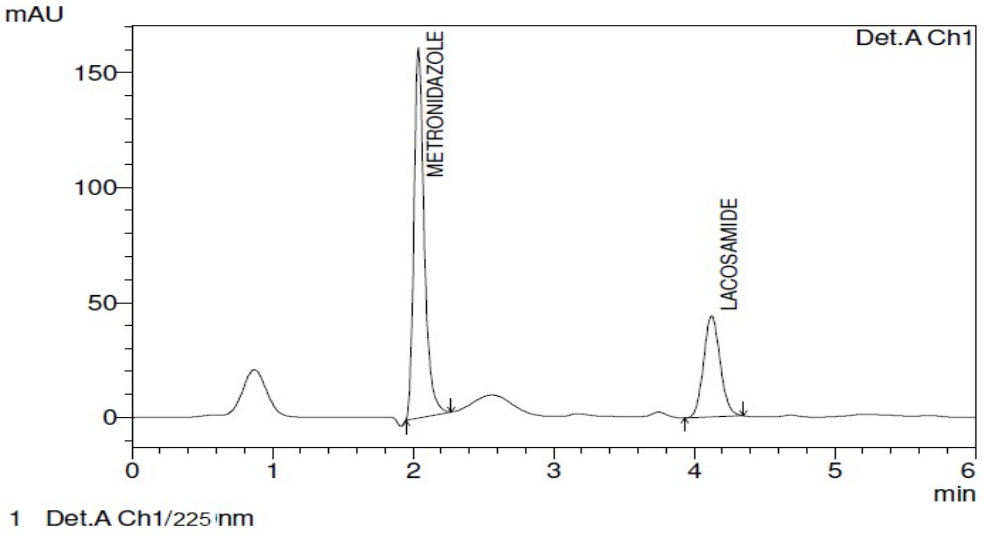

Figure 1: Chromatogram of Lacosamide (drug) and Metronidazole (IS) extracted from human plasma

Table 1:Short-term stability of Lacosamide and Metronidazole

Injection No.	Drug AQS MQC Response		Internal Standard AQS MQC Response	
	Fresh Stock	**Room Temp Stock**	**Fresh Stock**	**Room Temp Stock**
1	350102	369157	773756	775086
2	366084	378150	811492	765722
3	363671	381151	800167	751104
4	354704	374597	779912	768995
5	362553	343207	817412	764962
6	361273	322295	815818	787663
N	**6**	**6**	**6**	**6**
Average	**359731.2**	**361426.0**	**799759.6**	**768921.8**
SD	**6069.72**	**23516.76**	**18854.30**	**12104.64**
% CV	**1.69**	**6.51**	**2.36**	**1.57**
% Stability		**98.54**		**97.10**
% Change (100 - % stability)		**1.46**		**2.90**
Stock concentration µg/ml	**1017.03**	**1036.91**	**100.15**	**99.16**
Correction factor		**0.9808**		**1.0099**

Table 2: Long-term stability of Lacosamide and Metronidazole

Injection No.	Drug AQS CC8Response		Internal Standard AQS CC8Response	
	Fresh Stock	**Refrigerator Stock**	**Fresh Stock**	**Refrigerator Stock**
1	350102	350700	773756	784387
2	366084	358108	811492	746579
3	363671	364108	800167	738336
4	354704	332224	779912	762074
5	362553	312948	817412	773376
6	361273	316171	815818	805779
N	**6**	**6**	**6**	**6**
Average	**359731.2**	**339043.1**	**799759.6**	**768421.7**
SD	**6069.72**	**21809.04**	**18854.30**	**24890.15**
% CV	**1.69**	**6.43**	**2.36**	**3.24**
% Stability		**92.44**		**97.03**
% Change (100 - % stability)		**7.56**		**2.97**
stock concentration µg/ml	**1017.03**	**1036.91**	**100.15**	**99.16**
Correction factor		**0.9808**		**1.0099**

A simple, efficient, reproducible and economic reversed phase high performance liquid chromatographic (RP-HPLC) method was developed and validated for the quantitative determination of Lacosamide in human plasma. Metronidazole was considered as internal standard for the analysis. Standard stock solutions for HPLC analysis were prepared by dissolving Lacosamide and Metronidazole in diluent. In the HPLC measurement, sample detection was carried out at 225nm using an ultraviolet (UV) detector. The compounds were separated using a mobile phase consisting of a 10mM Potassium dihydrogen buffer (pH 3.0) and Methanol in the ratio of 25: 75 v/v on a Ascentis ODS-2, $C_{18,}$ (4.6 X 150 mm, 5µ) at a flow rate of 1.0ml/min. The total run time for the assay was 6.0min. In the optimized conditions, a standard retention time of 4.15min for Lacosamide and 2.05min for Metronidazole was observed.In the developed conditions, Number of theoretical plates was found to be 10650±165, tailing factor was found to be 1.23±0.12 in six replicate injections. The resolution between the standard drug and internal standard was found to be 10.65±0.96. Hence, the developed method accepts the system suitability conditions.

Selectivity is the ability of an analytical method to differentiate and quantify the analyte in the presence of other components in the sample. To evaluate the selectivity of the assay, blank samples of the appropriate biological matrix were prepared from six different sources. Results conforms that there were no chromatographic and spectral impurities were detected bythe developed method. Hence the proposed method was selective for Lacosamide only. The proposed method was applied for the determination of the studied drugs in the plasma samples. The specificity of the method was investigated by observing any interference encountered from the common excipients and found that no interfere was observed with the proposed method. The average percent recoveries of different concentrations were based on the average of three replicate determinations. Hence the developed method was specific.

The method was validated over the range of 0.23 to 13.46µg/ml with regression equation of y = 0.1272x - 0.0007 (r^2=0.9975). The repeatability was evaluated by applying the proposed method for the determination of three concentrations of Lacosamide in pure forms on three successive times. The low % error and low % RSD indicates high accuracy and high precision of the proposed method respectively.

The extraction efficiency of Lacosamide and IS were determined by comparing the peak areas measured after extraction of plasma samples in triplicate at three concentrations (LQC, MQC and HQC) with those found after direct injection of aqueous (un-extracted) samples into the chromatographic system at the same concentration levels. Acceptable recoveries for Lacosamideranges from 62.6% to 66.5% were observed. The mean recovery was found to be 64.13%. High recovery values were observed for

Lacosamide indicates that the method was accurate. The recovery rage of Metronidazole was found to be 68.44% to 73.91%. The mean recovery for internal standard was found to be 70.62 %. High recovery values were observed for metronidazole indicates that the method was accurate.

The stability of Lacosamide in plasma and processed samples, during the analysis and usual storage conditions were investigated. No significant decrease in the measured concentration or change in chromatographic pattern was observed. Stability was assessed by comparing the stock dilutions of Lacosamide and Internal Standard prepared from the freshly prepared stock solutions (comparison) against stock dilutions of Lacosamide and internal standard prepared from the stock solutions stored at 10°C (stability). Long term stock solution stability was evaluated by comparing the mean response of stability samples against mean response ratios of comparison samples. The percent stabilities obtained were 92.44% and 97.03% for Lacosamide and Metronidazole respectively (Table 1 and 2). The Freeze-thaw stability values for the calibration curve standards of Lacosamide in plasma after 3 FT cycles were 96.18 % and 98.47% at low and high concentrations respectively. The Bench top stability values of Lacosamide in plasma after 8.00 hrs were 96.79% and 99.34% at low and high concentrations respectively. The In-injector stability values of Lacosamide in human plasma after 48.00 hrs were 97.45% and 100.23% at low and high concentrations respectively.

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