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DEVELOPMENT AND VALIDATION OF STABILITY INDICATING RP-HPLC METHOD FOR SIMULTANEOUS ESTIMATION OF LAMOTRIGINE AND VALPROIC ACID AND THEIR DOSAGE FORMS IN BIORELEVANT DISSOLUTION MEDIA

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ABSTRACT

This study was aimed to develop Lamotrigine and Valproic acid marketed formulation and to develop stability indicating HPLC method for their simultaneous estimation of Lamotrigine and Valproic acid in pure forms and in its final dosage formsin biorelevant media as per ICH guidelines. Isocraticmode HPLC method was performed; the flow rate was 1.0 ml/min, injected volume 10µL, the mobile phases contains Phospahte buffer 3.5 pH and Acetonitrile with ratio of 30:70 and UV detection was accepted at 220nm. Lamotrigine and Valproic acid and their combined dosage form were exposed towards thermal, oxidative, acid base hydrolytic stress condition, the stressed sample were analyzed. The technique was validated regarding linearity, precision, accuracy, system suitability, and robustness. The used technique is precise for the evaluation of Lamotrigine and Valproic acid in presence of their degradation products and impurity. The technique was linear over the series of 20-100 µg/mL and 120-600µg/mL for Lamotrigine and Valproic acid respectively. The mean recovery intended for the accuracy studies were set up toward within the limits for Lamotrigine and Valproic acid respectively. The proportion of relative standard deviation (%RSD) was set up to be under critical value. Our developed analytical technique is a stability signifying, economical in addition to biorelevant media which is useful in the quality control of Lamotrigine and Valproic acid in pharmaceutical tablet dosage forms.

INTRODUCTION

Lamotrigine, is an anticonvulsant prescription use to take care of epilepsy and bipolar disorder.[1] For epilepsy, this includes focal seizures, tonic-clonic seizures, and seizures in Lennox-Gastaut syndrome.[2] In bipolar disorder, it is use to take care of acute episode of depression, fast cycling inside bipolar category II, and avoid reappearance into bipolar type I.[2]Common side effects contain drowsiness, headache, vomiting, dilemma with management, in addition to rash.[2] Serious side effects consist of deficient in red blood cells, increased risk of suicide, Stevens-Johnson syndrome, with allergic reactions.[2] There are concern to make

use of during pregnancy or else breastfeeding can consequence in harm.[3] Lamotrigine is a phenyltriazine, producing it chemically dissimilar as of other anticonvulsants.[2] How it works is not accurately clear.[2] It appears to increase the action of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter inside the central nervous system and decrease voltage-sensitive sodium channels.[4][5]

Valproate (VPA), mainly used to take care of epilepsy and bipolar disorder and to avoid migraine headaches.[6] They are useful for the avoidance of seizure in those through absence seizures, partial seizures, and generalized seizures.[6] They know how to exist specified intravenously or via mouth.[6] Long and short acting formulations of tablets exist.[6]Common side effects contain nausea, vomiting, drowsiness, and a dried up mouth.[6] Serious side effects can include liver problems and regular monitoring of liver function tests is therefore recommended.[6] Further serious risk comprise pancreatitis and an better suicide risk.[6] The remedy is identified toward causing serious abnormality inside the infant if taken at the stage of pregnancy.[7][8] Because of this it is not classically suggested inside women of childbearing time who contain migraines.[6]It is indistinct precisely how valproate works.[6][9] Proposed mechanism comprise of affecting GABA level, jamming voltage-gated sodium channel, as well as inhibiting histone deacetylases.[10][11] Valproic acid is a divided short-chain fatty acid (SCFA) prepared from valeric acid.[10]There is indication to valproic acid might effect early growth plate ossification in kids plus young people, ensuing into decrease height.[12][13][14][15] Valproic acid be able to too cause mydriasis, a dilation of the pupils.[16] There is proof that show valproic acid might raise the possibility of polycystic ovary syndrome (PCOS) in women with epilepsy or bipolar disarray. Studies cover revealed this risk of PCOS is privileged in women by epilepsy compare to persons with bipolar disarray.[16].

Lamotrigine$C_9H_7Cl_2N_5$is an antiepileptic drug belonging in the phenyltriazine class and the IUPAC name is 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine. Valproic acid, $C_8H_{16}O_2$supplied since the sodium salt valproate semisodium or divalproex sodium, is a fatty acid by anticonvulsant property and the IUPAC name is 2-propylpentanoic acid.

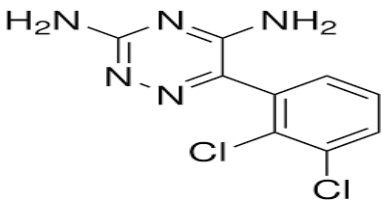

Fig-01: Chemical structure for Lamotrigine

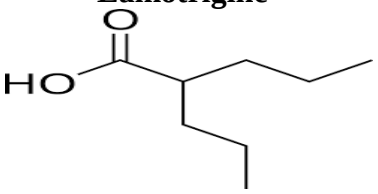

Fig-02: Chemical structure for Valproic acis

In the scientific Literature survey [17-22] reveals that various analytical methods have been reported for the assay of Lamotrigine and Valproic acid in pure form and in pharmaceutical formulations. Many methods have been reported in the literature for the evaluation of Lamotrigine [23-29] and Valproic acid[30-35] individually. The present analysis was intended at developing an entirely validated RP-HPLC technique for the simultaneous evaluation of Lamotrigine and Valproic acidic bulkiness and pharmaceutical combined dosage form in biorelevant dissolution medium (FaSSIF) [36-37] that is more efficient, simple, specific as well as exact than the previous method.

MATERIALS AND METHODS

Lamotrigine and Valproic acid standard is obtained as a generous gift sample from Syncorp Clincare Technologies Pvt. Ltd., Hyderabad, India. Lamotrigine and Valproic acid tablets labelled to contain Lamotrigine and Valproic acid (12.5mg & 30mg) manufactured by Takeda Pharmaceuticals North America, Inc, were purchased from local marketplace. All the chemical use of HPLC grade, obtain from S D Fine-Chem Limited, Mumbai, India. All HPLC solvents and solution were filtered throughout Nylon membrane filter of 0.45µ pore size.

HPLC Instrumentation & Conditions:

The HPLC method was used are WATERS, Software: Empower2, 2695 separation module, UV detector. UV/VIS spectrophotometer LABINDIA UV 3000+, pH meter (Adwa – AD 1020), Weighing machine (Afcoset ER-200A), Pipettes and Burettes, Beakers (Borosil).

PREPARATION OF THE LAMOTRIGINE& VALPROIC ACID STANDARD & SAMPLE SOLUTION:

Standard Solution Preparation:

Correctly weigh up and transport 20 mg of Lamotrigine and 120 mg of Valproic acid working standard into a 100 ml fresh dried up volumetric flask insert about 7 ml of Diluent and sonicate to dissolve it totally and make quantity up to the mark with the similar solvent. (Stock solution)Further pipette 3.0 ml of the exceeding stock solution into a 10ml volumetric flask and dilute up to the mark with diluent.

Sample Solution Preparation: Accurately weigh and transfer equivalent to 20 mg of Lamotrigine and 120 mg of Valproic acid sample(synthetic mixture) into a 100 ml clean dry volumetric flask add about 7 mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)Further pipette 3 ml of the over stock solution into a 10ml volumetric container and dilute equal to the mark by diluent.

Procedure: Inject 20 µL of the standard, sample into the chromatographic method and calculate the area used for Lamotrigine and Valproic acid peak and estimate the %Assay via using the formulae.

Preparation of phosphate buffer: Correctly weigh and dissolve 6.8gms of Potassium dihydrogen ortho phosphate in 1000ml of water and regulate the pH-3.5 with orthophosphoric acid and degassed during an ultrasonic water bath for 10 minutes and next filtered through 0.45 µ filter under vacuum filtration.

Preparation of mobile phase: Accurately measured 300 ml (30%) of Phospahte Buffer and 700 ml of Acetonitrile HPLC (70%) were mixed and degassed in an ultrasonic water bath for 10 minutes and then filtered through 0.45 µ filtered under vacuum filtration.

DILUENT PREPARATION:

Preparation of blank Fasted State Replicated IntestinalFluid (FaSSIF): Correctly weigh 1.74g of Sodium hydroxide pellet 19.77g of Sodium dihydrogen orthophosphate, and 30.93g of Sodium chloride dissolve in 5 L of purify water and regulate the pH 6.5 accurately by using 1N Hydrochloric acid.

Preparation of FaSSIF: Correctly weighed 3.3g of sodium taurocholate mix in 500 ml blank FaSSIF solution, add 11.8 mL of a solution to 100mg/mL lecithin in methylene chloride, and form an emulsion. The methylene chloride was eliminate under vacuum at 40°C. After that draw a vacuum for 15 minutes at 250mbar and too follow in 15 minutes by 100mbar. These result gave in a clear, solution, have no visible odour intended for methylene chloride. After that, it was cool to room

temperature and adjust the quantity up to 2L by blank FaSSIF

METHOD DEVELOPMENT:

Optimized chromatographic conditions:

Instrument used : Waters HPLC with auto sampler with UV detector.

Temperature : Ambient(25° C)

Mode of separation : Isocratic mode

Column : InertsilODS(4.6 x 100mm, 5µm))

Buffer : Phosphate buffer pH 3.5

Mobile phase : Phospahte buffer 3.5 pH and Acetonitrile (30:70)

Flow rate : 1 ml per min

Wavelength : 220 nm

Injection volume : 10 µl

Run time : 10 min.

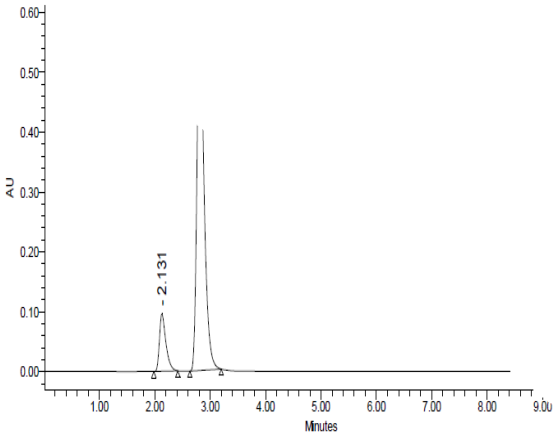

Fig-03: Chromatogram for Lamotrigine and valproic acid (Optimized chromatographic conditions)

METHOD VALIDATION

System Suitability Studies

System-suitability [14] test are the main branch of method development and are use to make sure satisfactory appearance of the chromatographic technique. Tailing factor for the peaks due to Lamotrigine and Valproic acid in Standard solution must not be more than 2. Theoretical plates intended for the Lamotrigine and Valproic acid peaks in Standard solution must not be less than 2000.Resolution for the Lamotrigine and Valproic acid peaks in standard solution must not be less than 2.

Precision: The standard solution be inject for six times and calculated the region for every six Injections in HPLC. The %RSD intended for the region of six replicate injections was found to be within the particular limit.

Intermediate Precision/Ruggedness: To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different day.The standard solutions prepared in the precision were injected on the other day, for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Specificity: For Specificity Blank and Standard are injected into system. There is no any interference of any peak in blank with the retention time of the analytical peaks.

Accuracy: Inject the standard solution, Accuracy -50%, Accuracy -100% and Accuracy -150% solutions. Calculate the Amount found and Amount added for Alogliptin&Pioglitazone and calculate the individual recovery and mean recovery values.

Linearity: Inject every point into the chromatographic method and calculate the peak region.Plot a graph [16] of peak area against concentration (on X-axis concentration and on Y-axis Peak region) and estimate the correlation coefficient.

Robustness: As part of the Robustness, calculated change in the Flow rate, Mobile Phase composition, Temperature difference was prepared to estimate the, impact on the technique.

Degradation Studies: The International Conference on Harmonization (ICH) law

allowed stability test of new drug substance and products require for stress testing be carried out to clarify the inherent stability character of the active material. The plan of this work was to carry out the stress degradation studies on the Lamotrigine and Valproic acid using the planned method.

Hydrolytic degradation below acidic condition: Pipette 1.5 ml of above solution into a 10ml volumetric flask and 3 ml of 0.1N HCl was added. Then, the volumetric flask be set aside at 60ºC for 24 hours and after that neutralize with 0.1 N NaOH and make up to 10ml with diluent. Filter the solution with 0.44 microns syringe filter and place inside vials.

Oxidative degradation: Pipette 1.5 ml above stock solution into a 10ml volumetric flask with 1ml of 30% w/v of hydrogen peroxide added in 10 ml of volumetric flask and the quantity be made equal to the mark with diluent. The volumetric flask be then set aside on room temperature for 15 min. Filter the solution with 0.45 microns syringe filter and put in vials.

Photo degradation: Pipette 1.5 ml above stock solution into a 10ml volumetric flask and expose toward sunlight for 24hrs and the volume be made up to the mark with diluent. Filter the solution with 0.45 microns syringe filter and put in vials.

RESULTS AND DISCUSSION

System Suitability Studies (For Lamotrigine)

1. Tailing factor Obtained from the standard injection is 1.45
2. Theoretical Plates Obtained from the standard injection is 3568.55

System Suitability Studies (For Valproic acid): Tailing factor Obtained from the standard injection is 1.35

2. Theoretical Plates Obtained from the standard injection is 5239.73

Hydrolytic degradation below alkaline condition: Pipette 1.5 ml of above solution into a 10ml volumetric and add 3ml of 0.1N NaOH was added in 10ml of volumetric flask. Then, the volumetric flask was kept at 60ºC for 24 hours and then neutralized with 0.1N HCl and make up to 10ml with diluent. Filter the solution with 0.44 microns syringe filters and place in vials.

Thermal induced degradation: Lamotrigine and Valproic acid sample was taken in Petri dish and set aside in Hot air oven on 110^0 C for 3 hours. After that the sample was taken and dilute amongst diluents and inject into HPLC and examine.

3. Resolution Obtained from the standard injection is 3.04

PRECISION: The results are summarized for Lamotrigine and Valproic acid

Table-01: Repeatability date for lamotrigine & valproic acid

Injection	Area for Lamotrigine	Area for Valproic acid
Injection-1	789316	5523508
Injection-2	785334	5528488
Injection-3	780020	5591669
Injection-4	786180	5523942
Injection-5	781227	5539053
Injection-6	782839	5567550
Average	784152.7	5545701.7
Standard Deviation	3450.5	27917.4
%RSD	0.4	0.5

Acceptance Criteria: The % RSD for the area of six standard injections results should not be more than 2%**.**And the above table shows % RSD for both the drugs in mixture were less than 2%.

SPECIFICITY: For Specificity Blank and Standard are injected into system. There is no any interference of any peak in blank with the retention time of the analytical peaks.

Table-02The accuracy results for Lamotrigine

%Concentration (at specification Level)	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	396812	10	10.08	100.85	99.58
100%	787039	20	20.00	100.01	
150%	1173386.0	30	29.82	99.40	

Table-03 The accuracy results for Valproic acid

%Concentration (at specification Level)	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	2754176	60	59.84	99.73	99.86
100%	5551291.7	120	120.61	100.51	
150%	8229366.3	180	178.79	99.33	

Acceptance Criteria: The % Recovery for each level should be between 98.0 to 102.0%

LINEARITY: Linearity Results: (for Lamotrigine)

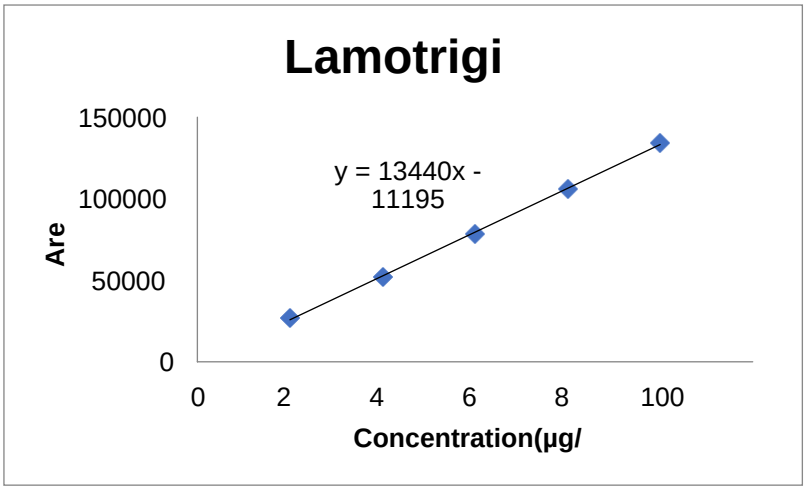

Fig-04: Calibration curve for Lamotrigine

Table-04:Linearity results for Lamotrigine

S. No	Linearity Level	Concentration	Area
1	I	20	268654
2	II	40	520739
3	III	60	783140
4	IV	80	1061084
5	V	100	1342518
Correlation Coefficient			0.999

Linearity Results: (for Valproic acid)

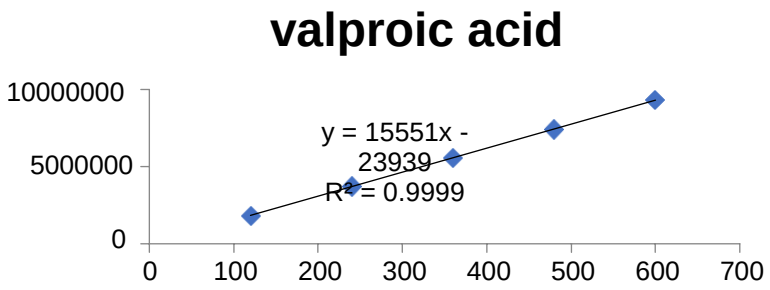

Fig-05: Calibration curve for Valproic acid

Table-05: Linearity results for Valproic acid

S. No	Linearity Level	Concentration	Area
1	I	120	1832427
2	II	240	3726834
3	III	360	5582709
4	IV	480	7407799
5	V	600	9322648
Correlation Coefficient			0.999

Acceptance Criteria: Correlation coefficient should be not less than 0.999.

LOD & LOQ: The Minimum concentration level at which the analyte can be reliable detected (LOD) & quantified (LOQ) were found to be 0.09 & 0.30µg/ml for lamotrigine respectively and 0.11 & 0.36 for Valproic acid.

DEGRADATION STUDIES:

The results of the stress studies indicated the specificity of the method that has been developed. Ruxolitinib was stable in photolytic and acidic stress conditions.

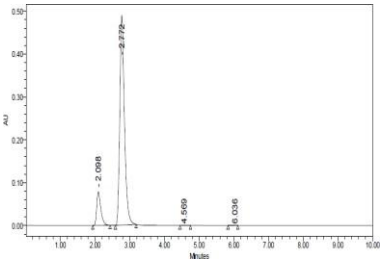

Fig- 6: Chromatogram for acidic degradation

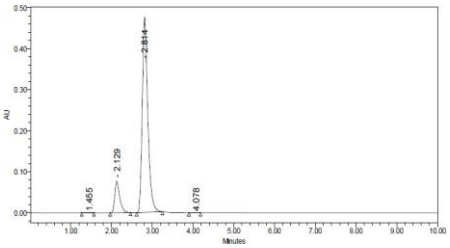

Fig-7: Chromatogram for basic degradation

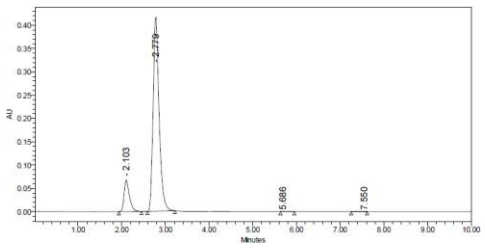

Fig- 8: Chromatogram for thermal degradation

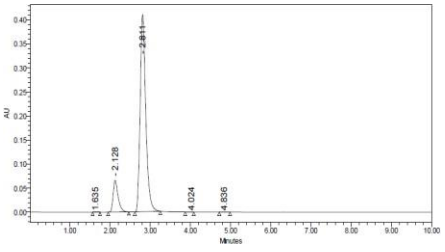

Fig- 9: Chromatogram for photolytic degradation

	Lamotrigine		Valproic acid	
Sample Name	Area	% Degraded	Area	% Degraded
Standard	785386		5512235	
Acid	763563	2.78	5312622	3.62
Base	757893	3.50	5286737	4.09
Peroxide	759376	3.31	5297856	3.89
Thermal	735422	6.36	5215762	5.38
Photo	745353	5.10	5257689	4.62

Table-6: Degradation results for Lamotrigine and Valproic

CONCLUSION

The results of the analysis of pharmaceutical dosage form indicated that the developed RP-HPLC method is highly accurate, precise and robust and are in good agreement with the labeled claim of the drug.A sensitive& selective RP-HPLC method has been developed & validated for the analysis of lamotrigine & valproic acid in API by using bio relevant dissolution media. Further the proposed RP-HPLC method has excellent sensitivity, precision and reproducibility.

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