IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Determination Of Few Commercial Drugs And Pharmaceuticals Using *P*-CA By Charge Transfer Complexation With Spectrophotometry

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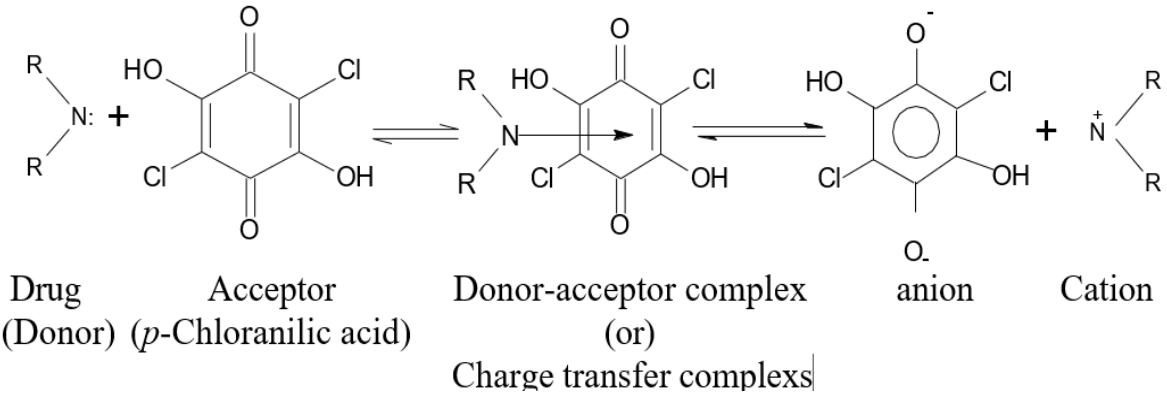
ABSTRACT

Simple, sensitive, selective and Precise methods are developed for the UV-Visible Spectrophotometric methods have been developed for the estimation of five drugs *VIZ*., Lamotrigine (LTG), Loratadine (LOR), Losartan Potassium(LOS), Quetiapine fumarate (QTF) and Warfarin sodium (WAR). The method involves the addition of *p*- chloranilic acid to the drugs possessing a lone pair of electrons results in the formation of a charge transfer complex of the n–π type. The complex is formed by the lone pair of electrons donated by an n - donor to *p*-Chloranilic acid, a charge transfer reagent as an electron acceptor, through which a partial ionic bond (D^+A^-) is formed. ***p***-CA solution in acetonitrile displays a maximum absorption peak at 450nm. The formation of colored solutions and the appearance of new peak are attributed to the formation of charge transfer ion pair complexes (D^+A^-).The broad peak with spike at 520nm is attributed to the radical anion of ***p***-CA. In the present study area under curve (AUC) has been considered for the purpose of quantification of drugs as AUC is more accurate and precise than selecting one wavelength because AUC combines optical densities at the all the wave length. This method has been applied for the estimation of drugs in their pure form as well as in tablet formulation. The results of analysis have been validated statistically for linearity, accuracy, precision, LOD and LOQ.



KEYWORDS: UV-Visible Spectrophotometer, Drugs,*p*- chloranilic acid, acetonitrile, Quantification, Validation.

INTRODUCTION

1. Lamotrigine**:** Lamotrigine (fig.1) Chemically it is 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5- diamine. It is an anticonvulsant drug; belongto drug class of phenyltriazine. It is used to treat epilepsy, bipolar disorder and neurological lesions and also act as a tranquilizer [1]. Like other anticonvulsant, it also behaves as an effective mood stabilizer. UV-Spectroscopy [2-3], HPLC [4-5], LC/MS [6], UPLC [7], appear in the literature for the determination of Lamotrigine in bulk and pharmaceutical formulation.

2. Loratadine**:** Loratadine (fig.2) is chemically 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]- cyclohepta[1,2-b]pyridine-11-ylidine)-1-piperidinecarboxylic acid. Loratadine is a derivative of azatadine and second-generation histamine H1 receptor antagonist used in the treatment of allergic rhinitis and urticarial [8]. Unlike most classical antihistamines (histamine H1 antagonists) it lacks central nervous system depressing effects such as drowsiness. It is a white powder not soluble in water, but very soluble in organic solvents. UV-Spectrophotometry [9-10], HPLC [11-12], LC/MS [13-14].

3. Losartan Potassium**:** Losartan potassium (fig.3) chemically 6-methoxy-2-[(4-methoxy-3,5- dimethylpyridin-2-yl)methylsulfinyl]-1H-benzimidazoleis widely used for the treatment of hyper tension and cardiovascular diseases in combined pharmaceutical preparations. Losartan potassium and its principal active metabolites block the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotens in II to angiotens in II receptor type1(AT1)receptor found in many tissues (vascular smooth muscle, adrenal gland). Losartan potassium has been studied and determined by several procedures and are exhaustively reviewed. UV-Spectroscopy [15-16], HPLC [17-18], LC/MS [19-20]and Conductometry [21].

4. Quetiapine fumarate**:** Quetiapine fumarate (fig.4) is chemically known as {2- (2-(4-dibenzo[b,f] [1,4]thiazepine-11-yl-1-piperazinyl) ethoxy) ethanol , fumaric acid–a dibenzo thiazepine derivative is one of the most recent a typical' anti psychotic drugs It is a selective mono aminergic antagonist with high Nity for the serotonin Type 2 (5HT2) and dopamine type 2 (D2) receptors. QTF is prescribed for the treatment of schizophrenia and other psychotic or schizoactive disorders [22]. QTF was approved by the FDA for the treatment of Bipolar I (Bipolar II) disorder as amono therapeutic agent. UV- Spectroscopy [23-24], HPLC [25-26], LC/MS [27] and NMR [28].

5. Warfarin sodium**:** warfarin sodium (fig.5) is chemically 3-(α-acetonyl benzyl)-4- hydroxyl coumadin and is a racemic mixture of the R- and S-enantiomers. Its empirical formula is $C_{19}H_{15}NaO_4$.The pharmacologic function of the compound is an anticoagulant that inhibits the synthesis of warfarin K-dependent coagulation factors. The treatment aims at preventing further extension of the formed clots and secondary thromboelic complications that may result in serious and possible fatal sequelae. Crystalline warfarin sodium is an isopropanol clathrate [29]. HPLC method [30], X-ray diffraction method [31], spectrophotometric method [32-33], Florimetry [34] Calorimetry [35] and LC/MS [36], methods for the estimation of drug.

Structure of Drugs**:**

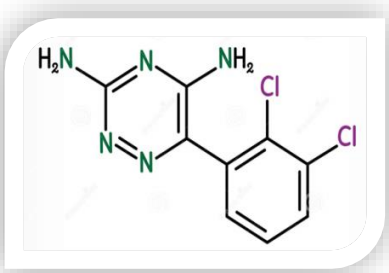


Figure.1 Lamotrgine

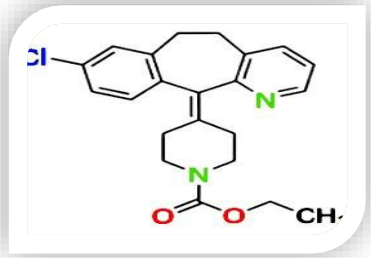


Figure.2 Loratadine

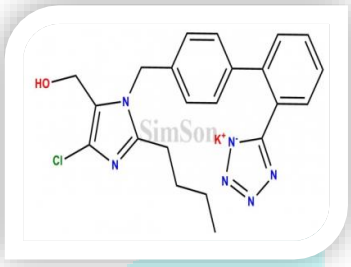


Figure.3 Losartan Potassium

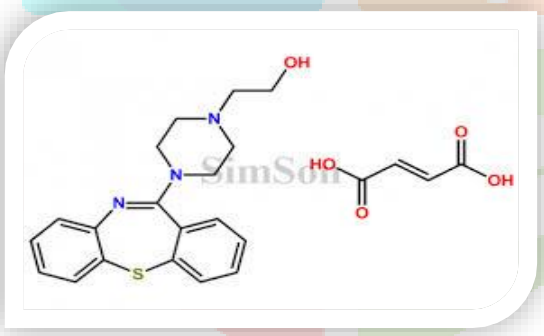


Figure.4 Quetiapine fumarate

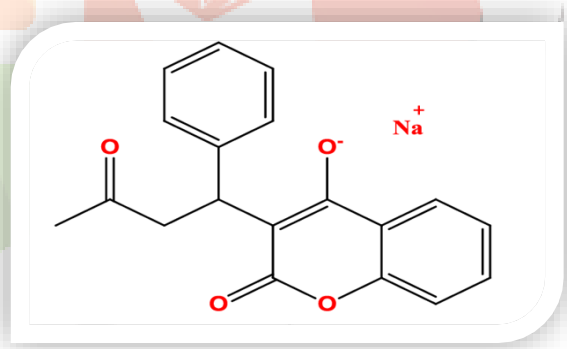


Figure.5 Warfarin sodium

MATERIALS AND METHODS

Reagents and standards**:** The pharmaceutical grade drugs were supplied by Dr.Reddy's laboratory and Arabindo pharmaceutical, Hyderabad. *p*- Chloranilic acid, acetonitrile and Solvents purchased from S.D.fine chem. Pvt.Ltd, Mumbai, India. Whatman filter paper no.42 was used for filtration purpose. All the reagents used were of AR grade and triple distilled water was used throughout the investigation. Tablets were purchased from the Medplus and Apollo medical shops.

Instrumentation and Optical characteristics: All absorbance measurements were recorded on Shimadzu140 double beam spectrophotometer as well as on Elico 159 single beam and Elico SL-2l0 UV-Visible double spectrophotometers using matched pair of Quartz cells of 10mm path length. A high precision Analytical Dhona200 balance was used for weighing the reagents.

Preparation of standard stock solution**:** *p*- chloranilic acid of (9.569 x10^{-3}*M*) stock solution was prepared by dissolving of sample in100ml standard flask with in acetonitrile solvent. Standard stock solution of drugs was

prepared by dissolving accurately weighed 40mg drug to separate100ml volumetric flasks. The stock solutions of LTG, LOR, LOS, QTF and WAR were further diluted with the same solvent to obtain working concentrations.

Table .1The range of concentration of drugs used for Charge Transfer Complexation with ***p*-CA**

Drugs	**Working Concentration**	**Range**
Lamotrgine	$50\mu gmL^{-1}$	$50\text{-}450\mu gmL^{-1}$
Loratadine	$40\mu gmL^{-1}$	$40\text{-}360\mu gmL^{-1}$
Losartan Potassium	$50\mu gmL^{-1}$	$50\text{-}450\mu gmL^{-1}$
Quetiapine fumarate	$40\mu gmL^{-1}$	$40\text{-}360\mu gmL^{-1}$
Warfarin sodium	$40\mu gmL^{-1}$	$40\text{-}360\mu gmL^{-1}$

Assay procedure**:** In to a series of 10mLvolumetric flasks, different volume of standard solution of drug was transferred. To each flask, 1mL of ($9.569 \times 10^{-3}M$) *p*-CA solution in acetonitrile was added and remaining volume was made up to the mark by solvent.When the pale yellow colored solution of *p*-CA mixed with drugs purple colors were observed. The absorbance of the solution was measured after 2or3 min of mixing against blank at 520nm. The spectra of each sample at 2 or 3 different concentrations have been recorded on scan mode and for the remaining optical density were noted on fixed wavelength mode at 520 nm.

RESULTSANDDISCUSSION

Effect of concentration of reagent: When various concentrations of 2% of *p*–Chloranilicacid (0.2, 0.4,0.6,0.8,1.0,1.2,1.4,1.6,1.8, 2.0, 2.2, 2.4mL) was added to fixed concentration of various drugs *viz.*,50 $\mu gmL^{-1}$of **LTG**, 40$\mu gmL^{-1}$of **LOR**, 50$\mu gmL^{-1}$of **LOS**, 40$\mu gmL^{-1}$of **QTF**, 40μgmL^{-1} of **WAR**. A plot of volume of reagent and the absorbance showed that 1.8mL of reagent solution is enough ($9.569 \times 10^{-3}M$) to develop the purple color to its maximum intensity after that a plateau was observed. Therefore an excess of reagent *i.e.* 1mL of reagent in a total volume of 10 mL was used throughout the work.

Effect of concentration of Drug: Different volumes of drug of random concentration were added to fixed volumes of acceptor Solutions developed coloration. Absorbance of solutions was measured at 520nm. Beer's law was obeyed up to certain extent of concentration above which linearity was not observed. This concentration was taken as optimum concentration and stock was prepared. The stock was further diluted to get a minimum of 8 to 10 points in the range of Beer's law plot. Similarly when the concentration is below certain limit points scattered. This was taken roughly a measure of limit of detection which is further checked by following the procedure for the determination of LOD and LOQ.

Effect of time: The interaction of *p*-CA with drugs resulted in the formation of colored product which stabilized within 2 mints of mixing. The developed color remained stable at room temperature for about an hour. After two hours many solutions turned purple. After a day all solutions turned black hence the measurements were made immediately after mixing the solutions.

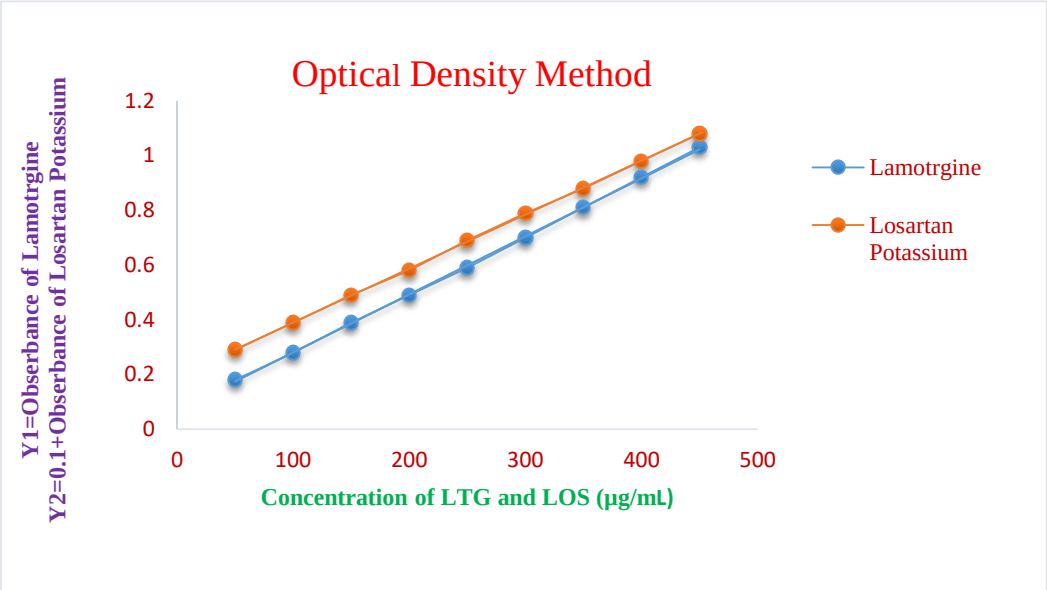


Fig.6 Calibration curve of L**TG and** L**OS (OD Method)**

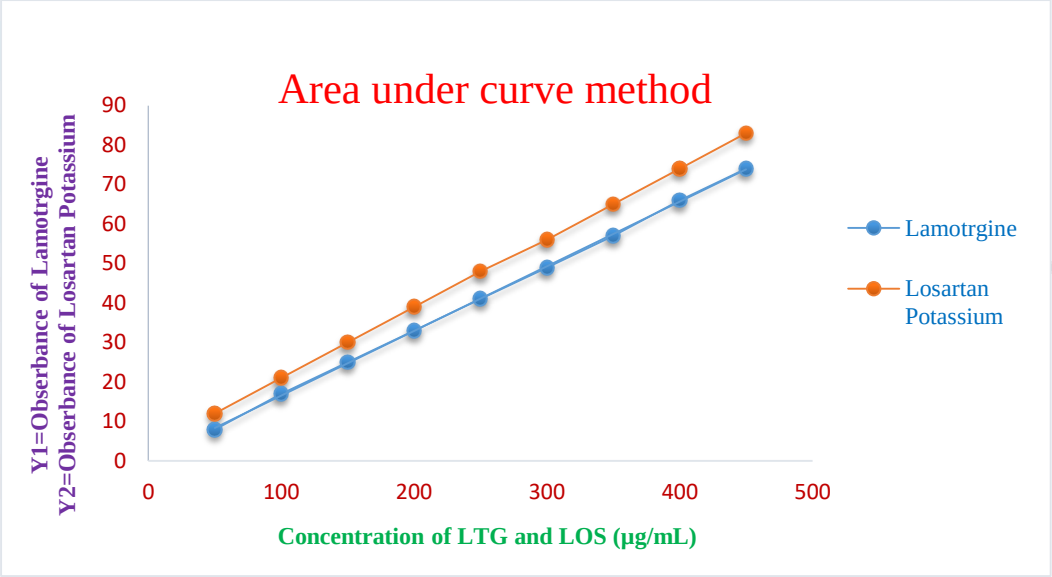


Fig.7 Calibration curve of LTG and LOS (AUC Method)

Effect of organic solvent: Various solvents such as carbon tetrachloride, chloroform, 1, 2 dichloroethane, methanol and acetonitrile have been tried to select suitable solvent for the analysis of the drug. Acetonitrile is found to be the suitable solvent as it produces maximum optical density with affixed concentration of drug while other solvents mentioned above are found to be unsuitable as they produced lower absorbance due to incomplete dissociation of complex. Hence acetonitrile is used throughout the work.

Structure activity relationship**:** From the slopes of Calibration curve and from stability constants and it is clear that the donor ability of the drug is in the order: QTF>LOS>LTG>WAR>LOR. From the structures of the drugs it is clear that **QTF** has three nitrogen's 1&2 are tertiary but 2 is resonance with ring, 3 is sp2 nitrogen**.LOS** has six nitrogen's all are involving in resonance.**LTG** has five nitrogen's, two are primary aminesbut resonance with ring, and three are sp2 nitrogen's.**WAR** has O^- group. **LOR** has 2 nitrogen's1isinpyridineringand2isadjacenttothecarbonyl group, hence it is less basic than all drugs.

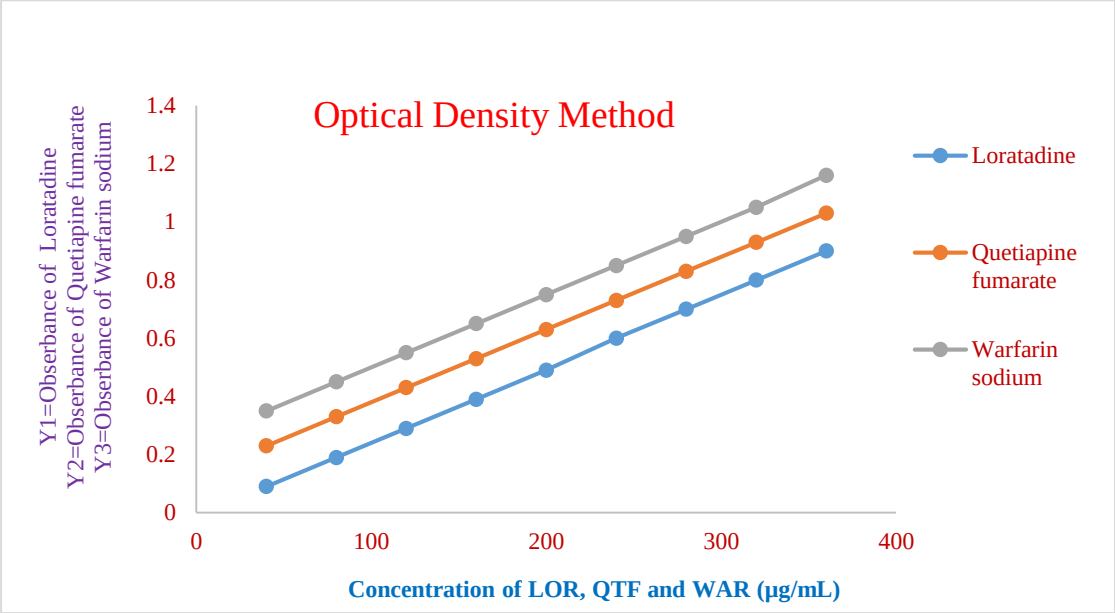


Fig.8 Calibration curve of LOR, QTF and WAR (OD Method)

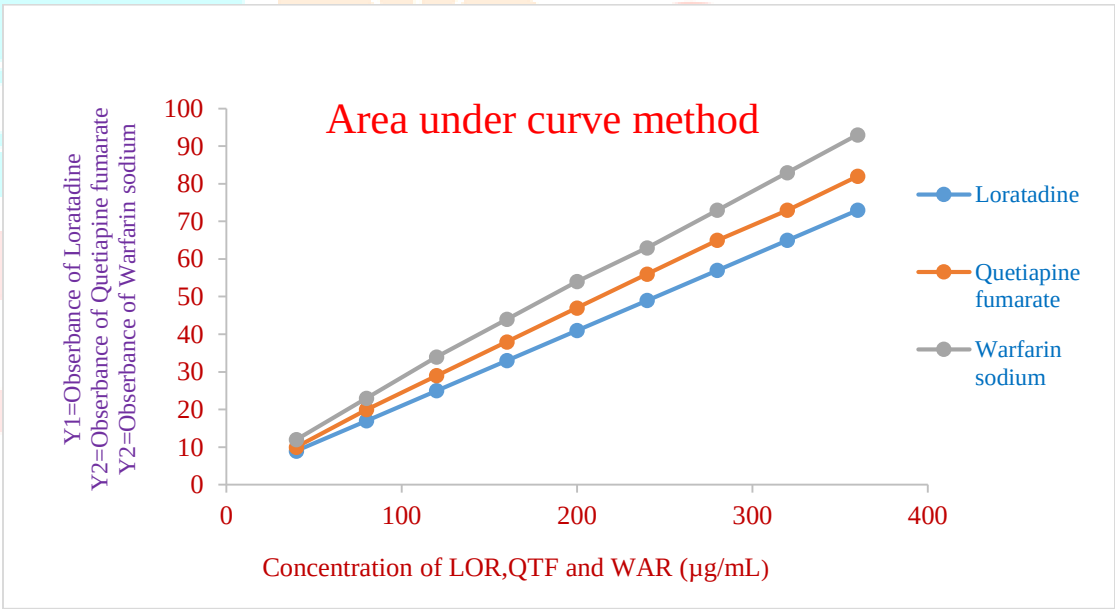


Fig.9 Calibration curve of LOR, QTF and WAR (AUC Method)

Validation of the proposed methods: The AUC (Area under curve) was calculated usingExcel programme. This is taken between 400 to 700 nm as this area is minimally interfered by ***p*-CA** absorption. After recording optical densities and calculating AUC for four replicates a commonly used analytical parameter called "relative response" (O.D / Conc. (µg mL^{-1}) and AUC / Conc. (µg mL^{-1}) have been calculated. The points between 95% and 105% of average relative response only are considered for construction of calibration. The calibration graphs are shown in (figures 6-9).The different concentrations of donors have been mentioned (Table.1). Calibration curves were linear for all the drugs whose limits are mentioned. The methods developed have been validated in terms of guidelines of international conference of harmonization (ICH) *viz.*, selectivity, precision, accuracy, linearity, LOD, LOQ and robustness. The methods are selective and can differentiate the analyte from the excipients. The precision is tested by repeating each experiment at least 6 times while the accuracy has been tested by taking known weight of sample and performing recovery experiments. (Table.4). Limits of calibration, LOD, LOQ, have been determined as mentioned earlier. The robustness of the methods is examined by performing the experiments on three different spectrophotometers with excellent tally of absorbance values. The methods developed have also been applied for the analysis of pharmaceuticals. The recovery experiments performed show high accuracy and precision and the

results are compared to the available validated reported methods on each drug. The values %RSD and t-and F tests are in the permissible range of experimental errors (Table 5) and show that the methods can be used in both pharmaceutical and drug industries.

Table 2.Analytical parameters for the determination of drugs by Charge Transfer Complexation with ***p*-CA (**AUC Method**)**

Parameter	LTG	LOR	LOS	QTF	WAT
λ_{max}(nm)	520	520	520	520	520
Beer'sLawLimits (µg mL^{-1})	50-450	40-360	50-450	40-360	40-360
Molarabsorptivity (L $mol^{-1}cm^{-1}$)	$0.1051x10^7$	$0.4640x10^7$	$0.3307x10^7$	$0.4508x10^7$	$0.1434x10^7$
Sandal sensitivity (µg cm^{-2})	0.0054	0.0047	0.0053	0.0050	0.0039
LOD (µgmL^{-1})	0.1362	0.2830	0.0539	0.1343	0.1523
LOQ (µgmL^{-1})	0.4128	0.8576	0.1633	0.4071	0.4617
Intercept,(A)	0.394	1.653	1.419	-0.458	-0.531
Slope,(B)	0.185	0.209	0.187	0.197	0.251
Correlation Coefficient, (R)	0.997	0.994	0.997	0.998	0.999
StandardDeviation of Intercept (Sa)	0.0076	0.0179	0.0030	0.0080	0.0115
StandardDeviation of Slope (Sb)	0.0066	0.0101	0.0116	0.009	0.0058
Regression equation,(y) Y=bx+a	0.185x +0.394	0.209x +1.653	0.187x +1.419	0.197x -0.458	0.251x -0.531

Table.3Analytical parameters for the determination of drugs by Charge Transfer Complexation with ***p*-CA (**OD Method**)**

Parameters	LTG	LOR	LOS	QTF	WAT
λ_{max}(nm)	520	520	520	520	520
Beer'sLawLimits (**µ**g mL^{-1})	50-450	40-360	50-450	40-360	40-360
Molarabsorptivity ($Lmol^{-1}cm^{-1}$)	$0.1051x10^7$	$0.1721x10^7$	$0.3307x10^7$	$0.4508x10^7$	$0.1434x10^7$
Sandalsensitivity (**µ**g cm^{-2})	0.5	0.5	0.5	0.5	0.5
LOD (**µ**gmL^{-1})	48.6773	7.4402	17.8474	31.3644	4.95
LOQ (**µ**gmL^{-1})	147.5071	22.5462	54.0832	95.0438	15.0
Intercept,(A)	+0.070	+0.004	+0.093	+0.030	+0.005
Slope,(B)	0.002	0.002	0.002	0.002	0.002
Correlation Coefficient,(R)	0.984	0.998	0.989	0.996	0.998
StandardDeviationof Intercept (Sa)	0.0045	0.0005	0.0015	0.0057	0.0008
StandardDeviationof Slope (Sb)	0.0005	0.001	0.0007	0.0020	0.0005
Regression equation,(y) Y=bx+a	0.002x +0.070	0.002x +0.004	0.002x +0.093	0.002x +0.030	0.002x +0.005

Procedure for analysis of Pharmaceuticals**:**

Five tablets of (Lamosyn-25mg) were weighed and ground into fine powder with the help of a mortar and pestle. Weight equivalent to 50mg of Lamotrigine was transferred in 100mLvolumetric flask and 100 mLof Methanol was added and shaken well for 10 mints. The content was filtered using whatman No. 42 filter paper in the beaker. The residue is washed with 30 mL of Methanol. Methanol was evaporated by heating on water bath .To that content Acetonitrile was added and serial dilutions are done accordingly.

Ten tablets of (Alaspan-10mg) were weighed and ground in to fine powder. Weight equivalent to 40mg of Loratadine was transferred in 100mL volumetric flask and 50mL of Methanol was added and shaken well for 5 mints. The content was filtered using whatman No.42filter paper in the beaker. The residue is washed with 20mL of Methanol. Methanol was evaporated by heating on water bath. To that content Acetonitrile was added and serial dilutions are done accordingly.

Ten tablets of (Repace-50mg) were weighed, finely powdered and mixed thoroughly. An accurately weighed amount of powder equivalent to 50 mg of Losartan potassium was transferred into a 50 mL volumetric flask and was dissolved with double distilled water and shacked for 10 min and the solution filtered using a whatman No. 42 filter paper. Water was evaporated by heating on water bath. To that content Acetonitrile was added and serial dilutions are done accordingly.

Ten tablets of (Qutan-50mg) were weighed and ground in to fine powder. Weight equivalent to 50mgof Quetiapine fumarate was transferred in 100mLvolumetricflask and 50mL of Methanol was added and shaken well for 5 mints. The content was filtered using whatmanNo.42 filter paper in the beaker. The residue is washed with 20mL of Methanol. Methanol was evaporated by heating on water bath. To that content Acetonitrile was added and serial dilutions are done accordingly.

Three tablets of (Coumadin-300mg) were weighed and ground into fine powder. Weight equivalent to 50 mg of Warfarin sodium was transferred in 100mL volumetric flask and dissolved with double distilled water. The solution filtered using whatman No. 42 filter paper into the beaker. Water was evaporated by heating on water bath. The compound is washed with 50 mL of chloroform. The chloroform was evaporated by heating on water bath. To that content Acetonitrile was added and serial dilutions are done accordingly.

Table4.Determination of accuracy and precision of the methods on pure Drug sample

Drug	Taken (µgmL^{-1})	Found (µgmL^{-1})	Error(%)	Recovery (%)	RSD (%)	Proposed methodmean ±SD
LTG	3.0	3.02	0.66	100.66	0.537	100.04 ±0.537
	3.5	3.49	0.29	99.71		
	4.0	3.99	0.25	99.75		
LOR	2.0	2.01	0.50	100.50	0.411	100.02 ±0.411
	4.0	3.99	0.25	99.75		
	6.0	5.99	0.17	99.83		
LOS	2.5	2.49	0.40	99.60	0.365	99.97 ±0.364
	3.0	3.01	0.33	100.33		
	3.5	3.5	0.00	100.00		
QTF	3.5	3.48	0.57	99.43	0.482	99.94 ±0.482
	4.0	4.0	0.00	100.00		
	5.0	5.02	0.39	100.39		
WAR	1.0	1.0	0.00	100.00	0.290	100.02 ±0.290
	3.0	3.01	0.33	100.33		
	4.0	3.99	0.25	99.75		

Table 5.Results of assay of tablets by the proposed method and statistical evaluation and recovery Experiment by standard addition method.

Tablet	Drugin tablet (µgmL^{-1})	Drug added (µg mL^{-1})	Total found (µg mL^{-1})	Error (%)	Recovery (%)	RSD (%)	Reference method mean ± SD	Proposed method mean ± SD	t-test	F-test
Lamosyn (LTG) 	0.50 0.50 0.50 2.0 4.0 6.0	0.3 0.6 0.9 0.0 0.0 0.0	0.81 1.09 1.39 2.0 3.98 5.99	1.25 0.90 0.71 0 0.5 0.17	101.25 99.10 99.29 100 99.5 99.83	0.776	100.46 ±0.507	99.82 ±0.774	1.104	0.257
Alaspan (LOR) 	0.50 0.50 0.50 1.0 3.0 5.0	0.3 0.5 0.7 0.0 0.0 0.0	0.81 1.01 1.20 0.99 3.01 4.98	1.25 1 0 1 0.33 0.4	101.25 101 100 99 100.33 99.6	0.847	99.5 ±0.56	100.19 ±0.848	0.168	0.314
Repace (LOS) 	0.50 0.50 0.50 2.0 3.0 6.0	0.2 0.4 0.6 0.0 0.0 0.0	0.69 0.9 1.11 1.98 3.01 3.98	1.43 0.00 0.90 1 0.33 0.5	98.57 100.00 100.90 99 100.33 99.5	0.869	99.65 ±0.418	99.72 ±0.867	0.175	0.174
Qutan (QTF) 	0.50 0.50 0.50 2.0 4.0 6.0	1.0 2.0 3.0 0.0 0.0 0.0	0.71 0.90 1.11 2.99 3.48 3.99	1.40 0.00 0.90 0.33 0.57 0.25	101.40 100.00 100.90 99.67 99.43 99.75	0.601	99.89 ±0.63	99.68 ±0.599	0.573	0.396
Coumadin (WAR) 	0.50 0.50 0.50 3.5 3.0 3.5	1.0 1.5 2.0 0.0 0.0 0.0	1.49 2.01 2.48 2.52 3.01 3.51	0.67 0.5 0.8 0.8 0.33 0.29	99.33 100.50 99.20 100.8 100.33 100.29	0.653	99.74 ±0.76	100.075 ±0.653	0.83	0.578

APPLICATION

These methods are economical compared to other sophisticated analytical instruments, hence can be used for routine analysis of commercially available formulation.

CONCLUSIONS

The obtained results from the methods for the determination of above mentioned drugs indicate that methods are simple, accurate and precise. We observed the quantification of drugs as AUC is more accurate and precise than selecting one wavelength because AUC combines optical densities at the all the wave length. The methods are economical compared to other sophisticated analytical instruments, hence can be used for routine analysis of commercially available formulations.The method is suitable for the determination of these drugs in tablet formation without interference from commonly used recipients. The solvent used for the method are inexpensive and simple to prepare, and could be used in a quality control laboratory for routine drug analysis.

ACKNOWLEDGEMENT

Author is thankful to the Principal and staff, Government Degree College-Malkajgiri, for permission to carryout research work for providing facilities.

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