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NEW DIFFERENCE SPECTROPHOTOMETRIC AND VISIBLE SPECTROPHOTOMETRIC METHODS FOR QUANTITATIVE ESTIMATION OF LAMOTRIGINE IN BULK AND PHARMACEUTICAL DOSAGE FORMS

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Abstract

New, simple and rapid Difference spectrophotometric & visible spectrophotometric methods were developed and validated for the quantitative estimation of Lamotrigine in bulk and pharmaceutical dosage forms using Schimadzu UV1800 instrument with UV Probe4.0 software. The analysis of samples was carried out by using quartz cuvette. The methods were optimized with instrumental conditions absorbance mode as measurement mode. 314nm, 520nm was selected as absorption maximum for difference spectrophotometric method & visible spectrophotometric method respectively. The analytical methods were validated as per ICH Q2A (R1) guidelines with respect to linearity, accuracy, precision, selectivity, LOQ and LOD. Difference spectrophotometric method was linear over a concentration range of 2-10µg/ml, Limit of Detection was found to be 0.33µg/mL and Limit of Quantification was found to be 1.01µg/mL. Relative standard deviation for intra-day precision and inter-day precision were within the acceptable limits. The mean recovery was found to be 99.76 %. Visible spectrophotometric method was linear over a concentration range of 2-10µg/ml, Limit of Detection was found to be 0.124µg/mL and Limit of Quantification was found to be 0.39µg/mL. Relative standard deviation for intra-day precision and inter-day precision were within the acceptable limits. The mean recovery was found to be100.01 %. From the results, it can be concluded that the developed methods were effective for quantitative determination of Lamotrigine (LTG) in bulk and pharmaceutical preparations without any interference of other constitute in the formulation. Tablets of different brand names were analyzed by the proposed method and assay of the drug was calculated. The developed methods could be readily adapted to routine quality control of Lamotrigine (LTG) by ordinary laboratories.

Keywords: Lamotrigine, Difference spectrophotometry, visible spectrophotometry, validation.

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INTRODUCTION

Lamotrigine (LTG) is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. It inhibits the voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids. Its chemical name is 6-(2, 3-dichlorophenyl)-1, 2, 4-triazine-3, 5-diamine, as its molecular formula and molecular weight are $C9H7N5Cl_2$ and 256.09 grams/mole. LTG is a white to Pale cream-colored powder. The chemical structure of the drug is given in Fig.1 [1-8].

Fig.1: Chemical structure of Lamotrigine (LTG)

Literature survey reveals that only few analytical methods have been reported for the estimation of Lamotrigine in bulk& pharmaceutical formulation. Hence an attempt has been made to develop simple, accurate, sensitive, rapid and economic method for the estimation of Lamotrigine in Pharmaceutical dosage forms using UV-Visible Spectrophotmetry [9-15].

MATERIALS AND METHODS

Table 1: List of Chemicals and Standard

S.No	Name	Manufacturer/Supplier	Grade
1	Hydrochloric Acid (HCL)	S D fine chemicals limited(SDFCL),Mumbai	AR
2	Sodium Hydroxide (NaOH)	SDFCL, Mumbai	AR
3	Methanol	Sisco Research Laborataries pvt, ltd, Mumbai	AR
4	Water	SDFCL, Mumbai	AR
5	BM Reagent	Otto kemi	AR
6	Sodium Nitraite	SDFCL	AR
7	Lamotrigine(Bulk Drug)	Gift Sample from Aurobindo Pharmaceuticals, Hyderabad	-

Table 2: List of Instrumens

S.No	Instrument Name	Make and Model
1	UV-Visible Spectrophotometer	Shimadzu UV-1800
2	p^H-meter	ELICO, LI 127
3	Digital Balance	Shimadzu BL-220H
4	Ultra Sonic Bath Sonicator	PCI Analytics 6.5 li200H
5	Hot Air Oven	Tempo Equipment Private Limited

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DIFFERENCE SPECTROPHOTOMETRIC METHOD (METHOD-I)

Preparation of standard solution (100µg/ml)

Standard Lamotrigine of 100µg/mL solution was prepared by dissolving 100.0 mg of Lamotrgine working standard in 30mL of methanol and it was sonicated for 5 minutes to dissolve and the volume was made upto 100mL with methanol and mixed well. From this 100µg/ml solution was prepared by taking 5mL of Lamotrigine standard solution into 30mL of methanol taken in a 50mL volumetric flask and was sonicated for 2 minutes to dissolve. When a clear dissolved solution was observed, the volume was made upto the mark with methanol and mixed well [16-20].

Determination of absorption maximum (λ_{max})

The difference absorption spectra of Lamotrigine was constructed by taking the solution in 0.1N NaOH in sample cell and the solution in 0.1N HCL in reference cell .The absorbance of resulting solutions was measured in UV region i.e., 200 - 400nm which shows a maximum absorbance at 314 nm .

Selection of analytical concentration ranges

From the working standard stock solution of lamotrigine(100µg/ml), appropriate aliquots like 0.2,0.4,0.6,0.8,1 ml solutions were pipette in 10ml graduated tubes. The solution in each tube was made up with 0.1N NaOH of one set and with 0.1N HCL of another set to obtain working standard concentration ranging from 2-10µg/ml. The absorbance of these solutions was measured at 314 nm by taking 0.1N NaOH prepared concentrations in sample cell and 0.1 N HCL prepared concentrations in reference cell.

Calibration curve for Lamptrigine (2-10µg/ml)

Fresh aliquots of Lamotrigine ranging from 0.2-1ml from stock solution (100µg/ml) were transferred into a series of 10ml volumetric flasks. The solution in each tube was made up with 0.1N NaOH of one set and with 0.1N HCL of another set to obtain working standard concentration ranging from 2-10µg/ml.

Difference absorption spectrum had shown peak at 314.0nm in UV-region by taking the working standard solution dissolved in 0.1N NaOH (sample cell) and in 0.1N HCl (reference cell). The graph of difference absorbance and concentration was plotted as shown in the figure:2.The regression equation and coefficient correlation was given in the table 3.

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RESULTS AND DISCUSSION

DEVELOPMENT AND OPTIMISATION

Difference spectrophotometric method (Method -I)

New difference spectrophotometric method was developed and optimised by Shimadzu UV-1800 instrument using difference absorbance technique.

Difference absorption of lamotrgine

The absorption maximum of 314nm taken from difference absorption spectrum was selected as wavelength for spectrophootmetric determinations. The difference absorption spectrum was shown fig:2

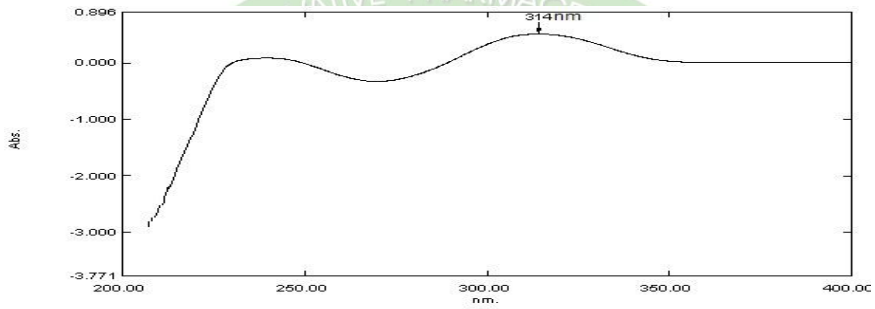

Fig. 2: Difference Absorption Spectrum of Lamotrigine

Selection of analytical concentration ranges

From the working standard stock solution of lamotrigine(100µg/ml), appropriate aliquots like 0.2,0.4,0.6,0.8,1 ml solutions were pipette in 10ml graduated tubes. The solution in each tube was made up with 0.1N NaOH of one set and with 0.1N HCL of another set to obtain working standard concentration ranging from 2-10µg/ml. The absorbance of these solutions was measured at 314 nm by taking 0.1N NaOH prepared concentrations in sample cell and 0.1 N HCL prepared concentrations in reference cell. New UV method was developed for quantitation of pure lamotrigine and in tablets by using following optimised instrumental conditions as shown in Table 3.

Table 3: Optimized UV conditions

λmax	314nm
Beer's law range	2-10µg/ml
Sandell's sensitivity (µg/cm^2.0.001/ absorbance units)	0.016
Molar absorptivity(litre/moles/cm)	4.468x10^4
Regression equation(y)	y= 0.02550 x + 0.00897
Slope	0.02550
Intercept	0.00897
Coefficient of determination(r^2)	0.99944
Standard deviation of Intercept	9.18x10^{-3}

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Verification of beer's law

A linear and proportional relationship was observed between the concentration and absorbance in the range 2-10µg/mL. This is used for quantitation of drug in pure and formulations.

Method validation

The developed method was validated as per ICH Q2(R1) guidelines.

Linearity

Five points calibration curve were obtained in a concentration range from 2-10 µg/ml for lamotrigine. The response of the drug was found to be linear in the investigation concentration range and the linear regression equation was y =0.02550x+0.00897 with correlation coefficient 0.99944.

Table 4: Standard calibration curve data for Lamotrigine

S.No	Volume of stock solution transferred (ml)	Final Volume (mL)	Concentration µg/mL	Absorbance* A
1	0.2	10	2	0.058
2	0.4	10	4	0.111
3	0.6	10	6	0.165
4	0.8	10	8	0.213
5	1	10	10	0.262

*Average of three determinations

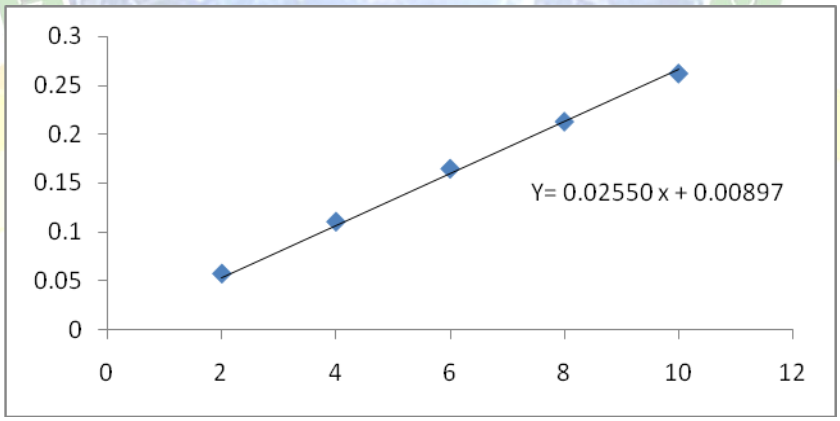

Fig: 3 Standard calibration curve for Lamotrigine

Limit of Detection (LOD) and Limit of quantitation (LOQ)

The LOQ and LOD reported as a means to analyse the sensitivity.

Limit of Detection (LOD)

LOD calculated by using standard deviation method was found to be 0.33µg/mL.

$$LOD = 3.3\sigma/S = 3.3x0.00153/0.0151 = 0.33\mu g/ml$$

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Limit of Quantification (LOQ)

LOQ calculated by using standard deviation method was found to be 1.01µg/mL.

$$LOQ = 10\sigma/S = 10x0.00153/0.0151 = 1.01\mu g/ml$$

The LOD and LOQ for lamotrigine were found to be 0.33µg/ml and 1.01µg/ml respectively.

Precision

The precision of the developed analytical method was assessed by checking repeatability, intra-day precision and inter-day precision.

Repeatability

The precision of the instrument was checked by repeatedly checking (n= 6) solution of Lamotrigine (10µg/ml) and measuring respective absorbance. The results were reported in terms of relative standard deviation and were found to be not more than 2 %.

Table 5: Repeatability data of pure Lamotrigine

S.No	Concentration µg/mL	Absorbance	Mean Absorbance* ±SD	%RSD
1	10	0.265	0.265±0.000632	0.23
2	10	0.264		
3	10	0.265		
4	10	0.265		
5	10	0.265		
6	10	0.264		

*Average of six determinations

The results revealed that %RSD values were within the limits hence the method is repeatable.

Intra-day precision

The intraday precision of the proposed method was determined by analyzing the corresponding concentration (50%,100%.150%) 3 times on the same day and the results were reported in terms of relative standard deviation.

Table 6: Intra-day precision data for Lamotrigine

S.No	Concentration (µg/mL)	Morning Mean Absorbance*A	Afternoon Mean Absorbance* A	Evening Mean Absorbance* A	Mean*±SD	%RSD
1	4	0.111	0.110	0.110	0.110±0.0007	0.64
2	5	0.125	0.122	0.122	0.123±0.0017	1.4
3	6	0.165	0.162	0.162	0.163±0.0017	1.06

* Average of 3 determinations

The results revealed that the %RSD values were within limits hence the method may be precise.

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Inter-day precision

The inter-day precision of the proposed method was determined by analyzing the corresponding concentrations (50%,100%,150%) on 3 different days and the results were reported in terms of relative standard deviation.

The results shows that all the calculated %RSD values are below 2, therefore the method may be precise.

Table 7: Inter-day precision data for Lamotrigine

S.No	Concentration (µg/mL)	1st day Mean Absorbance* A	2nd day Mean Absorbance* A	3rd day Mean Absorbance* A	Mean*±SD	%RSD
1	4	0.110	0.108	0.107	0.108±0.0015	1.4
2	5	0.122	0.122	0.121	0.121±0.001	0.82
3	6	0.162	0.161	0.159	0.160±0.0017	1.08

* Average of 3 determinations

Accuracy

The analytical accuracy is the nearness of the results obtained against the real values .At each level of lamotrigine concentration. The results of obtained for accuracy studies for the drug substance and drug product were reported in terms of %RSD and % recovery respectively.

For drug substance

Acuuracy data for lamotrigine drug substance was shown in Table 8.

Table 8: Accuracy data for Lamotrigine drug substance

S.No	Accuracy level	Concentration (µg/ml)	Absorbance	Concentration From standard curve (µg/ml)	Mean*± SD	%RSD
1	80%	4	0.112	4.04	4.02±0.024	0.00059
			0.112	4.04		
			0.111	4.00		
2	100%	5	0.123	4.5	4.6±0.0624	1.35
			0.127	4.68		
			0.126	4.62		
3	120%	6	0.164	6.08	6.13±0.0866	1.4
			0.164	6.08		
			0.168	6.23		

* Average of 3 determinations

From the above data it was found that the %RSD (acceptance criteria <2%) values are within the acceptance limits.

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For drug product (Recovery study)

The recovery was assessed by determining the agreement between the measured standard concentration and added known concentration to the sample. The test was done by spiking the pre-analysed tablet powder with pure LMT at three different levels (25%, 50% and 75 %) the recovery percentage values ranged between 99.03 and 100.24%.

Table 9: Recovery data for Lamotrigine drug product

S.No	Amount added	Amount found	%Recovery	Mean
1	2	2.00	100	99.03
		1.96	98.1	
		2.04	102	
2	4	3.92	98.06	100.03
		4.00	100	
		3.96	99.04	
3	6	5.96	99.36	100.24
		6.07	101.3	
		6.00	100	

Assay of Lamotrigine tablets

The average absorbances of the six dilutions of concentration (5µg/mL) of LAMITAL and LAMOSYN (6µg/mL) were estimated and %purity was calculated.

Table 10: Assay values of lamotrigine

Formulation	Labelled claim	Amount obtained	%Recovery
Lamosyn	25mg	25.16	100.6
Lamital	25mg	25.49	101.98

VISIBLE SPECTROPHOTOMETRIC METHOD (METHOD- II)

A Visible Spectrophotometric method was developed using BM Reagent based on diazotization reaction for estimation of lamotrigine in bulk and formulation. It obeys Beer's law in the range of 2-10µg/ml.

Determination of absorption maximum (λ_{max}):

Lamotrigine10µg/mL solution was scanned on a Shimadzu uv-1800 UV-Visible spectrophotometer in the wavelength range of 400-800nm. From the absorption spectrum of Lamotrigine the λ_{max} of Lamotrigine was 520nm

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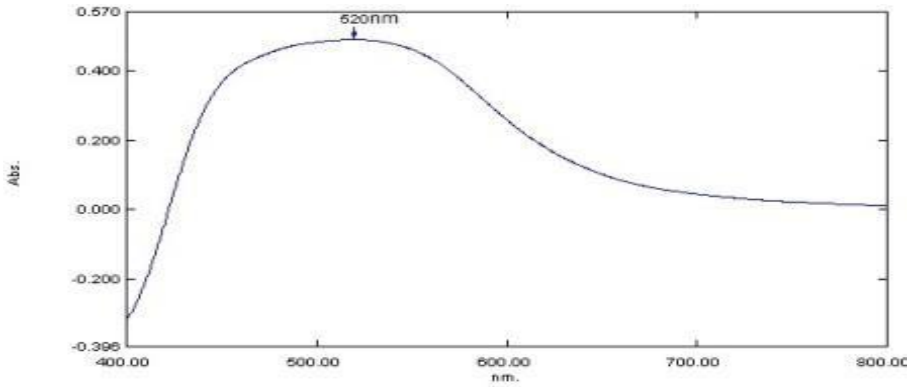

Fig. 4: Visible spectrum of lamotrigine

Selection of analytical concentration ranges

Various concentrations were prepared by taking 0.2 to 1mL from standard stock solution into a series of 10mL graduated tubes. To the solution in each tube add 1mL of 2N HCL and 1ml of NaNO 3 and kept on icebath for 10 minutes than add 1ml of Ammonium Sulfamate after 1 minute add 1ml of BM reagent. Then the final volume was made up to the mark with water.The absorbance of these solutions was measured at 520nm against reagent blank which was illustrated in figure 4.

New UV method was developed for quantitation of pure lamotrigine and in tablets by using following optimised instrumental conditions as shown in table

Table 11: Optimized colorimetric condition

λmax	520nm
Beer's law range	2-10µg/ml
Sandell's sensitivity (µg/cm^2.0.001/ absorbance units)	0.0125
Molar absorptivity(litre/moles/cm)	4.468x10^4
Regression equation(y)	y= 0.00619 x + 0.10525
Slope	0.00619
Intercept	0.10525
Coefficient of determination(r^2)	0.999
Standard deviation of Intercept	9.18x10^{-3}

Verification of beer's law

A linear and proportional relationship was observed between the concentration and absorbance in the range 2-10µg/mL. This is used for quantitation of drug in pure and formulations.

Validation of Visible spectrophotometric method developed for quantitative estimation of Lamotrigine

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Validation was done for the developed UV method as per ICH Q2(R1) guidelines and all the parameters were found to be within acceptable limits.

Linearity

Five points calibration curve were obtained in a concentration range from 2-10 µg/ml for lamotrigine. The response of the drug was found to be linear in the investigation concentration range and the linear regression equation was y =0.00619x+0.10525 with correlation coefficient 0.999. The spectra of Lamotrigine (2-10µg/mL) were shown in Fig.4.

Table 12: Calibration curve data for lamotrigine

S.No	Volume of lamotrigine stock solution transferred (ml)	Final Volume (ml)	Concentration µg/ml	Absorbance* A
1	0.2	10	2	0.117
2	0.4	10	4	0.131
3	0.6	10	6	0.143
4	0.8	10	8	0.154
5	1	10	10	0.168

*Average of three determinations

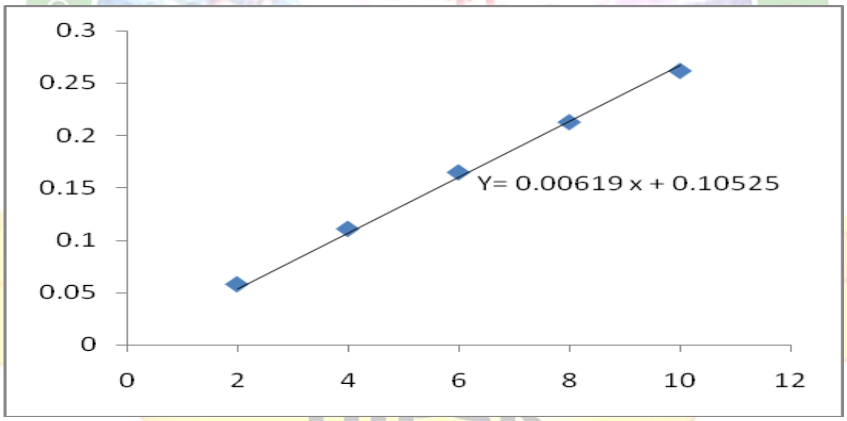

Fig. 5: Standard calibration curve for lamotrigine

The proposed method was found to be linear at concentration of 2-10µg/mL for lamotrigine. The coefficient of determination was found to be 0.9999 which is well within the acceptance limits

Limit of Detection (LOD) and Limit of quantitation (LOQ)

The LOQ and LOD reported as a means to analyse the sensitivity.

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Limit of Detection (LOD)

LOD calculated by using standard deviation method was found to be 0.124µg/mL.

LOD= 3.3σ/S

= 3.3x0.0041/0.10894

= 0.124µg/ml

Limit of Quantification (LOQ)

LOQ calculated by using standard deviation method was found to be 0.39µg/mL.

LOQ = 10σ/S

= 10x0.0041/0.10894

= 0.39µg/ml

The LOD and LOQ for lamotrigine were found to be 0.124µg/ml and 0.39µg/ml respectively.

Precision

The precision of the developed analytical method was assessed by reporting repeatability, intra-day precision and inter-day precision.

Repeatability

The precision of the instrument was checked by repeatedlchecking (n= 6) solution of Lamotrigine (10µg/ml) and measuring respective absorbance. The results were reported in terms of relative standard deviation and were found to be not more than 2 %.

Table 13: Repeatability data of pure Lamotrigine

S.No	Concentration µg/mL	Absorbance A	Mean*±SD	%RSD
1	10	0.162	0.162±0.001	0.61
2	10	0.162		
3	10	0.162		
4	10	0.161		
5	10	0.161		
6	10	0.162		

*Average of six determinations

The results revealed that %RSD values were within the limits hence the method is repeatable.

Intra-day precision

The intraday precision of the proposed method was determined by analyzing the corresponding concentration (50%,100%,150%) 3 times on the same day and the results were reported in terms of relative standard deviation. The results were shown in Table.14

DOI: 10.21276/IJIPSR.2018.06.05.698

Table 14: Intra-day precision data for Lamotrigine

S.No	Concentration (µg/mL)	Morning Mean Absorbance * A	Afternoon Mean Absorbance* A	Evening Mean Absorbance* A	Mean*±SD	%RSD
1	4	0.131	0.130	0.130	0.130±0.0007	0.67
2	5	0.137	0.136	0.136	0.136±0.001	0.73
3	6	0.142	0.141	0.141	0.141±0.001	0.70

***** Average of 3 determinations

The results revealed that the %RSD values were within limits hence the method may be precise.

Inter-day precision

The inter-day precision of the proposed method was determined by analyzing the corresponding concentrations on 3 different days and the results were reported in terms of relative standard deviation. The results were shown in Table 15. The results shows that all the calculated %RSD values are below 2, therefore the method may be precise.

Table 15: Inter-day precision data for Lamotrigine

S.No	Concentration (µg/mL)	1st day Mean Absorbance *A	2nd day Mean Absorbance* A	3rd day Mean Absorbance* A	Mean*±SD	%RSD
1	4	0.130	0.130	0.129	0.129±0.001	0.77
2	5	0.136	0.135	0.134	0.135±0.001	0.74
3	6	0.141	0.140	0.139	0.140±0.001	0.71

* Average of 3 determinations

Accuracy

The analytical accuracy is the nearness of the results obtained against the real values .At each level of lamotrigine concentration. The results of obtained for accuracy studies for the drug substance and drug product were reported in terms of %RSD and % recovery respectively.

For drug substance

Acuuracy data for lamotrigne drug substance was shown in Table 16.

DOI: 10.21276/IJIPSR.2018.06.05.698

Table 16: Accuracy data for Lamotrigine drug substance

S.No	Accuracy level	Concentration (µg/ml)	Absorbance	Concentration From standard curve (µg/ml)	Mean*± SD	%RSD
1	80%	4	0.130	3.99	3.95±0.058	1.4
			0.130	3.99		
			0.129	3.89		
2	100%	5	0.137	5.12	5.06±0.092	1.5
			0.137	5.12		
			0.136	4.96		
3	120%	6	0.142	5.93	5.97±0.081	1.29
			0.143	6.07		
			0.142	5.93		

* Average of 3 determinations

From the above data it was found that the %RSD (acceptance criteria <2%) values are within the acceptance limits.

For drug product (Recovery study)

The recovery was assessed by determining the agreement between the measured standard concentration and added known concentration to the sample. The test was done by spiking the pre-analysed tablet powder with pure LMT at three different levels (25%, 50% and 75 %) the recovery percentage values ranged between98.93-101.93. The results were shown in Table 17.

Table 17: Recovery data for Lamotrigine drug product

S.No	Amount added	Amount found	%Recovery	Mean
1	2	2.04	102	101.83%
		2.03	101.5	
		2.04	102	
2	4	3.93	98.44	98.93%
		3.99	99.9	
		3.93	98.8	

Assay of Lamotrigine tablets

The average absorbances of the six dilutions of concentration (5µg/mL) of LAMITAL and LAMOSYN (6µg/mL) were estimated and %purity was calculated. The results are shown in Table 18.

Table 18: Assay values of lamotrigine

Formulation	Labelled claim	Amount obtained	%Recovery
Lamosyn	25mg	24.61	98.44
Lamital	25mg	24.95	99.8

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CONCLUSION

From the results, it can be concluded that the developed methods were effective for quantitative determination of Lamotrigine (LTG) in bulk and pharmaceutical preparations without any interference of other constitute in the formulation. Tablets of different brand names were analyzed by the proposed method and assay of the drug was calculated. The developed methods could be readily adapted to routine quality control of Lamotrigine (LTG) by ordinary laboratories.

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