WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 16, 1127-1139. Research Article ISSN 2277– 7105

OXIDATIVE SPECTROPHOTOMETRIC DETERMINATION OF COMMERCIAL DRUGS USING POTASSIUM PERMANGANATE AND AMARANTH DYE AS A COUPLE IN ACIDIC MEDIUM

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Article Received on
03 July 2018,

Revised on 23 July 2018,
Accepted on 12 August 2018

DOI: 10.20959/wjpr201816-13190

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ABSTRACT

Simple, sensitive and selective methods are developed for the spectrophotometric determination of drugs, viz., Cefdinir (CEF), Ceftriaxone (CET), Doxycycline (DOX), Losartan (LOT) and Ranitidine HCl (RAN), based on their reactivity towards Acidic Potassium Permanganate ($KMnO_4$). Beers law is obeyed in the concentration of 3-27 µg mL^{-1}, 4.5-31.5 µg mL^{-1}, and 6.5-45.5µg mL^{-1} and 10-70 µg mL^{-1}., 8-56 µg mL^{-1} for CEF, CET, DOX, LOT and RAN respectively. The methods involve the addition of excess $KMnO_4$ of known concentration in the presence of 2N Sulphuric Acid (H_2SO_4), Reactants are allowed to react and the unreacted $KMnO_4$ is estimated by the measurement, linear relationship is observed between absorbance of Amaranth dye (λ_{max} =519nm) and Concentration of drug and formed a basis for quantification. These methods have been applied for the determination of drugs in their pure form as well as in tablet formulations. These methods have been validated in terms of guidelines of ICH.

KEYWORDS: Spectrophotometry, Drugs, $KMnO_4$, Amaranth dye, Determination, Validation.

INTRODUCTION

Cefdinir (CEF)

Cefdinir is chemically known as [6R-[6a, 7β (Z)]]-7-[[(2-amino-4-thiazolyl) hydroxyimino) acetyl] amino]-3-ethyl-8-oxo-5-Thia-1-azabicyclo- (4.2.0.)- Oct- 2- one- 2-carboxylic acid (Fig-1a). It is a semisynthetic, cephalosporin bacteriocidal antibiotic, broad-spectrum, third-

generation cephalosporin. It is used to treat bacterial infections such as pneumonia, bronchitis, ear infection, sinusitis, pharyngitis, tonsillitis and skin infections. Analysis of Cefdinir in bulk, pharmaceutical dosage forms and biological samples has been accomplished by several methods HPLC[1], LC-MS[2], electrochemical[3], RP-HPLC.[4,5]

Ceftriaxone (CFT)

Ceftriaxone is chemically known as (6R,7R, Z)- 7- (2- (2-aminothiazol-4-yl)- 2- (methoxyimino) acetamido)-3 -((6-hydroxy-2- methyl- 5- oxo- 2, 5- dihydro-1, 2, 4-triazin-3-ylthio) methyl)- 8- oxo- 5- thia- 1- aza-bicyclo [4.2.0]oct-2-ene-2-carboxylic acid, is a third-generation cephalosporin antibiotic(Fig-1b). It is used as a routine prophylactic antibiotic for the patients undergoing orthopedic surgery. It has also been used in the treatment of leptospirosis, Lyme disease and gonorrhea. Literature review showed various methods for the determination of cephalosporins. These methods include spectrophotometry[6], HPLC.[7,10]

Doxycycline Hyclate (DOX)

Doxycycline Hyclate is Hydrochloride hemi ethanol hemihydrate of (4S,4aR,5S,5aR,6R,12aS)-4- (dimethyl amino)-3,5,10,12,12a-pentahydroxy-6-methyl- 1,11-dioxo-1,4,4a,5,5a,6,11, 12a-octahydrotetracene-2-carboxamide (Fig-1c). DOX is frequently used to treat chronic prostatitis, sinusitis, syphilis, chlamydia, pelvic inflammatory disease, acne, rosacea, and rickettsia infections. Several methods have been described for the determination of DOX both in pharmaceutical preparations and biological samples, such as fluorimetry[11] phosphorimetry[12] thin layer chromatography[13] liquid chromatography[14] sequential injection chromatography[15] LCMS[16] micellar electro kinetic capillary chromatography[17] flow injection spectrophotometry[18] capillary ion selective electrodes based potentiometry.[19] A fast thin layer chromatography fluorescence scanning densitometry (TLCF) technique[20] has been developed for the determination of DOX in honey, serum and urine samples.

Losartan potassium (LOT)

Losartan potassium chemically 6-methoxy-2-[(4-methoxy-3, 5-dimethylpyridin-2-yl) methylsulfinyl]-1H-benzimidazole is widely used for the treatment of hypertension and cardiovascular diseases in combined pharmaceutical preparations (Fig-1d). Losartan potassium and its principal active metabolites block the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to angiotensin II receptor type 1 (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[21,22], RP-HPLC[23,24], UP-LC.[25]

Ranitidine (RAN) Hydrochloride

Ranitidine hydrochloride (RAN), chemically N, N dimethyl-5-[2-(1-methylamine-2- nitro vinyl)-ethyl thio methyl] furfuryl amine hydrochloride is a H2-receptor antagonist and is widely used in short term treatment of duodenal ulcer and in the management of hyper secretary conditions [(Fig-1e).]. It is also used to depress acid production in various other conditions. Several methods have been reported for the determination of ranitidine in bulk, pharmaceutical dosage forms, and/or biological fluids. These methods include kinetic spectrophotometry[26], HPLC[27], voltammetry[28], potentiometry[29] and polarography.[30]

Structures of Drugs

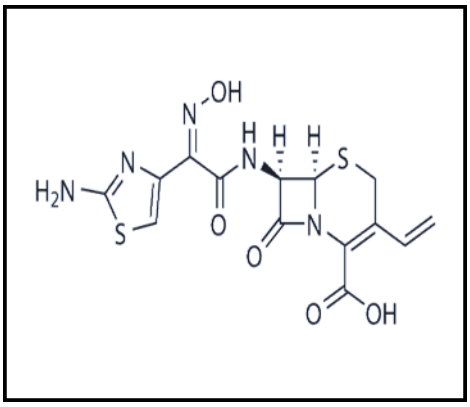

Figure 1(a): Cefdinir.

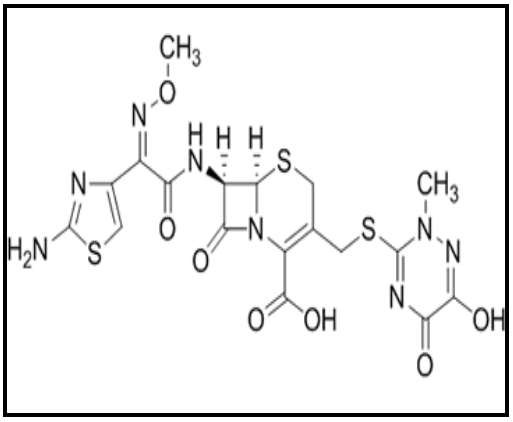

Figure 1(b): Ceftriaxone.

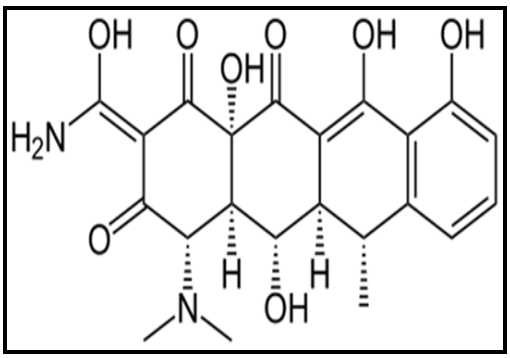

Figure 1(c): Doxycycline hyclate.

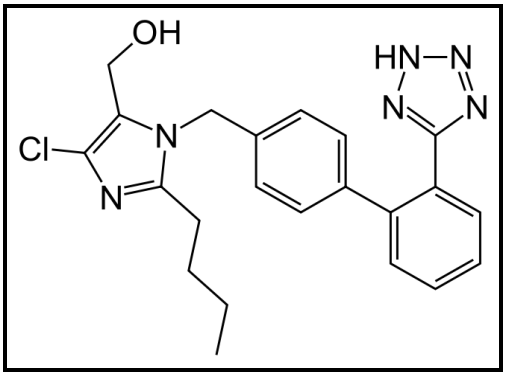

Figure 1(d): Losartan potassium.

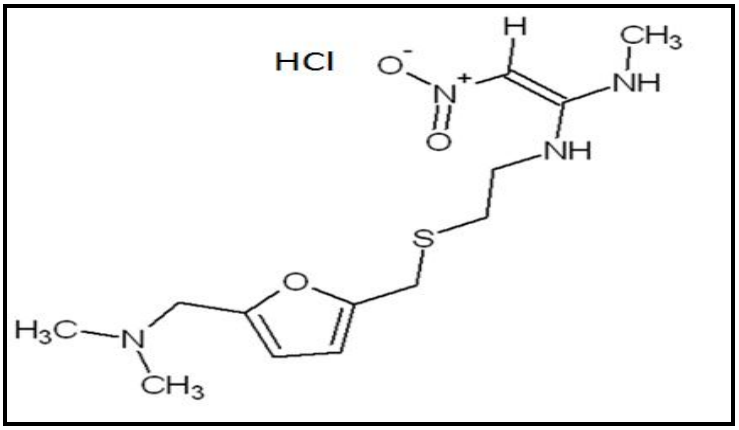

Figure 1(e): Ranitidine HCl.

Through survey of literature on the above mentioned drugs revealed that quantification based on use of KMnO4 an oxidizing reagent and Amaranth dye as analytical reagent have not been yet reported. The present work is an attempt to develop accurate, simple, sensitive, and cost effective method for the analysis of the above drugs.

EXPERIMENTAL

Reagents and standards

The pharmaceutical grade drugs were supplied by Dr.Reddy's laboratory and Arabindo pharmaceutical, Hyderabad. $KMnO_4$, Amaranth and H_2SO_4 were 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 Shimadzu 140 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 10 mm path length. A high precision Analytical Dhona 200 balance was used for weighing the reagents.

Preparation of standard stock solution

Potassium Permanganate

Potassium Permanganate (0.001M) stock solution was prepared by dissolving 0. 158 gm. of sample in 100 ml standard flask with triple distilled water and further diluted to get working concentration 39µg mL^{-1}.

Amaranth dye

Amaranth dye **(**8×10^{-4}**M)** solution was prepared by dissolving 0.0483 in 100 ml standard flask with triple distilled water. Stock solution of Amaranth were further diluted to the working concentration of 353 µg mL^{-1} respectively.

Sulphuric acid

Prepared by diluting the concentrated acid (Merck, Mumbai, India, and Sp. gr. 1.84, 98.0%) with water appropriately to get 2 N acid.

Drug solution

Standard stock solution of drugs were prepared by dissolving accurately weighed 40 mg drug to separate 100ml volumetric flasks. The stock solutions of Cefdinir (CEF), Ceftriaxone (CET), Doxycycline (DOX), Losartan (LOS), and Ranitidine HCl (RAN) were further diluted with the same solvent to obtain working concentrations.

RESULTS AND DISCUSSION

Method Development

Aliquots of pure drug solution (1 to 7 mL) were transferred into a series of 10 mL calibrated flask. To each flask, 1mL of Sulphuric acid was added and followed by 1mL of KMnO4 solution (39 µg mL^{-1}). The contents were mixed and the flasks were set aside for 10 min under occasional shaking and wait for 10 min. Finally, 1mL of Amaranth solution (353 µg mL^{-1}) was added to each flask, diluted to the mark with water and the absorbance of solution was measured at 519 nm against a reagent blank after 10 min.

The calibration curve was constructed for all the drugs by plotting the absorbance versus the concentration of drugs. The absorbance data was collected for six replicate and absorbance to concentration ratio called the relative response was determined. The relative responses between 95% to 105% of average only are considered for construction of the calibration curves (figure 2).

Factors affecting absorbance

a. Effect of acid concentration

The reaction was performed in a series of 10 mL volumetric flasks containing series of drug samples of 1mL to 7mL. To this series add 1mL of H2SO4 followed by 1mL of KMnO4 solution. These flasks were set aside for10 min with occasional shaking, later 1mL of

Amaranth dye was added, then completed to 10 mL total volume with water. It was found that the maximum absorbance was obtained at 1.0 mL of 2N H_2SO_4. Above this volume, the absorbance decreased. Therefore a volume of 1.0 mL of 2N H2SO4 was used for all measurements.

b. Effect of concentration of Drug

Different volumes of drug of random concentration was added to a fixed volumes of Amaranth, KMnO4 and H2SO4. Solutions developed coloration. Absorbance of solutions was measured at 519 nm. 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.

c). Effect of time

A series of drug solution i.e. 1-7 mL of the drug solution was transferred in to separate 10 mL calibrated flasks. To each flask 1mL of 2N H2SO4 acid solution was added followed by 1mL of KMnO4 solution. The contents were mixed and the flasks were allowed to heat for 10min. These were cooled and 1mL of Amaranth dye solution was added to each flask. After 5 min all solutions turned black hence the measurements were made immediately after mixing the solutions.

Accuracy and Precession studies

Accuracy of the methods developed is determined from the recovery studies on pure drug sample. At least four known concentration of solutions of drugs in Beer's law limit were taken and recovery studies were performed. Excellent recovery showed the validity of the calibration curves for each drug.

Precession of the method is demonstrated by repeating experiment (n=6) and % RSD is worked out % RSD being less than case speaks the high precession of the methods.

Analysis of Pharmaceutical preparation

1. Cefdinir: Five tablets of Adinir 300mg were weighed and ground in to fine powder. Weight equivalent to 10mg of Cefdinir was transferred in 100ml volumetric flask and made up to mark with water. And the solution filtered using a whatman No. 42 filter paper. The resultant of the solution was further diluted to get a required concentration.

2. Ceftriaxone: Five tablets of Aacef 250mg were weighed and ground in to fine powder. Weight equivalent to 10mg of ceftriaxone was transferred in 100ml volumetric flask and made up to mark with water. And the solution filtered using a whatman No. 42 filter paper. The resultant of the solution was further diluted to get a required concentration.

3. Doxycycline hyclate: Three tablets of (Doxine-300mg) were weighed and ground in to fine powder. Weight equivalent to 10mg of Doxycycline hyclate sodium was transferred in 100ml volumetric flask and made up to mark with water. And the solution filtered using a whatman No. 42 filter paper. The resultant of the solution was further diluted to get a required concentration for the analysis of the drug.

4. Rantidin HCl: Five tablets of (Aciloc 300mg) were weighed and ground in to fine powder. Weight equivalent to 10mg of Rantidin HCl was transferred in 100ml volumetric flask and made up to mark with water. And the solution filtered using a whatman No. 42 filter paper. The resultant of the solution was further diluted to get a required concentration for the analysis of the drug.

5. Losartan potassium: Ten tablets of (Actilop 50mg) were and ground in to fine powder. Weight equivalent to 10mg of Losartan potassium was transferred in 100ml volumetric flask and made up to mark with water. And the solution filtered using a whatman No. 42 filter paper. The resultant of the solution was further diluted to get a required concentration for the analysis of the drug.

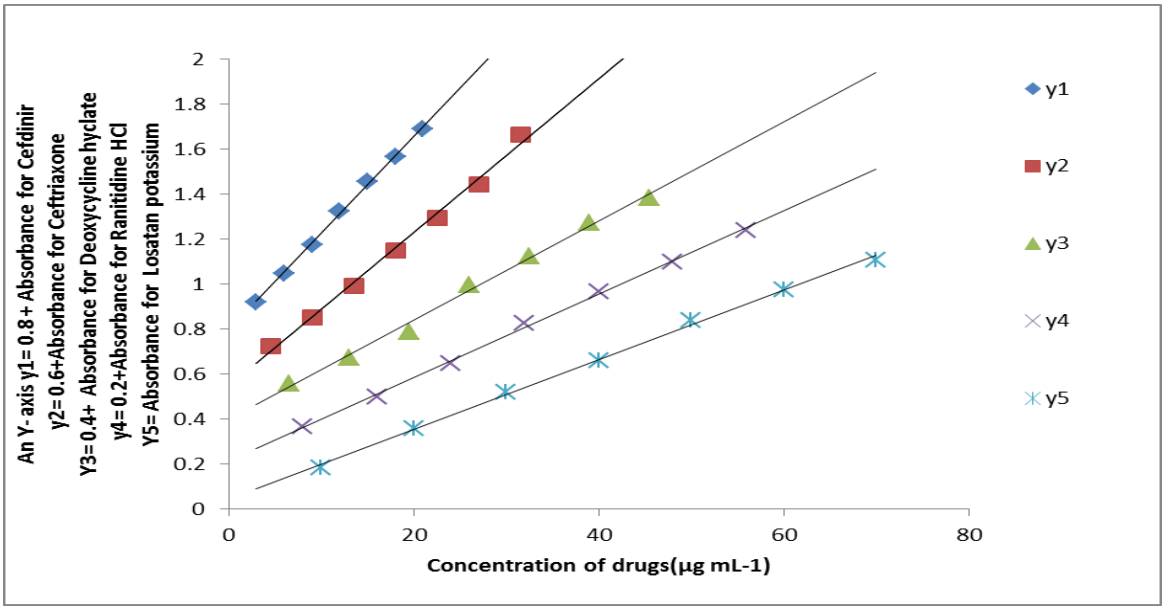

Figure 2: Calibration curves of drugs CEF, CFT, DOX, RAN and LOT.

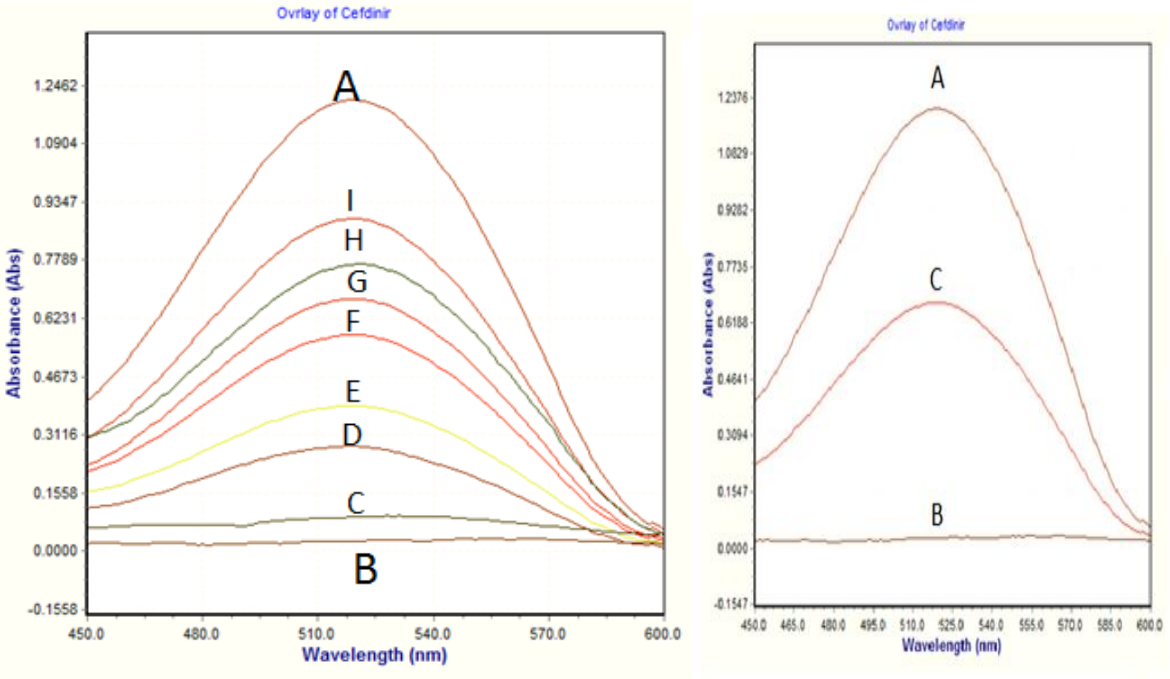

Figure 3): Overlain absorption spectra of cefdinir (C-I).

Figure-2 a) Absorption spectra of Amaranth dye (A) b) Neutralization of KMnO4 with Amaranth dye(B).

Table 1: Analytical and regression parameters of spectrophotometric methods.

Parameter	CEF	CFT	DOX	LOT	RAN
λ_{max} (nm)	519	519	519	519	519
Beer's Law Limits (**µ**g mL^{-1})	3-27	4.5-31.5	6.5-45.5	10-70	8-56
Molar absorptivity (L $mol^{-1}cm^{-1}$)	16880	16995	9815	5741	7982
Sandell sensitivity* (**µ**g cm^{-2})	0.023	0.032	0.048	0.067	0.055
*LOD (**µ**g mL^{-1})	0.161	0.351	0.566	0.88	0.513
LOQ (**µ**g mL^{-1})	0.488	1.064	1.714	2.667	1.556
Intercept, (a)	-0.005	-0.026	0.007	0.045	0.014
Slope, (b)	0.043	0.031	0.021	0.015	0.018
Correlation Coefficient, (R)	0.998	0.999	0.997	0.998	0.998
Standard Deviation of Intercept (Sa)	0.0021	0.0033	0.0036	0.0040	0.0028
Standard Deviation of Slope (Sb)	0.0031	0.0076	0.0043	0.0038	0.0024
Regression equation,(y) Y**=bx+a	0.043x - 0.005	0.031x - 0.026	y = 0.021x + 0.007	0.015x + 0.045	0.018x + 0.014

*Limit of determination as the weight in **µ**g / mL of solution, which corresponds to absorbance of A = 0.001 measured in a cuvette of cross –sectional area $1cm^2$ and path length of 1 cm. Y** =a+bX, where Y is the absorbance and x concentration of drugs in **µ**g / mL.

Table 2: Determination of accuracy and precision of the methods on pure drug sample.

Drug	Taken (µg/mL)	Found (µg/mL)	Error(%)	Recovery (%)	RSD (%)	Proposed method mean ± SD
CEF	5.0 10 15	5.02 9.99 14.99	0.40 0.10 0.07	100.40 99.90 99.97	0.537	100.09 ±0.271
CFT	7 14 21	7.01 13.99 20.97	0.15 0.07 0.14	100.15 99.93 99.86	0.411	99.98 ±0.151
DOX	10 20 30	9.99 20.03 30.0	0.10 0.15 0.00	99.90 100.15 100.00	0.365	100.02 ±0.126
LOT	20 40 60	20.48 39.90 60.20	0.24 0.25 0.33	100.24 99.75 100.33	0.482	100.10 ±0.312
RAN	20 30 40	20.0 30.09 39.85	0.00 0.30 0.37	100.00 100.30 99.63	0.290	99.98 ±0.336

Table 3: Results of assay of tablets by the proposed method and statistical evaluation and recovery experiment by standard addition method.

Tablet	Amount of drug taken in tablet (µg/ml)	Amount of drug found in tablet (µg/ml)	Er (%)	Recovery (%)	RSD (%)	Proposed method mean ± SD	Reference method mean ± SD	T-test	F-test
Adinir (CEF)	5 10 15 20	4.99 10.02 15.03 19.92	0.10 0.20 0.20 0.40	99.90 100.20 100.20 99.80	0.206	100.03 ±0.206	100.12 ±0.065	1.807	2.672
Aacef (CFT)	6 12 18 24	6.03 11.98 18.10 23.92	0.50 0.16 0.56 0.33	100.50 99.84 100.56 99.67	0.453	100.14 ±0.453	100.31 ± 0.514	0.707	0.907
Doxine (DOX)	8 16 24 32	7.98 15.98 24.12 32.08	0.25 0.12 0.50 0.25	99.75 99.88 100.50 100.25	0.343	100.09 ±0.343	102.1 0.500	8.617	0.988
Aciloc (RAN)	15 25 35 45	15.03 24.97 34.92 45.04	0.20 0.12 0.23 0.09	100.20 99.88 99.77 100.09	0.195	99.98 ±0.195	99.04±0.192	1.57	3.490
Actilop (LOT)	10 20 30 40	10.04 20.03 29.96 39.90	0.40 0.15 0.13 0.25	100.40 100.15 99.87 99.75	0.291	100.04 ±0.291	99.79±0.32	0.692	2.25

Analytical Data

A linear correlation was found between absorbance at λmax and concentration of all drugs in the ranges given in table 1. Regression equation analysis of the Beer's law data using the method of least squares was made to evaluate the slope (b), intercept (a) and correlation coefficient (r) for each drug and the values are presented in table 1. The optical characteristics such as Beer's law limits and sandell sensitivity values for both methods are given in table 1. The limits of detection (LOD) and quantization (LOQ) calculated according to ICH guidelines are also presented in table 1 and reveal the very high sensitivity of the methods.

$LOD = 3.3S_a/b$

$LOQ = 10S_a/b$ where S_a = standard deviation of intercept (n=6), b= slope of Calibration plot

CONCLUSIONS

The obtained results from the methods for the determination of above mentioned drugs indicate that methods are simple, accurate and precise. 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

Authors are thankful to HOD of Chemistry, Osmania University, for providing facilities.

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