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STABILITY INDICATING RP-HPLC METHOD FOR THE DETERMINATION OF LACOSAMIDE AND ITS IMPURITIES IN PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

A simple, sensitive, and precise high performance liquid chromatographic method for the determination of related substances of Lacosamide in pharmaceutical formulation has been developed, validated and used for the determination of related substances in commercial pharmaceutical products. The developed method was found to be specific, precise, linear, accurate, rugged and robust. LOQ Values for all the known impurities were below reporting thresholds. The method was validated for specificity, linearity, accuracy, precision, robustness and solution stability. Recovery was found to be in the range of 90-110%. The validation parameters and recovery studies were carried out and reported. The obtained results were satisfactory and good agreement as per the ICH guidelines

Keywords: Lacosamide, HPLC, Related substances, Method Development, Stability indicating.

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INTRODUCTION

Lacosamide was used in the treatment of diabetic neuropathic pain and partial onset seizures in adults with epilepsy. It is a functionalized amino acid with a novel mechanism of action. It possesses excellent oral absorption, negligible protein binding, minimum interaction with other antiepileptic drugs and is excreted mainly in the urine. The drug shows electrophysiological characters, modulates some voltage-gated sodium channels interacting with slow inactivated sodium channels and binding with collapsing response mediator protein (1).

The chemical name of lacosamide is (*R*)-2-(acetylamino) -*N*-benzyl-3-methoxypropanamide ($C_{13}H_{18}N_2O_3$). Lacosamide Impurities Classification

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as per API are Benzyl Amine Impurity, Hydroxy Amino Impurity, Hydroxy Impurity, Acetamide Impurity, O-Acetyl Impurity, N-Methyl Impurity.

The literature survey reveals that there are available UPLC Methods, HPTLC, UV Spectroscopic methods for assay of Lacosamide. Furthermore, to the best of our knowledge; no stability-indicating HPLC method is reported in the literature for Stability Indicating Related substances of Lacosamide injection (2-10).

The objective of the present work is to describe the degradation behaviour of Lacosamide under hydrolysis (acid, base and neutral), oxidation, thermal and photolysis conditions. To optimize the liquid chromatography conditions to separate the drug from its degradation products on a reverse phase HPLC, C18 column and to establish a validated stability-indicating assay and its impurities method by UV detection.

MATERIALS AND METHODS

Acetonitrile, HCl, peroxide, NaOH and Potassium dihydrogen phosphate from Merck PVT Ltd, Mumbai. VIMPAT (lacosamide) injection 200 mg/20 mL Injection was obtained from UCB Pharma, SA.

Chromatographic conditions

Separation was carried out using Column- Inertsustain HP C18 (100 mm x 4.6 mm, 3 µm), Mobile phase – A : pH 2.0 Buffer: Acetonitile – (ratio 98:2), Mobile phase - B: Acetonitrile: Water (ratio 60:40), Diluent : Water and Acetonitrile (90:10), Mode : Gradient (Table-1), Flow Rat : 1.5 mL/min, Injection Volume : 10 µL, Wave Length : 210 nm, Detector : UV-detector.

Table-1 Gradient program for optimized method

Time	MP-A%	MP-B %
0.00min	95.0 %	05.0 %
05.00 min	90.0 %	10.0 %
15.00min	70.0 %	30.0 %
25.00 min	65.0 %	35.0 %
28.00 min	95.0 %	05.0 %
35.00 min	95.0 %	05.0 %

Preparation of solutions

Preparation of diluted standard solution

50 mg of Lacosamide working standard was transferred in 100 ml volumetric flask and then 35ml of diluent was added, sonicate to dissolve and make up volume with diluent. Pipette out 5ml of above solution and transferred into 100ml volumetric flask and adjusted the volume with diluent and mix well. Further transfer 4ml of above solution and transferred into 100ml volumetric flask and adjusted the volume with diluent and mix well.

Preparation of test solution

Pipette 5mL of Lacosamide injection into a 100 ml volumetric flask and then added 70 ml diluents shake well and adjusted the final volume with diluent and mixed.

Forced degradation studies (11, 12)

Forced degradation study was carried out using the following conditions

Acid Degradation

To the test solution 1N HCl was added and kept at Room Temperature for 18hrs.

Base Degradation

To the test solution 0.1N NaOH was added and kept at RT for 18hrs.

Peroxide Degradation

To the test solution 10% peroxide was added and kept aside for 48min at RT.

Thermal Degradation

Test solution was subjected for Thermal degradation by keeping solution at 60^{o}C for 120hrs.

Water Degradation

Test solution was subjected for Water degradation by adding water to the solution at 60^{o}C for 48min.

UV/Visible Degradation

Test solution was subjected for UV/Visible degradation by subjecting to the UV radiation in UV chamber at 60^{o}C for 48min.

RESULTS AND DISCUSSION

Good reproducibility was produced in the Gradient elution using mobile phase Mobile phase – A : pH 2.0 Buffer: Acetonitile – (ratio 98:2), Mobile phase - B: Acetonitrile: Water (ratio 60:40), flow rate-1.5 mL/min at 210 nm.

The test solution was forced degraded using acid, base, peroxide, thermal, humidity and UV/Visible (Fig-1-7). The results of the forced degraded Lacosamide impurities were given in Table 2-7.

Table-2 Results for forced Degradation Studies for Benzyl Amine

S.No	Degradation	Stress conditions	% of Benzyl amine impurity
1	Acid	1N HCl 18hrs at RT	0.068
2	Base	0.1N NaOH 18hrs at RT	1.288
3	Peroxide	10% peroxide 48min at RT	0.061
4	Thermal	120hrs at 60^{o}C	ND
5	Water	48min at 60^{o}C	ND
6	UV/Visible	)0 Watt/m2 & 1.2 million lux hrs	ND
7	Humidity	120 hrs at 90% RT	ND

Table-3 Results for forced Degradation Studies for Hydroxy amino

S.no	Degradation	Stress conditions	% of Hydroxy amino impurity
1	Acid	1N HCl 18hrs at RT	0.006
2	Base	0.1N NaOH 18hrs at RT	1.201
3	Peroxide	10% peroxide 48min at RT	ND
4	Thermal	120hrs at 60^{o}C	ND
5	Water	48min at 60^{o}C	ND
6	UV/Visible	)0 Watt/m2 & 1.2 million lux hrs	0.002
7	Humidity	120 hrs at 90% RT	0.002

Table-4 Results for forced Degradation Studies for Hydroxy Impurity

S.No	Degradation	Stress conditions	% of Hydroxy impurity
1	Acid	1N HCl 18hrs at RT	0.040
2	Base	0.1N NaOH 18hrs at RT	0.124
3	Peroxide	10% peroxide 48min at RT	0.220
4	Thermal	120hrs at 60^{o}C	0.021
5	Water	48min at 60^{o}C	0.017
6	UV/Visible	200Watt/m2 & 1.2 million lux hrs	0.021
7	Humidity	120 hrs at 90% RT	0.017

Table-5 Results for forced Degradation Studies for Acetamide Impurity

S.No	Degradation	Stress conditions	% of Acetamide impurity
1	Acid	1N HCl 18hrs at RT	ND
2	Base	0.1N NaOH 18hrs at RT	0.015
3	Peroxide	10% peroxide 48min at RT	0.031
4	Thermal	120hrs at 60^{o}C	ND
5	Water	48min at 60^{o}C	ND
6	UV/Visible	200 Watt/m2 & 1.2 million lux hrs	ND
7	Humidity	120 hrs at 90% RT	ND

Table-6 Results for forced Degradation Studies for O-Acetyl Impurity

S.No	Degradation	Stress conditions	% of O-Acetyl impurity
1	Acid	1N HCl 18hrs at RT	ND
2	Base	0.1N NaOH 18hrs at RT	ND
3	Peroxide	10% peroxide 48min at RT	0.028
4	Thermal	120hrs at 60^{o}C	0.021
5	Water	48min at 60^{o}C	ND
6	UV/Visible	200 Watt/m2 & 1.2 million lux hrs	0.024
7	Humidity	120 hrs at 90% RT	0.021

Table-7 Results for forced Degradation Studies for N-Methyl Impurity

S.No	Degradation	Stress conditions	% of N-Methyl impurity
1	Acid	1N HCl 18hrs at RT	ND
2	Base	0.1N NaOH 18hrs at RT	ND
3	Peroxide	10% peroxide 48min at RT	ND
4	Thermal	120hrs at 60^{o}C	ND
5	Water	48min at 60^{o}C	ND
6	UV/Visible	0 Watt/m2 & 1.2 million lux hrs	ND
7	Humidity	120 hrs at 90% RT	ND

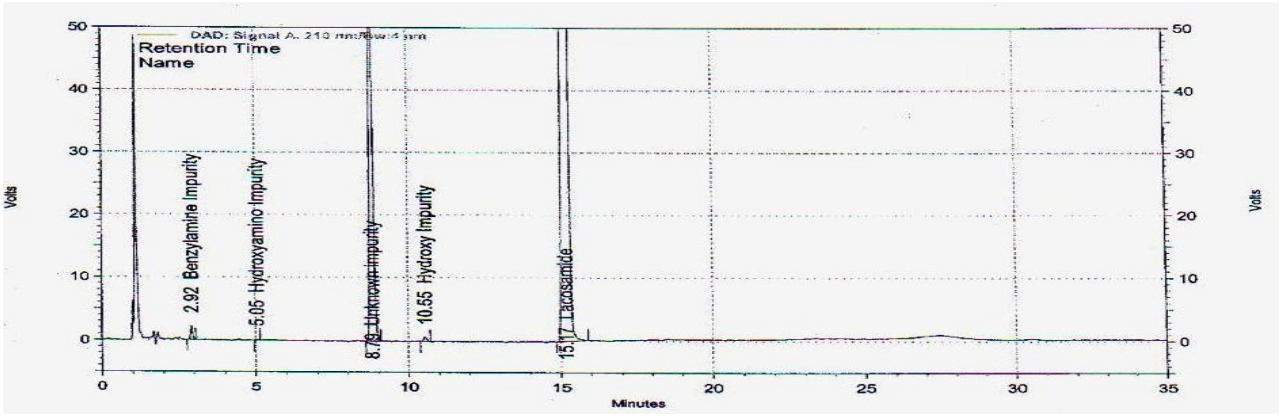

Fig-1 Acid stressed sample chromatogram

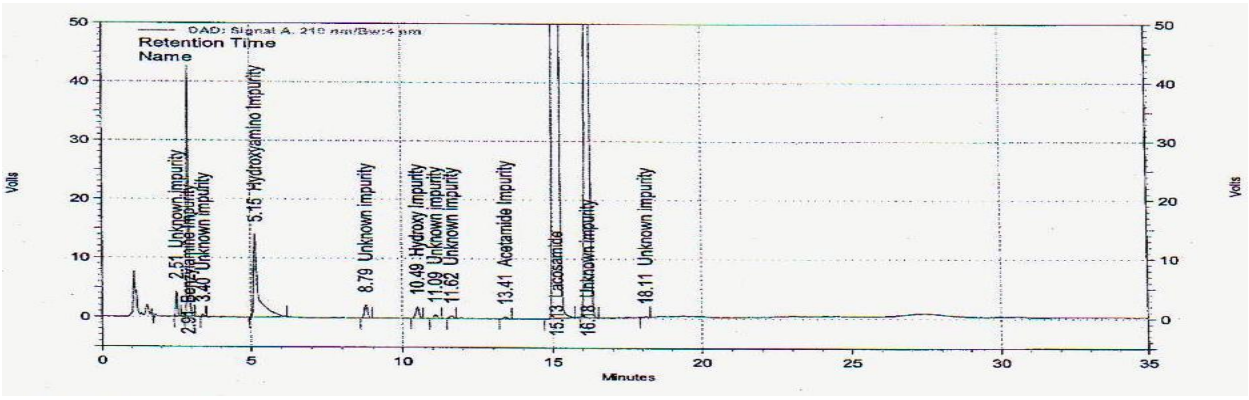

Fig-2 Base stressed sample chromatogram

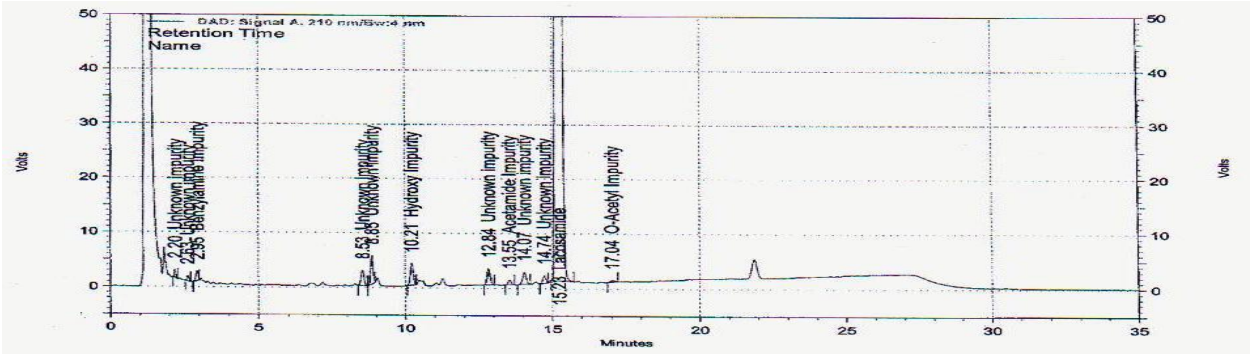

Fig- 3 Peroxide stressed sample chromatogram

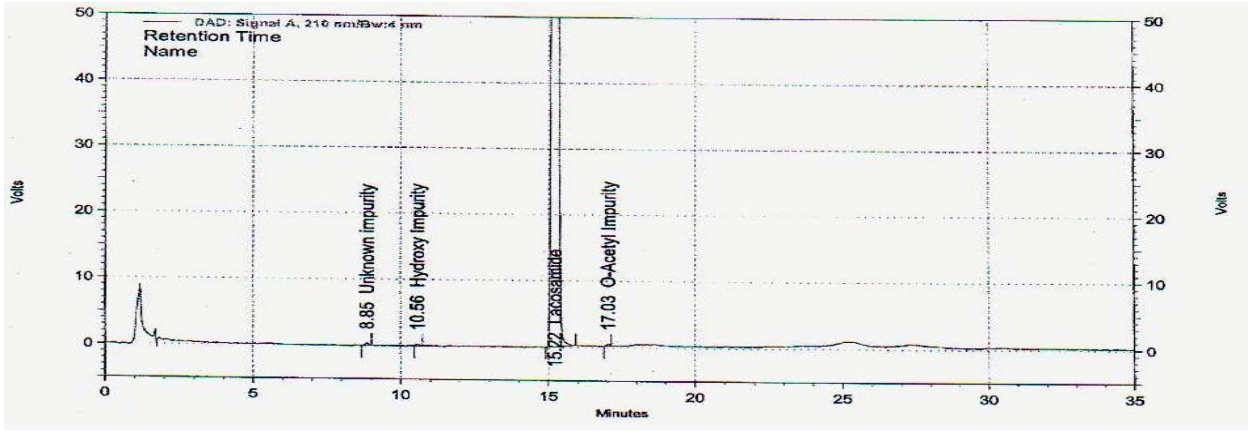

Fig-4 Water stressed sample chromatogram

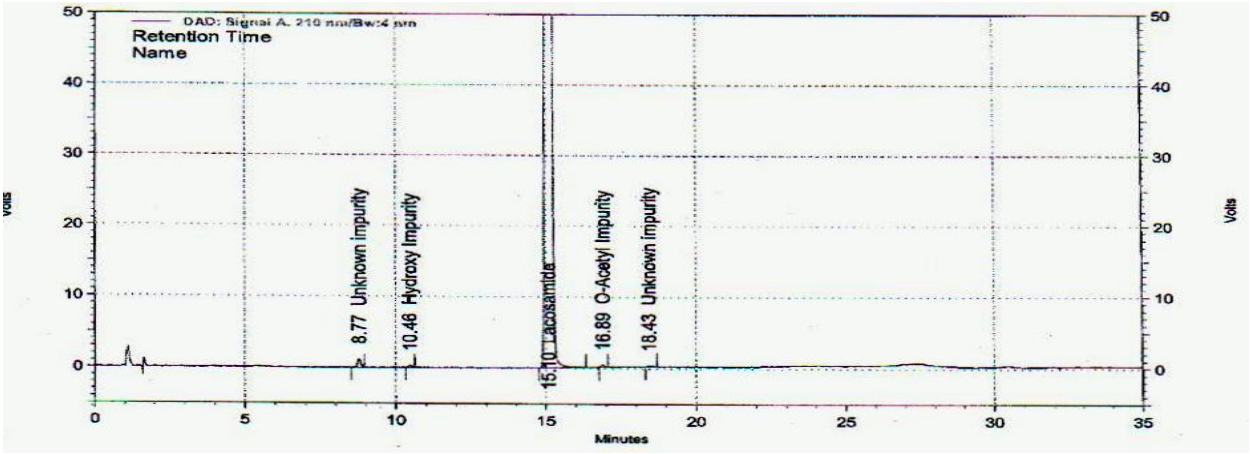

Fig-5 Thermal stressed sample chromatogram

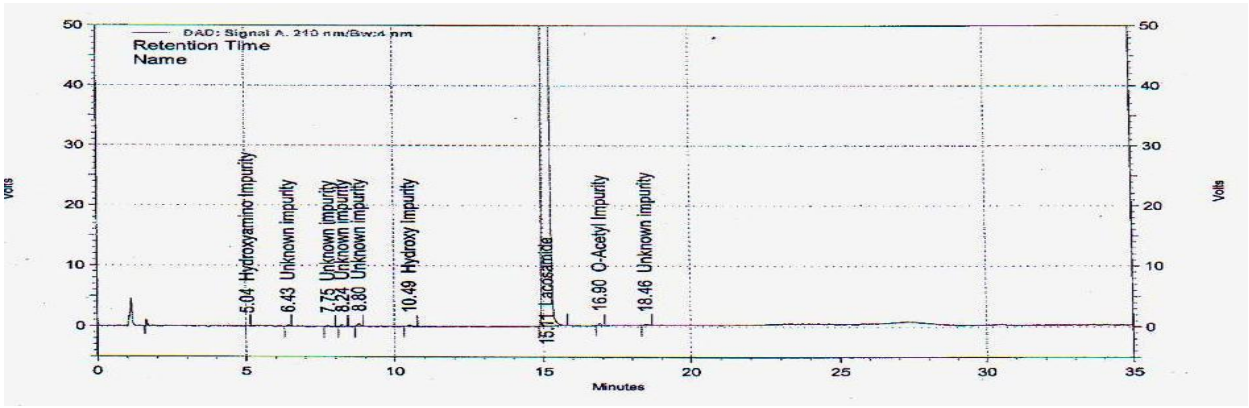

Fig-6 Light stressed sample chromatogram

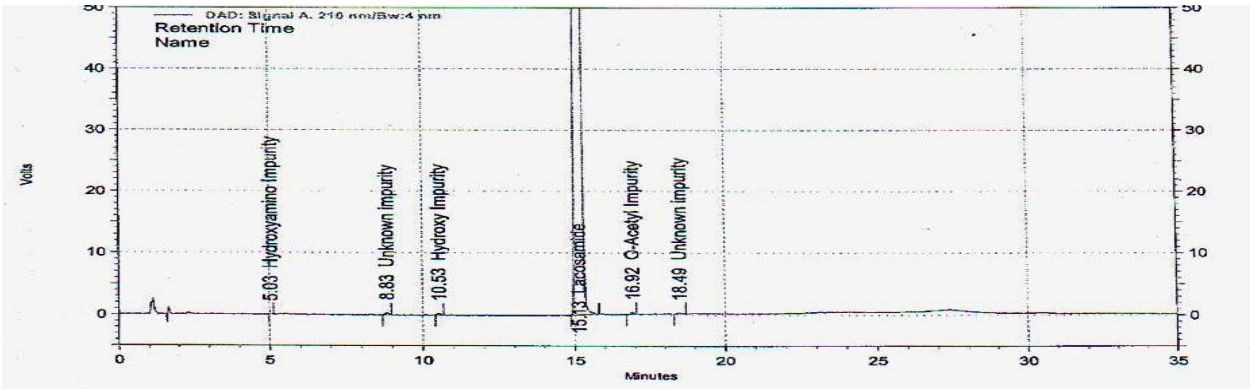

Fig-7 Humidity stressed sample chromatogram

CONCLUSION

An HPLC method for forced degradation studies in the commercial drug products and in the injection formulation was validated in this study. Lacosamide and its impurities which may co exist with it as impurities or as degradants gave chromatograms of very well resolved peaks under acid, alkali, peroxide, thermal and photolytic stress conditions. Based on the forced degradation studies carried out, proposed analytical method can be considered as stability indicating method and can be used for stability studies for effective evaluations

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