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Development of simple, precise UV spectroscopic methods for the estimation of Lamotrigine in bulk and marketed tablet

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Abstract

Two Simple and precise UV spectroscopic methods were developed for the estimation of lamotrigine in bulk and marketed tablets. The methods developed by using two solvent systems viz., Acetonitrile: Distilled water (1:1) and Methanol: 0.1N HCl (3:1) were validated as per ICH guidelines. The two proposed solvent systems validated for linearity, accuracy, precision, robustness, ruggedness and solution stability. The percent recovery in the marketed tablet formulation was found to be good agreement with the label claim. The methods validated statistically and the results suggest these methods can employed for the routine analysis of lamotrigine in bulk and marketed tablet formulations.

Keywords: Lamotrigine; UV spectroscopy; Validation; Accuracy; Precision

1. Introduction

Lamotrigine is class of drug used to treat epilepsy and stabilize mood in bipolar disorder[1]. Lamotrigine (figure 1) is a phenyltriazine, making it chemically different from other anticonvulsants, appears to inhibit release of excitatory neurotransmitters via voltage-sensitive sodium channels and voltage-gated calcium channels in neurons[2,3]. Several methods for determination of lamotrigine and its metabolites in biological matrices have been developed viz., reversed phase HPLC[4-12], gas chromatography with nitrogen phosphorus detector[13], capillary electrophoresis[14, 15] chromatography thermo spray mass spectrometry[16], immune fluorometric assay[17] and radioimmunoassay[18]. Reported methods were found to expensive and tedious, so an attempt is made to develop two solvent systems and validated for the estimation of lamotrigine by UV spectroscopic method in bulk and marketed tablets.

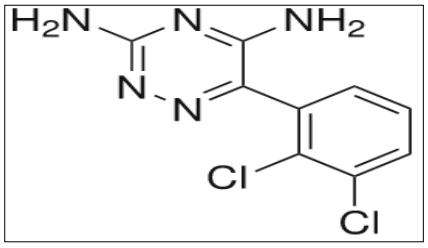

Figure 1 Chemical structure of Lamotrigine

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2. Material and methods

2.1. Materials

Lamotrigine obtained as gift sample (Magnus Pharma Ltd, Nepal). Lamez-25 (Intas pharmaceuticals ltd, south Sikkim, India) and Lamosyn-25(Sun Pharma Laboratories ltd, Jammu, India) tablets procured from local retail community pharmacy. All reagents, solvents used were of analytical grade (SD Fine-Chemicals, Bangalore, India). UV-1900 UV-VIS Spectrophotometer-Shimadzu Corp/Japan; UV-1700 PharmaSpec UV-VIS Spectrophotometer-Shimadzu Corp, Kyoto Japan. A double beam Shimadzu Ultraviolet/Visible recording spectrophotometers connected to a compatible computer and supported with UV Probe software used for spectrophotometric measurements

2.2. Methods

2.2.1. Preparation of Lamotrigine standard stock solution

Transfer accurately weighed 25mg of Lamotrigine into a 25 ml volumetric flask to this add 20 ml of solvent blend viz., Methanol: 0.1N HCl (3:1) solution, shake for 5 min and sonicate for 5min to dissolve completely, then make the volume with same medium solution to obtain 1 mg/ml concentration. Similarly prepare standard stock solution in Acetonitrile: Distilled water (1:1) solution.

2.2.2. Preparation of Lamotrigine working standard solution

Transfer accurately measured 2.5 ml of Lamotrigine standard stock solution into a 25 ml volumetric flask. To this add 20 ml of Methanol: 0.1N HCl (3:1) solution, then make the volume with Methanol: 0.1N HCl (3:1) solution to obtain 0.1 mg/ml concentration. Similarly prepare the working standard solutions in Acetonitrile: Distilled water (1:1) solution.

2.2.3. Preparation of working test standard solution for tablets

Triturate accurately weighed 2 tablets to get fine powder. Weigh accurately triturated powder equivalent to 25 mg of Lamotrigine and transfer into 25 ml volumetric flask, add 25 ml of Methanol: 0.1N HCl (3:1) solution, extract the content by shaking for 90 min and sonicate for 10 min. filter the content through whatmann filter paper No.44. Appropriately dilute working standard solution with Methanol: 0.1N HCl (3:1) solution and Acetonitrile: Distilled water (1:1) solution separately to obtain working standard solution and these solutions used for further studies.

2.2.4. Determination of absorption maxima (λ max)

Appropriately dilute the working standard solution with Methanol: 0.1N HCl (3:1) solution and Acetonitrile: Distilled water (1:1) solution separately in 10ml volumetric flask to get 10 µg/ml solution, scan this solution in the range of 200 to 400 nm using double beam UV spectrophotometer, and observe the characteristic peak at standard wavelength (nm).

2.3. Validation

The validation of proposed methods carried out as per ICH guideline

2.3.1. Range

Appropriately dilute the Lamotrigine working standard solution with Methanol: 0.1N HCl (3:1) solution in a series of 10 ml volumetric flask to obtain 2-40 µg/ml concentrations and measure the absorbance at 265 nm keeping Methanol: 0.1N HCl (3:1) solution as blank. Similarly prepare series of Lamotrigine working standard solution i.e. 2-40 µg/ml concentrations in Acetonitrile: Distilled water (1:1) solution, measure the absorbance at 307 nm, keeping Acetonitrile: Distilled water (1:1) solution as blank.

2.3.2. Linearity

The linearity is the ability of analytical procedure to produce test results, which are proportional to the concentration (amount) of analyte in samples within a given concentration range, linearity should be determined by using a minimum of six standards. Appropriately dilute the Lamotrigine working standard solution with Methanol: 0.1N HCl (3:1) solution in a series of 10ml volumetric flask to obtain 1-24 µg/ml concentrations and measure the absorbance at 265 nm keeping Methanol: 0.1N HCl (3:1) solution as blank. Similarly prepare series of Lamotrigine working standard solution i.e. 1-24 µg/ml concentrations in Acetonitrile: Distilled water (1:1) solution, measure the absorbance at 307 nm, keeping Acetonitrile: Distilled water (1:1) solution as blank, plot the concentration vs. absorbance curve and regression equation was computed.

2.3.3. LoD and LoQ

Limit of detection (LoD) is the lowest amount of an analyte detected in a sample and Limit of quantitation (LoQ) is the lowest amount of an analyte quantified in a sample with a suitable precision and accuracy. Both are determined based on standard deviation (SD) of response and slope (S) by using the following equations

$$(LoD=3.3xSD/S);$$

$$(LoQ=10xSD/S)$$

2.3.4. Precision

Precision of proposed solvent systems was carried out at different concentrations prepared by diluting appropriately the Lamotrigine working standard solution in solvent systems under the study and express the results in terms of % RSD, similarly inter-day and intra-day precision were performed.

2.3.5. Robustness

A robustness study performs to check the influence of method parameters varied intentionally on the proposed solvent systems results. Dilute the Lamotrigine working standard solution separately with Methanol: 0.1N HCl (3:1) solution and Acetonitrile: Distilled water (1:1) solution in a series of 10ml volumetric flask to obtain 4 µg/ml, 8 µg/ml, 12 µg/ml (n=3) concentrations and measure the absorbance at actual wavelength i.e., 265 nm and 307 nm and small variated wavelength i.e., ±1-5 nm keeping Methanol: 0.1N HCl (3:1) solution and Acetonitrile: Distilled water (1:1) solution as blank. Interpret the results in terms of percentage RSD.

2.3.6. Ruggedness

A ruggedness study performs to check the influence of parameters varied intentionally on the proposed solvent systems results. Dilute the Lamotrigine working standard solution separately with Methanol: 0.1N HCl (3:1) solution and Acetonitrile: Distilled water (1:1) solution in a series of 10 ml volumetric flask to obtain 4µg/ml, 8µg/ml, and 12 µg/ml (n=3) concentrations and measure the absorbance at 265 nm and 307 nm by two different analyst and two different UV spectrophotometer. Interpret the results in terms of percentage RSD.

2.3.7. Accuracy

The most common technique for determining accuracy in analytical method development studies is the recovery method, recovery defined as the ratio of the observed result to the expected result expressed as a percentage. Standard addition method applied for recovery studied, in which a sample assayed with known amount of Lamotrigine (40%, 60% and 80%) added to the test working standard solvent systems under the study, and the sample assayed as percent recovered.

2.3.8. Solution stability

The stability of stock solutions of Lamotrigine in proposed solvent systems studied at room (25°C) and refrigerated temperature (2-8°C). The samples were stored in tightly sealed glass containers protected from light. Appropriately dilute the standard stock solutions of proposed solvent systems in a series of 10 ml volumetric flask and the absorbance measured at 0hr and 24 hr time interval.

3. Results and discussion

The optimum wavelengths of maximum absorption of the proposed solvent systems were found to be 265 nm and 307 nm respectively for Methanol: 0.1N HCl (3:1) and Acetonitrile: Distilled water (1:1) with characteristic peak.

The best fit values for two proposed solvent systems are given in table 1, 2 and linearity curve in figures 3. A linear relationship found in the concentration range of 1-24 µg/ml for both solvent systems. The goodness of fit study suggest good correlation coefficient (R square - 0.9999 and 0.9999 for proposed solvent systems) shows the validity of Beer's law with intercept response < 2% calculated by the least square method indicating functional linearity between the concentration of analyte and the absorbance. Based on the standard deviation of the response and the slope the limit of detection values for Lamotrigine for the proposed solvent systems found to be 0.1381 ± 0.0104 µg/ml, 0.118 ± 0.0081 µg/ml and limit of quantitation values found to be 0.418 ± 0.0104 µg/ml, 0.357 ± 0.0081 µg/ml with % RSD values less than 2.

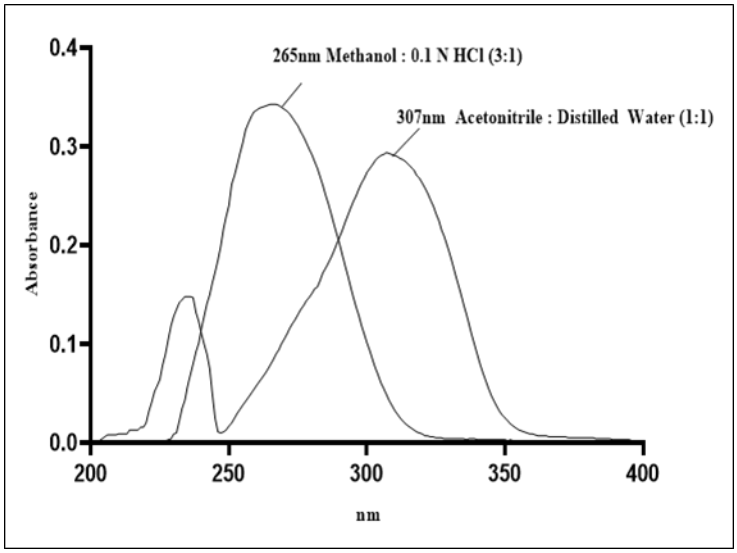

Figure 2 Absorption maxima of Lamotrigine in Methanol: 0.1N HCl (3:1) solution and Acetonitrile: Distilled water (1:1) solution

Table 1 Linearity curve data for proposed solvent systems

Concentration (µg/ml)	**Absorbance mean ± SD (n=5)**	
	Methanol: 0.1N HCl (3:1)	**Acetonitrile: Distilled water (1:1)**
1	0.025±0.005	0.241±0.180
2	0.053±0.005	0.025±0.005
3	0.075±0.005	0.053±0.005
4	0.101±0.001	0.075±0.005
5	0.125±0.001	0.101±0.001
6	0.152±0.001	0.125±0.001
8	0.203±0.001	0.152±0.001
10	0.251±0.005	0.203±0.001
12	0.299±0.005	0.251±0.005
14	0.348±0.001	0.299±0.005
16	0.399±0.002	0.348±0.001
20	0.504±0.001	0.399±0.002
24	0.601±0.002	0.504±0.001

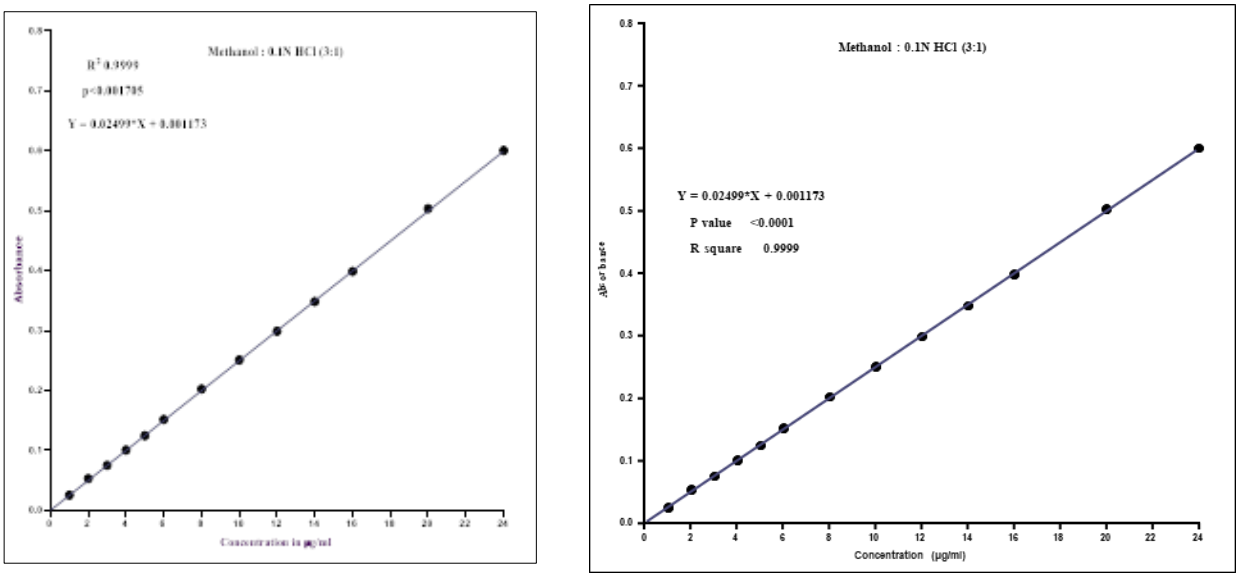

Figure 3 Linearity curve of Lamotrigine

Table 2 Statistical data of linearity curve for proposed methods

Parameters	Acetonitrile: Distilled water (1:1)	Methanol:0.1N HCl (3:1)
Best-fit values		
Slope	0.02506	0.02499
Y-intercept	-0.0006075	0.001173
X-intercept	0.02424	-0.04696
1/slope	39.90	40.02
95% Confidence Intervals		
Slope	0.02484 to 0.02528	0.02484 to 0.02514
Y-intercept	-0.002113 to 0.0008985	-0.0006057 to 0.002953
X-intercept	-0.03613 to 0.08370	-0.1187 to 0.02412
Goodness of Fit		
R square	0.9999	0.9999
Sy.x	0.001056	0.001705
Equation	Y = 0.02506*X - 0.0006075	Y = 0.02499*X + 0.001173

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. The precision of the proposed solvent systems were justified from the absorbance values obtained viz., six replicates in repeatability studies, three concentrations and three replicates in intra and inter day studies of a fixed amount of Lamotrigine in proposed solvent systems. The SD and % RSD calculated for the proposed solvent systems and are given in table 3, 4. The percentage RSD values for repeatability studies, intraday and inter day studies is less than 2 % indicate proposed solvent systems were precise and reproducible.

Table 3 Repeatability precision data

Concentration (µg/ml)	Amount Recovered (n=5)	
	Acetonitrile: Distilled water (1:1)	Methanol:0.1N HCl (3:1)
2	1.99	1.97
2	1.95	1.98
2	2.02	1.96
2	1.98	2.04
2	2.01	2
2	2.04	1.95
%Recovery Mean ± SD	99.99±1.136	99.15±1.24
% RSD	1.15	1.01

Table 4 Inter day and intraday precision data

Intraday precision*						
Amount tested (µg/ml)	**Methanol:0.1N HCl(3:1)**			**Acetonitrile : Distilled Water (1:1)**		
	Amount recovered (µg)	**% Recovery Mean ± SD (n=3)**	**% RSD**	**Amount recovered (µg)**	**% Recovery Mean ± SD (n=3)**	**% RSD**
4	4.11	102.77±0.60	0.58	4.05	101.38±1.59	1.56
8	8.25	103.12±0.52	0.50	8.20	102.60±0.52	0.50
12	12.44	103.70±0.20	0.19	12.31	102.89±0.40	0.38
Inter day precision#						
Amount tested (µg/ml)	**Methanol:0.1N HCl(3:1)**			**Acetonitrile : Distilled Water (1:1)**		
	Amount recovered	**% Recovery Mean ± SD (n=3)**	**% RSD**	**Amount recovered**	**% Recovery Mean ± SD (n=3)**	**% RSD**
4	4	100±1.04	1.04	4.02	100.69±1.20	1.19
8	8.12	101.56±0.53	0.51	8.20	102.60±0.51	0.50
12	12.27	102.31±0.21	0.19	12.41	103.35±0.53	0.51
4	4.03	100.69±1.59	1.58	4.01	100.35±1.59	1.58
8	8.15	101.91±0.60	0.59	8.12	101.56±0.53	0.51
12	12.29	102.43±0.34	0.34	12.33	102.77±0.35	0.33
4 8	3.94 8.15	98.61±1.20 101.90±0.30	1.22 0.29	4.02 8.08	100.34±1.59 101.04±0.90	1.59 0.89
12	12.35	102.89±0.53	0.51	12.35	102.89±0.53	0.52

* Three time intervals in a day # three day intervals

The proposed solvent systems analyzed for assay in two marketed tablet formulations and data given in table 5. The percentage recovery was within the permissible limit with RSD values less than 2%. The accuracy performed for the

proposed solvent systems by standard addition method and the percentage recovery found within the permissible limits with RSD values less than 2% indicate non-interference of the excipients in the formulations.. The Lamotrigine content of two marketed products determined by the proposed solvent systems was in good agreement with the label claim with % RSD values less than 2 and data given in table 6.

Table 5 Accuracy data of proposed methods for two marketed formulations

Brand name Labeled claim	Amount Added (Pure drug) (µg)	% Added (pure drug)	Amount recovered (µg)	% Recovery Mean ± SD (n=3)	% RSD
Methanol:0.1N HCl (3:1)					
LAMEZ-25	10	40	4.04	101.04±1.04	1.03
	10	60	6.08	101.38±0.69	0.68
	10	80	8.15	101.90±0.30	0.29
LAMOSYN-25	10	40	4.02	100.69±2.17	1.55
	10	60	6.11	101.85±1.06	1.04
	10	80	8.16	102.08±0.52	0.51
Acetonitrile: Distilled water (1:1)					
LAMEZ-25	10	40	3.98	99.35±3.12	1.15
	10	60	6.13	102.08±0.70	0.69
	10	80	8.19	102.43±0.31	0.29
LAMOSYN-25	10	40	4.04	101.04±1.04	1.04
	10	60	6.17	102.78±1.39	1.36
	10	80	8.27	102.95±0.30	0.29

Table 6 Drug content data in marketed tablet formulations

Brand name	Labeled Claim (µg/ml)	Methanol:0.1N HCl(3:1)			Acetonitrile: distilled water (1:1)		
		Amount Recovered (µg)	% Recovery Mean ± SD (n=3)	% RSD	Amount Recovered	% Recovery Mean ± SD (n=3)	% RSD
LAMEZ-25	4	4.04	101.04±1.04	1.03	4.06	101.73±1.59	1.56
	8	8.19	102.43±0.30	0.29	8.22	102.77±0.61	0.58
	12	12.31	102.43±0.35	0.34	12.32	102.66±0.21	0.19
LAMOSYN-25	4	4.05	101.04±1.05	2.15	4.11	102.77±2.17	1.72
	8	8.16	102.08±0.52	1.04	8.15	102.08±0.90	0.88
	12	12.28	102.31±0.20	0.51	12.33	102.77±0.35	0.34

Change in λ max of ± 2 nm to the actual λ max in robust analysis results significant different in the percentage recovery in both proposed solvent systems indicates the methods were not robust. In ruggedness, analysis by different analyst and change of instrument indicates the proposed solvent systems were significantly rugged. The robustness and ruggedness data given in tables 7, 8.

Table 7 Robustness data for proposed methods

λmax	**Concentration (µg/ml)**	**Amount Recovered (µg)**	**% Recovery Mean±SD (n=3)**	**% RSD**
Methanol:0.1N HCl (3:1)				
Actual 265 nm	4	3.96	98.95±1.04	1.05
	8	8.16	102.08±0.51	0.51
	12	12.30	102.54±0.20	0.19
267 nm (+2nm)	4	3.61	90.27±0.60	0.58
	8	7.12	89.06±0.52	0.50
	12	10.71	89.24±1.25	1.24
263 nm (-2nm)	4	3.75	93.75±1.04	1.02
	8	7.58	94.79±0.52	0.49
	12	11.45	95.48±0.35	0.32
Acetonitrile: Distilled water(1:1)				
Actual 307 nm	4	4.05	101.38±1.59	1.57
	8	8.21	102.60±0.52	0.50
	12	12.35	102.89±0.40	0.38
309 nm (+2nm)	4	3.59	89.93±2.16	2.11
	8	7.80	97.56±0.30	0.30
	12	11.93	99.42±0.53	0.53
305 nm (-2nm)	4	3.61	90.27±1.59	1.60
	8	7.80	97.57±0.30	0.30
	12	11.97	99.77±0.20	0.20

The results of stability study of Lamotrigine in proposed solvent systems were within the acceptable limit and indicate solutions in proposed solvent systems stable over the period of 24 hr.

Table 8 Ruggedness data for proposed methods

Parameter	**Concentration (µg/ml)**	**Amount Recovered (µg)**	**% Recovery Mean ± SD (n=3)**	**% RSD**
Methanol:0.1N HCl (3:1)				
Analyst-1	4	4.11	102.77±0.60	0.58
	8	8.25	103.12±0.52	0.51
	12	12.44	103.70±0.20	0.19
Analyst-2	4	3.95	98.95±1.04	1.05
	8	8.17	102.08±0.52	0.51
	12	12.31	102.54±0.20	0.19

UV-1700	4	4.03	100.69±1.59	1.58
	8	8.15	101.91±0.60	0.59
	12	12.29	102.43±0.34	0.34
UV-1900	4	4.11	102.77±0.60	0.58
	8	8.25	103.12±0.52	0.50
	12	12.44	103.70±0.20	0.19
Acetonitrile: Distilled water(1:1)				
Analyst-1	4	4.05	101.38±1.59	1.57
	8	8.20	102.60±0.51	0.51
	12	12.34	102.89±0.40	0.38
Analyst-2	4	3.93	98.26±0.60	0.61
	8	8.14	101.74±0.30	0.29
	12	12.27	102.31±0.20	0.19
UV-1700	4	4.02	100.34±1.59	1.59
	8	8.08	101.04±0.90	0.89
	12	12.35	102.89±0.53	0.52
UV-1900	4	4.05	101.38±1.59	1.57
	8	8.20	102.60±0.52	0.50
	12	12.34	102.89±0.40	0.39

4. Conclusion

The results and the statistical parameters demonstrate that the proposed UV spectrophotometric solvent systems are simple, rapid, specific, accurate and precise. Therefore, these solvent systems can use for the quantification of Lamotrigine in bulk and marketed tablet formulations without interference with commonly used excipients and related substances.

Compliance with ethical standards

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Conflict of interest

No conflict of interest to disclosed.

References

[1] Lamotrigine. The American Society of Health-System Pharmacists. Retrieved 2017.

[2] Lamotrigine. PubChem Open Chemistry Database. US: National Institutes of Health. Retrieved 2016.

[3] Goldsmith DR, Wag staff Antona J, Ibbotson TP et al. Lamotrigine. Drugs. 2003; 63 (19): 2029-50.

[4] Castel-Branco MM, Almeida AM, Falcao AC, Macedo TA, Caramona MM, Lopez FG. Lamotrigine analysis in blood and brain by high-performance liquid chromatography. J Chromatography B. 2001; 755 (1-2): 119-27.

[5] Barbosa NR, Mdio AF. Validated high-performance liquid chromatographic method for the determination of lamotrigine in human plasma. J Chromatography B. 2000; 741(2):289-93.

[6] Croci D, Salmaggi A, Grazia UD, Bernardi G. New High-Performance Liquid Chromatographic Method for Plasma/Serum Analysis of Lamotrigine. Therapeutic Drug Monitoring. 2001; 23(6):665-68.

[7] Vidal E, Pascual C, Pou L. Determination of lamotrigine in human serum by liquid chromatography. J Chromatography B.1999; 736(1-2): 295-98.

[8] Angelis-Stoforidis P, Morgan DJ, O Brien TJ, Vajda FJE. Determination of lamotrigine in human plasma by high-performance liquid chromatography. J Chromatography B.1999; 727(1-2): 113-18.

[9] Matar KM, Nicholls PJ, Bawazir SA, Al-Hassan MI, Tekle A. A rapid liquid chromatographic method for the determination of Lamotrigine in plasma. J Pharma Biomed Ana. 1998;17(3):525-31.

[10] Torra M, Rodamilans M, Arroyo S, Corbella J. Optimized procedure for lamotrigine analysis in serum by high-performance liquid chromatography without interferences from other frequently co-administered anticonvulsants. Thera Drug Monitoring. 2000; 22: 621-25.

[11] Ren S, Scheuer ML, Zheng W. Determination of Lamotrigine in Biologic Materials by a Simple and Rapid Liquid Chromatographic Method. Thera Drug Monitoring. 1998; 20(2): 209-14.

[12] Cooper JDH, Shearsby NJ, Taylor JE, FookSheung CTC. Simultaneous determination of lamotrigine and its glucuronide and methylated metabolites in human plasma by automated sequential trace enrichment of dialysates and gradient high-performance liquid chromatography, J Chromatography B 1997; 702(1-2): 227-33.

[13] Watelle M, Demedts P, Franck F, De Deyn PP, Wauters A, Neels H. Analysis of the Antiepileptic Phenyltriazine Compound Lamotrigine Using Gas Chromatography With Nitrogen Phosphorus Detection. Thera Drug Monitoring. 2000; 19(4): 460-64.

[14] Theurillat R, Kuhn M, Thormann W. Therapeutic drug monitoring of Analytical Method Development and Validation of Lamotrigine by High Performance Liquid Chromatography© Copyright reserved by IJPRS 161 lamotrigine using capillary electrophoresis: Evaluation of assay performance and quality assurance over a 4-year period in the routine arena. J Chromatography A. 2002; 979(1-2): 353-68.

[15] Shihabi ZK, Oles KS. Serum lamotrigine analysis by capillary electrophoresis. J Chromatography B. 1996; 68(1): 119-23.

[16] Doig MV, Clare RA. Use of thermo sprays liquid chromatography-mass spectrometry to aid in the identification of urinary metabolites of a novel antiepileptic drug, Lamotrigine. J Chromatography B. 1991; 554(1-2): 181-89.

[17] Sailstad JM, Findlay JW. Immunofluorometric assay for lamotrigine in Huron plasma, Thera Drug Monitoring. 1991; 13: 433-42.

[18] Biddlecombe RA, Dean KL, Smith CD, Jeal SC. Validation of a radioimmunoassay for the determination of human plasma concentrations of Lamotrigine. J Pharma Biomed Ana.1990; 8(8-12): 691-94.