International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS)
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2013; 3(4):140-148

Research Article

CONDUCTOMETRIC DETERMINATION OF CERTAIN PHARMACOLOGICAL DRUGS USING SILVER AND BISMUTH

Magda Ayad, Hisham Abdellatef, Mervat Hosny* and Nagla Kabil
Analytical Chemistry Department, Faculty of Pharmacy, Zagazig University, Zagazig, (EGYPT) Postal Code 44519

Corresponding Author: Mervat Hosny, **Email:** memaka89@yahoo.com

Abstract: Two simple, rapid and accurate conductometric methods were developed for determination of losartan potassium, pantoprazole sodium, sumatriptan succinate, rabeprazole sodium and lomefloxacine HCl in pure form as well as in their pharmaceutical formulations. The proposed methods based on using two different precipitating agents for conductometric determination of the cited drugs. Method (A) based on reaction of losartan potassium, pantoprazole sodium, sumatriptan succinate and rabeprazole sodium with silver nitrate forming a white precipitate. Method (B) based on reaction of lomefloxacine HCl, pantoprazole sodium and sumatriptan succinate with bismuth tetraiodide, forming an orange red precipitate. Different factors affecting the reaction as concentration of both silver nitrate and bismuth tetraiodide, type of solvents used and also formation of the bismuth tetraiodide were carefully studied to obtain the best results. The described procedures allowed the determination of the studied drugs in the range of 5-15mg/50 mL for (method A) and 0.5-10mg/50mL for (method B). The proposed methods were validated and successfully applied for the determination of the studied drugs in pure form and in their pharmaceutical preparations. The obtained results were statistically compared with reference methods and no significant differences were found.

Key**words:** Conductometric , silver nitrate , bismuth tetraiodide

INTRODUCTION

Losartan potassium[1a] is 2-Butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl] imidazole-5-methanol potassium(table 1). It is used in the management of hypertension. It's official in United State Pharmacopoeia USP30[2a] which describes HPLC for its analysis with UV detection at 254 nm. The reported spectrophotometric methods for the analysis of losartan were UV and derivative spectrophotometry[3,4]. Colorimetric reactions were based on losartan reaction with bromothymol blue[5] bromophenol blue[6] charge transfer complex with the [σ] acceptor iodine and various [π] acceptors such as TCNQ, p-CA and 2,4,7-trinitro-9-fluorenone[7]. Conductometric titration using HCl[8] was used for its determination. Chromatographic methods also used for drug determination as HPTLC[9], RPHPLC[10] and LC-MS[11], also capillary electrophoresis[12] was used.

Pantoprazol sodium[1b] is chemically known as sodium 5-(difluoromethoxy)-2{[(3,4–dimethoxy-2-pyridinyl) methyl] sulfinyl]–1H benzimidazole(Table 1). It's used as anti ulcerative agent . Several methods were developed for its determination such as HPLC [13], densitometric HPTLC [14], capillary electrophoresis [15], derivative UV spectrophotometry [16] and voltammetry [17]. Visible spectrophotometric method using ion pair formation with bromothymol blue[18] and charge transfer complexation reaction with TCNQ[19] were also reported. Different oxidants were used for its determination such as potassium permanganate[20], cerium (IV) sulphate[21] and N-bromosuccinimide[22].

Sumatriptan succinate [1c], 3-[2-(Dimethylamino) ethyl] –N-methyl-1H indole -5 - methane sulphonamide succinate . It is an anti migraine drug. It is official in United States Pharmacopoeia[2b], which suggests chromatographic methods for its determination in bulk and tablet formulations. Literature survey revealed that LC-Tandem MS[23], HPTLC[24] ,RP-HPLC[25] , voltametric[26] and spectrophotometric methods were reported for its determination . [27-29].

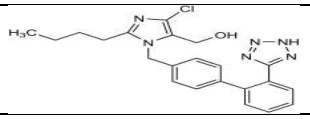
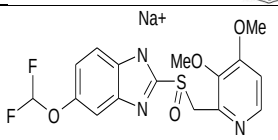
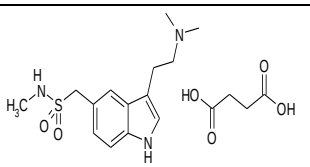
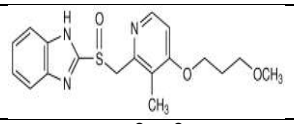
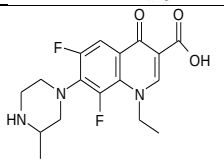
Rabeprazole sodium[1d] ,2-{{{4-(3-methoxypropoxy)-3-methyl-2-pyridinyl}methyl}sulfinyl}-1H-benzimidazole sodium salt(Table 1) .It is a proton pump inhibitor which suppresses gastric acid secretion by inhibiting the gastric H^+/K^+ ATPase at the secretory surface of the gastric parietal cell. Several chromatographic techniques such as HPLC[30], HPTLC[31] and LC[32] were used for drug determination. Different visible spectrophotometric methods were also used such as charge transfer complexation reaction[33], ion pair formation[34] and oxidation with different oxidants [35-37].

Lomefloxacin HCl[1e],antibacterial fluoroquinolone, is chemically known as (1-ethyl-6,8-difluoro-1,4-dihydro-7-(3- methyl-1-piperazinyl)- 4-oxo-3-quinolone carboxylic acid Table 1). It is highly efficient and safe in the treatment of urinary and respiratory tract infections. Several analytical techniques were used for its determination like chromatographic methods such as HPLC[38] and HPTLC[39]. Capillary electrophoresis[40] and voltammetry[41] were also used. Various methods of spectrofluorimetry[42-44] were used

for its determination. Validation of UV spectrophotometric method[45] was developed for the assay of the drug in tablets. Concerning visible spectrophotometry different reagents were reported for drug determination such as N-bromosuccinimide (NBS)[46], eriochrome black T[47] and ammonium vanadate[48].

An inspection of the performance characteristics of the reported methods for the studied drugs revealed that some of them suffer from some drawbacks as extraction, using of organic solvents, too many steps, heating at higher temperature and expensive chromatographic methods. On the other hand there were no or few reports for the conductometric determination of the cited drugs hence the present work aimed to demonstrate new, simple and accurate conductometric methods using aqueous medium for estimation of the mentioned drugs in pure and pharmaceutical dosage forms without interference from common additives. The suggested methods based on conductometric titration of the studied drugs with silver nitrate and bismuth tetraiodide where an insoluble salt was formed , conductance of the solution is measured as a function of the volume of titrant. The reported method can be readily adopted for routine analysis in quality control laboratories.

Table1: chemical structures of the drugs.

Drug name	Chemical structure
Losartan potassium	
Pantoprazole sodium	
Sumatriptan succinate	
Rabeprazole sodium	
Lomefloxacine HCl	

Instrumentation:
JENWAY model 470 Conductivity / TDS Meter (470 201), with Conductivity/Temperature Probe (027 298) was used.

MATERIALS AND REAGENTS
All reagents and chemical used were of analytical grade.

Reagents and chemicals
Silver nitrate (3 $x10^{-2}$ M) solution in distilled water.

Bismuth subnitrate (Evans Medical Ltd Speke,Liverpool) 2 $x10^{-3}$ M prepared by dissolving 0.3 g in 4 mL of HNO3 then completing to 100 mL with double distilled water .
Potssuim iodide (El-Nasr Pharm .Chem.Co.,Egypt) 3.37 $x10^{-1}$ M prepared by dissolving 5.6 g in 100 mL double distilled water.

Preparation of bismuth tetraiodide:
Equal volumes of 3.37 $x10^{-1}$ M potassium iodide and 2 $x10^{-3}$ M bismuth subnitrate solutions were used where potassium iodide put first then bismuth subnitrate solution was added slowly with good shaking.

Pure Samples
Losartan potassium, pantoprazole sodium , Sumatriptan succinate , Rabeprazole sodium and lomefloxacine HCl were kindly provided from SIGMA pharmaceutical industries.

Standard Drug Solutions:
For method A:
Aqueous solution of 1 mg/mL of losartan potassium, pantoprazole sodium ,sumatriptan succinate and rabeprazole sodium were prepared by dissolving 100 mg of the pure drug in 100 mL bi-distilled water.

For method B:
Aqueous solution of 0.5 mg/ mL of lomefloxacin HCl, pantoprazole sodium and sumatriptan succinate were prepared by dissolving 50 mg of the pure drug in 100 mL bi-distilled water.

Market Samples
Losartan® tablets (Arab company for pharmaceuticals and medicinal plants MEPACO MEDIFOOD(Egypt)containing 100 mg of losartan / tablet .
Pantazol® tablets (SIGMA Pharmaceutical industries (Egypt – SAE)) containing 40 mg of pantoprazole / tablet .
Sumigran® tablet (SIGMA pharmaceutical industries) containing 25 mg of sumatriptan succinate/tablet.
Bepra®tablet (Global Napi Pharmaceuticals) containing 20 mg of rabeprazole sodium/tablet.
Lomex® tablets (SIGMA Pharmaceutical industries (Egypt – SAE)) containing 400 mg of lomefloxacin HCl /tablet .
Orchcin®eye drops (Orchidia pharmaceutical Industries) containing 3mg of lomefloxacin /mL.

General procedures:
Aliquots of sample solution of (5-15 mL) and (1-20 mL)containing (5-15 mg) and (0.5-10 mg) for method A and B respectively were transferred to a 50 mL calibrated flask, volume was made up to the mark using distilled water. The contents of the calibrated flask were transferred to a beaker and the conductivity cell was immersed. Both silver nitrate and bismuth tetraiodide were used as titrants, the conductance was measured subsequent to each addition of reagent solution and after stirring for two min, corrected for dilution effect[49] by means of the following equation, assuming that conductivity is a linear function of dilution.

$$\Omega^{-1}correct = \Omega^{-1}obs\ [v_1+v_2/v_1] \quad (1)$$

where Ω^{-1}correct is the corrected electrolytic conductivity, Ω^{-1}obs is the observed electrolytic conductivity, v_1 is the initial volume and v_2 is the volume of reagent added.

A graph of corrected conductivity versus the volume of added titrant was constructed and end-point was determined. The nominal content of the compound under study is calculated from the following equation:

Amount of the drug (mg) = V.M.R / N

where V volume (mL) of the titrant, M molecular weight of the drug, R molarity of the titrant and N number of moles of the titrant consumed per mole of the drug.

ASSAY OF PHARMACEUTICAL FORMULATIONS:

Tablets: the contents of 10 tablets were pulverized , an accurately weighed amount equivalent to100 mg or 50mg of the studied drugs, for method A and B respectively ,were extracted by shaking with 100 mL distilled water , filtered, transferred to a 100 mL volumetric flask.

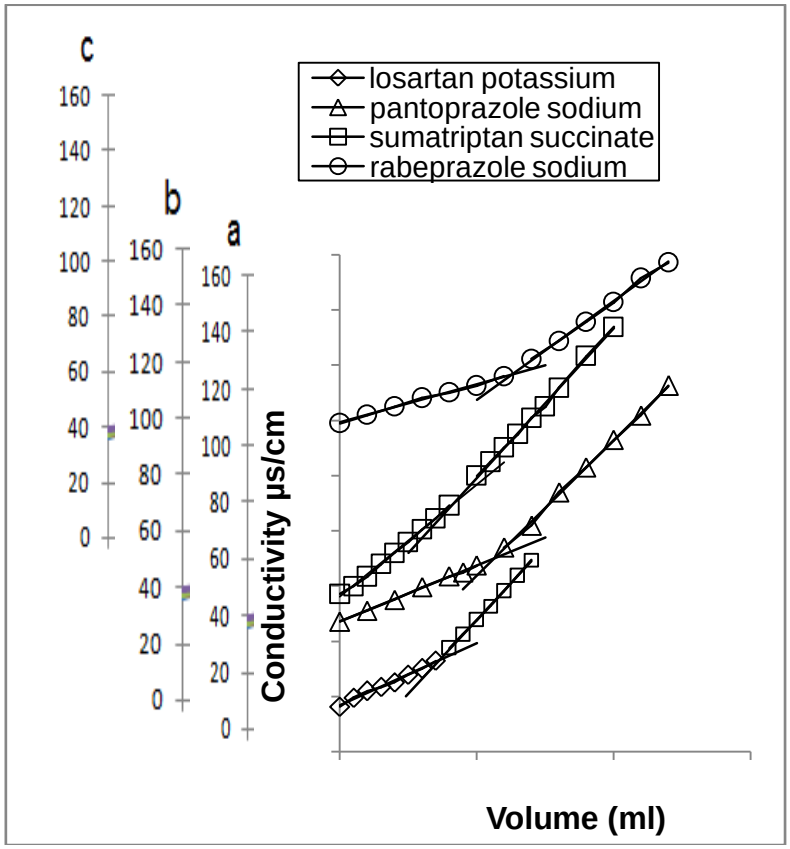
Eye drops: accurate volume of Orchcin® eye drop equivalent to 50mg of Lomefloxacin HCl was measured, completed to 100 mL with distilled water for (method B).

The procedures were completed as descried under the general procedures.

RESULTS AND DISCUSSION:

Conductometric methods of analysis are well suited for the determination of endpoints in precipitation titrations, where the shape of the titration curves can be predicted by summing the ionic conductance of the various species during the course of titration. On using silver nitrate as a titrant for the determination of Losartan potassium ,pantoprazole sodium, and rabeprazole sodium, a precipitate is formed through replacing Na^+ and K^+ by Ag^+ ion quantitatively forming insoluble silver salt with these drugs. On the other hand a precipitate of silver succinate was formed by titration of sumatriptan succinate with silver nitrate. Representative titration curves are shown in figure (1). Two straight lines are obtained, intersecting at the equivalence point .The first segment corresponds to the formed precipitate and the second segment represents the excess of AgNO3.

Losartan potassium + silver nitrate → Losartan silver ↓+ KNO3
Pantoprazole sodium + silver nitrate → pantoprazole silver ↓+NaNO3
Sumatriptan succinate + silver nitrate → Ag succinate ↓ + sumatriptan nitrate
Rabeprazole sodium + silver nitrate → rabeprazole silver ↓+NaNO3



Figure(1) : conductometric titration curve of 5mg of losartan potassium, (a) 7mg of pantoprazole sodium, (b) 5mg of sumatriptan succinate and (c)7mg of rabeprazole sodium using 3×10^{-2} M $AgNO_3$

Investigations were carried out to establish the most favorable conditions for the reaction . The optimum conditions for performing the titration in a quantitative manner were elucidated as described below.

1. Titrations in different media were attempted to obtain the best results. Preliminary experiments in:
(i) Aqueous solutions of both drug and reagent,
(ii) Ethanol solutions of both drug and reagent,
(iii) Drug and reagent solutions in ethanol–water (50%, v/v) mixture,
(iv)Methanol solutions of both drug and reagent,
(v)Drug and reagent solutions in methanol-water (50% v/v) mixture,
(vi)Acetone solutions of both drug and reagent and
(vii) Drug and reagent solution in acetone–water (50% v/v) mixture.
Preliminary experiments showed that procedure in aqueous media was the most suitable for successful results (higher conductance and most sharp end point.).

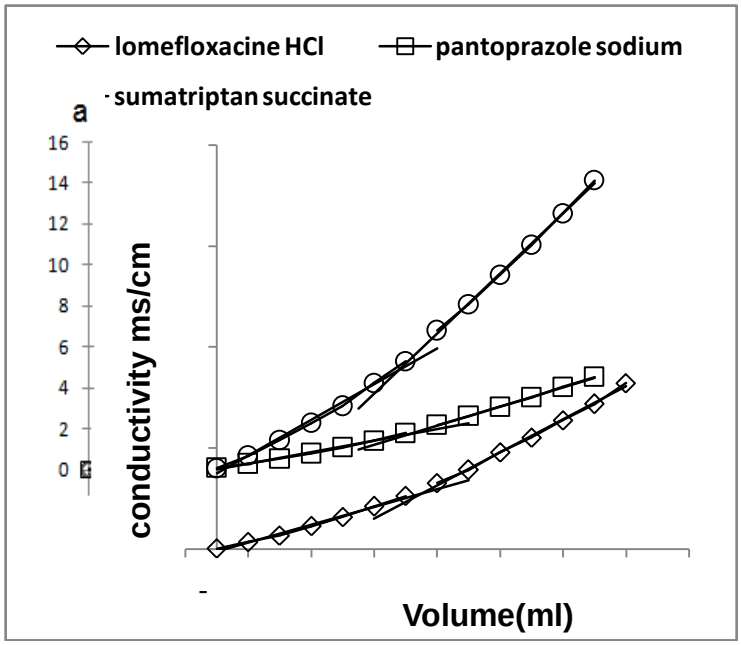
Reagent concentration:
Different concentrations of the reagents solution were tried ranging from $1x10^{-2}$ to $6x10^{-2}$ Molar solution. The optimum concentration of the reagent ($3x10^{-2}$ M) was choosen to achieve a constant and highly stable conductance reading within 1-2 min of mixing.

For method B
Bismuth tetraiodide, inorganic complex, has been used as a reagent for the spectrophotometric determination of some nitrogenous drugs. The method was based on the reaction between the cited drugs and excess of in situ generated bismuth tetraiodide. A reddish orange precipitate was formed that is attributed to ion pair formation between drugs and reagent. In this work, authors tried to form this inorganic complex in vitro, knowing its molarity and using it in the conductometric titration using aqueous medium. The use of this reagent in conductometric rather spectrophotometric methods has several advantages of being more easier, faster and accurate. The method determined the cited drugs without prior filtration or extraction and hence avoiding the use of organic solvents figure (2). Iodide reacts with bismuth forming different products as in the following equations

$Bi^{+3} + 3I^- \rightarrow BiI_3$ black precipiate

$Bi^{+3} + 4I^- \rightarrow (BiI_4)^-$

From the above equations we notice that volume of iodide was the controlling factor in the reaction hence studies of its concentration and volume were vital to get the required reagent.



Fi**gure (2):conductometric titration of 0.5 mg of lomefloxacin HCl , pantoprazole sodium(a) and sumatriptan succinate(a) using 2×10^{-3}bismuth tetraiodide**

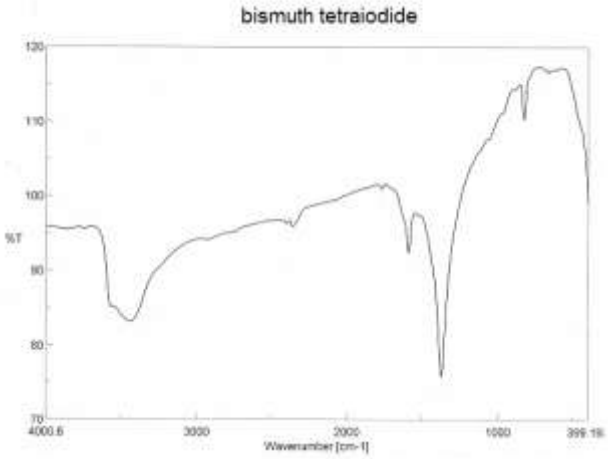
Effect of the concentation
First concentration of bismuth subnitrate and potassium iodide were carefully studied followed by the concentration of the formed reagent. The optimum concentration of the reagent ($2x10^{-3}$ M) was choosen to achieve a constant and highly stable conductance reading within 1-2 min of mixing.

Effect of solvent
Different solvents were attempted to obtain the best results. Distilled water, ethanol, methanol, acetone, ethanol-water (50%,v/v) mixture, methanol-water(50%,v/v) mixture and acetone-water(50%,v/v) mixture.

Preliminary experiments showed that procedure in aqueous media was the most suitable for successful results.

Elucidation of the reaction product of lomefloxacin and bismuth tetraiodide by means of IR
The reaction product was isolated and subjected to structural elucidation by means of infra red (IR). The IR spectrum of lomefloxacin HCl displays characteristic bands at 3428, 3054,2933,1724,1617 and 1532 cm^{-1} assigned to νOH , νCH (aromatic) , νCH (aliphatic) , νC=O(acid), νC=O(pyridone) and νC=C,respectively. On the other hand, the IR spectrum of bismuth tetraiodide has characteristic bands at 826.35,1375, 1591.95cm^{-1} due to ν (Bi-I) and ν (N=O) for

the last two peaks respectively and a strong, broad peak at 3440.38 cm^{-1} due to ν(OH) . The IR spectra of the formed ion associate shows both bands corresponding to drug and bismuth tetraiodide as νoH at nearly 3435 cm^{-1} , νC=O(acid) at nearly 1712 $cm^{-1}$and also νC=O (pyridine) at nearly 1617 cm^{-1} . In addition, the peak due to ν (Bi-I) at nearly 810cm^{-1}. The above arguments indicate that an ion associate has been formed figures (3-5).



Figure(3):IR spectrum of bismuth tetraiodide

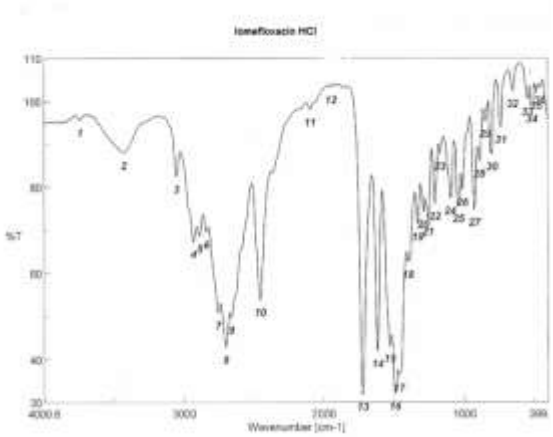


Figure (4):IR spectrum of lomefloxacin HCl

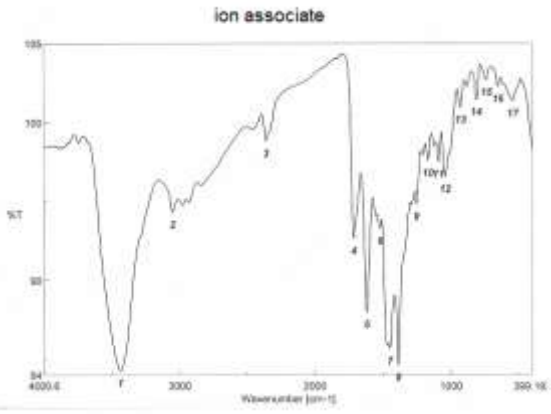


Figure (5): IR spectrum of the formed ion associate

Validation of the Studied Method

In order to address the validity of the proposed methods, statistical analysis of the data obtained from its application on the drug in the pure form and in formulations was performed.

Results in (Table 2) showed that the porposed method is satisfactorily accurate, precise and reproducible over a concentration range of(5-15mg/50mL) and(0.5 -10 mg/50mL) for methods A and B respectively.

For application (standard addition technique):

The methods were successfully applied for the determination of the studied drugs in their pharmaceutical formulations. Satisfactory results (table3) were obtained for the recoveries of the drugs and were in good agreement with the label claimed.

Studen t's t-test and varience ratio F-test, were applied to the results obtained compared with that obtained from reference one (4, 19, 29, 33, 45). Results showed that there is no significant difference between the proposed and reference method. Results of different statistical data are shown in (table 4).

Table(2):conductometric determination of the studied drugs in their pure forms using proposed methods

Method A							
Losartan Potassium		Pantoprazole sodium		Sumatriptan succinate		Rabeprazole Sodium	
Taken (mg)	Recovery %*	Taken (mg)	Recovery %*	Taken (mg)	Recovery %*	Taken (mg)	Recovery %*
5	99.45	5	99.76	5	99.26	5	100.69
7	100.79	7	99.83	7	99.12	7	99.67
9	99.85	9	100.00	9	99.17	9	100.38
11	100.63	11	99.56	11	100.34	11	99.90
13	100.00	13	100.00	13	99.05	13	100.00
15	100.00	15	100.00	15	100.00	15	99.24
Mean	100.12	99.86		99.49		99.98	
V	0.252	0.032		0.294		0.263	
S.D	0.502	0.179		0.542		0.513	
S.E.	0.177	0.063		0.192		0.181	

Method B					
Lomefloxacin HCl		pantoprazole sodium		Sumatriptan succinate	
Taken (mg)	Recovery %*	Taken (mg)	Recovery %*	Taken (mg)	Recovery %*
0.5	99.84	0.5	100.49	0.5	99.67
2.5	99.69	2.5	100.00	2.5	99.67
4.5	100.52	4.5	99.82	4.5	99.63
6.5	99.64	6.5	100.00	6.5	99.62
8.5	100.00	8.5	100.1	8.5	100.59
10	99.84	10	100.4	10	99.75
Mean	99.92	100.14		99.82	
V	0.102	0.067		0.144	
S.D	0.320	0.258		0.379	
S.E	0.113	0.091		0.134	

*Average of three different experiments

Table(3): conductometric determination of the studied drugs in their dosage forms using proposed methods

Method A											
Losartan Potassium			Pantoprazole sodium			Sumatriptan succinate			Rabeprazole sodium		
Taken (mg)	Added (mg)	Recovery %*	Taken (mg)	Added (mg)	Recovery * %	Taken (mg)	Added (mg)	Recovery *%	Taken (mg)	Added (mg)	Recovery * %
5		99.45	5		99.76	5		99.26	5		100.69
	5	99.45		5	99.76		5	100.50		5	100.69
	6	99.08		6	99.39		6	99.17		6	99.24
	7	100.79		7	98.96		7	99.12		7	99.67
	8	100.35		8	98.78		8	99.22		8	100.14
	9	99.85		9	98.65		9	99.17		9	100.38
	10	99.59		10	100.97		10	99.26		10	100.69
Mean		99.85	99.42			99.41			100.14		
V		0.391	0.747			0.289			0.339		
S.D		0.625	0.864			0.538			0.582		
S.E		0.255	0.353			0.219			0.238		
Method B											
Lomefloxacin tablets			Lomefloxacin eye drops			Pantoprazole sodium			Sumatriptan succinate		
Taken (mg)	Added (mg)	Recovery * %	Taken (mg)	Added (mg)	Recovery *%	Taken (mg)	Added (mg)	Recovery * %	Taken (mg)	Added (mg)	Recovery * %
0.5	-----	99.84	0.5	-----	99.84	0.5	-----	100.49	0.5	-----	99.67
	0.5	99.84		0.5	99.84		0.5	100.49		0.5	99.67
	1	100.00		1	100.00		1	99.19		1	100.00
	2	100.00		2	101.95		2	100.40		2	99.59
	3	100.26		3	100.26		3	100.54		3	99.72
	4	100.58		4	99.61		4	100.81		4	99.59
	5	99.22		5	100.78		5	100.16		5	99.67
Mean		99.98	100.41			100.27			99.71		
V		0.207	0.733			0.322			0.023		
S.D		0.455	0.856			0.567			0.152		
S.E		0.186	0.349			0.231			0.062		

*Average of three different experiments

Table (4): Statistical data for the determination of the studied drugs using proposed methods compared with reference methods.

Drug	Proposed procedures			Reference method
	Reagents			
		Silver nitrate	Bismuth tetraiodide	
Losartan potassium	Mean ± S.D.	100.12±0.502		100.32±0.554
	Variance	0.252		0.307
	Student-t-test	0.678(2.201)*		---
	F-test	1.218(4.39)*		---
	n	6		7
Pantoprazole sodium	Mean ± S.D.	99.86±0.179	100.14±0.258	99.94±0.128
	Variance	0.032	0.067	0.016
	Student-t-test	0.836(2.262)*	1.56(2.262)*	---
	F-test	2(5.19)*	4.19(5.19)*	---
	n	6	6	5
Sumatriptan succinate	Mean ± S.D.	99.49±0.542	99.82±0.379	100.13±0.254
	Variance	0.294	0.144	0.064
	Student-t-test	2.175(2.309)*	1.42(2.306)*	---
	F-test	4.59(5.41)*	2.25(5.41)*	---
	n	6	6	4
Rabeprazole sodium	Mean ± S.D.	99.98±0.513		99.87±0.652
	Variance	0.263		0.425
	Student-t-test	0.341(2.179)*		---
	F-test	1.616(3.97)*		---
	N	6		8
Lomefloxacin HCl	Mean ± S.D.		99.92±0.320	99.81±0.326
	Variance		0.102	0.107
	Student-t-test		0.611(2.201)*	
	F-test		1.05(4.39)*	
	N		6	7

*****Theoretical values of t and F at p = 0.05

Conclusion:

The proposed methods are easy and very useful for the determination of the studied drug in pharmaceutical formulations and can be an alternative to the more complex and expensive methods also can be applied in laboratories for routine analysis.

Acknowledgement

The authors wish to extend thanks to Arab company for pharmaceuticals and medicinal plants MEPACO MEDIFOOD(Egypt),SIGMA Pharmaceutical industries (Egypt – SAE) and Orchidia pharmaceutical Industries to providing suitable facilities.

REFERENCES:

1. Sweetman, SC. Martindale,; The complete drug reference ,Thirty sixth edition, **2009**; 1326(a), 1760(b), 625(c), 1765(d) and 295(e).
1. 2.The United State Pharmacopoeia USP30 -NF25, **2007**; 2499(a) and 3258(b).
2. Lastra O, Lemus I, Sa´nchez H., Pe´rez R. Development and validation of an UV derivative spectrophotometric determination of Losartan
3. potassium in tablets, *J.Pharm.Biomed.Anal.*,**2003**;33(2):175-180.
4. 4.Subbarao J, Rao Dr.P, Vidyadhara Dr.S, Rao B , Sasidhar R. UV spectrophotometic validation for identification and determination of losartan potassium in tablets, *International Journal Of Pharmacy and Technology*(IJPT) , **2012** ; 4 (1): 4137-4143.
5. Latheeshjlal L , Parthiban P , Alagarsamy V, Sunil M , Vaidhya mahul J, Rama mohan T. Spectrophotometric Determination of Lorsartan Potassium and its Dosage Form by Bromothymol Blue and Phosphate Buffer, *E-Journal of Chemistry*,**2010**; 7(1): 320-324.
6. Ahmed S, Karajgi S, Simpi C, Savita S, Kalyane N. Visible spectrophotometric methods for the estimation of losartan potassium and omeprazole in single component pharmaceutical formulations, *International Journal of Pharm Tech Research*,**2009**;1(4):1247-1250.
7. Darwish, I. Analytical study for the charge-transfer complexes of losartan potassium, *Analytica Chimica Acta*,**2005;** 549 : 212–220.
8. 8.Rossini P, Felix F, Angnes L. A simple and precise conductometric method for the determination of losartan in pharmaceutical products, *Central European Journal of Chemistry*, **2012**;10(6):1842-1849.

9. Sathe S, Bari S. Simultaneous analysis of losartan potassium, atenolol, and hydrochlorothiazide in bulk and in tablets by high-performance thin-layer chromatography with UV absorption densitometry, *Acta Chromatographica*,**2007**;19:270-278.
10. 10.Rao K., Srinivas K. RP-HPLC method for the determination of losartan potassium and ramipril in combined dosage form, *ind.j.pharm.sci*.,**2010**;72(1):108-111.
11. Shah H ,Kundlik M ,Patel N ,Subbaiah G, Patel D ,Suhagia B**,** Patel C . Rapid determination of losartan and losartan acid in human plasma by multiplexed LC-MS/MS, *Journal of Separation Scienc**e,***2009;** 32 (20): 3388-3394.
12. Quaglia M, Donati E, Carlucci G, Mazzeo P, Fanali S. Determination of losartan and hydrochlorothiazide in tablets by CE and CEC, *J. Pharm. Biomed. Anal***.,** **2002**; 29 (6):981-987.
13. 13.Patel B, Suhagia B, Patel M, Pate J.Determination of pantoprazole, Rabeprazole,Esomeprazole,Domperidone and itopride in pharmaceutical products by reverse phase liquid chromatography using single mobile phase, *Chromatographia*, **2007**;65:743-48.
14. 14.Agbaba D, Novovic D, Karljikovic-Rajic K, Marinkovic V. Densitometric determination of omeprazole,pantoprazole, and their impurities in pharmaceuticals. *J. Planar Chromatogr—Modern TLC* ,**2004**;17:169-72
15. 15.Daniela E, Rolf P, Reinhard K. Chiral resolution of pantoprazole sodium and related sulfoxide by complex formation with bovine serum albumine in capillary electrophoresis, *J .Chromatogr. A.*,**1997**;759:185-92.
16. 16.Patel KD ,Hasumati R, Sojitra JR, Kanani N. Simultaneous estimation of levosulpiride and pantoprazole sodium by first and second derivative spectroscopic methods in capsule dosage form,*Universal Journal of Pharmacy* , **2013**;2(1):160-167.
17. 17.Radi A. Square-wave adsorptive cathodic stripping voltammetry of pantoprazole,*Indian J Pharm Sci.*,**2008**;70(4):507-10.
18. 18.Kalaichelvi R, Rose MF, Vadivel K, Jayachandran E. Simple extractive colorimetric determination of pantoprazole sodium by acid-dye complexation method in solid dosage form, *Int. J. of chem. Res*., **2010**;1(1):6-8.
19. 19.Bebawy LI, Kelani KE, Fattah LA, Ahmad AKS. Study of 7,7′,8,8′-tetracyanoquinodimethane charge transfer complexes with some lone-pair-donating drugs. *Journal of Pharmaceutical Sciences,***1997**; 86(9): 1030–1033.
20. 20.Devi OZ, Basavaiah K, Vinay KB.Sensitive and selective spectrophotometric determination of pantoprazole sodium in pharmaceuticals using permanganate,*Chemical Industry and Chemical Engineering Quarterly*,**2010;**16(1):97-102.
21. 21.Devi OZ, Basavaiah K, Revanasiddappa HD, Vinay KB.Titrimetric and spectrophotometric assay of pantoprazole in pharmaceuticals using cerium(IV) sulphate as oxidimetric agent,J. Anal. Chem.,**2011**;66(5):490-495.
22. Basavaiah K, Anilkumar UR, Tharpa K.Spectrophotometric determination of pantoprazole sodium using N-bromosuccinimide, methyl orange and indigo carmine as reagents,*Iran.J.Chem.Chem.Eng*.**2009**;28(1):31-36.
23. 23.Cheng KN, Redrup MJ, Barrow A, Williams PN. Validation of aliquid chromatographic tandem mass spectrometric method for the determination of sumatriptan in human biological fluid, *J.Pharm.Biomed.Anal*., **1998**;17:399-408
24. 24.Tipre DN, Vavia PR.Estimation of Sumatriptan succinate in pharmaceutical dosage form by spectrophotometric and HPTLC methods, *Indian Drugs*,1**999**;36(8):501-505.
25. 25.Riddhi1 G, Dharamsi2 A. simultaneous estimation of sumatrirtan succinate and naproxen sodium in bulk drug and pharmaceutical dosage form by RP-HPLC method, *Journal of Drug Delivery & Therapeutics*, **2013** ;3(2) :93-97.
26. 26.Sagar K, Alvarez JMF, Hua C, Smyth MR, Munden R.Differential pulse voltammetric determination of sumatriptan succinate (1:1)in atablet dosage form,*J.Pharm.Biomed .Anal* .,**1992**;10(1):17-21.
27. Ramu BK, Raghubabu K. Estimation of sumatriptan succinate in bulk and formulation by visible spectrophotometry using aromatic aldehydes, *international journal of applied biology and pharmaceutical technology*, **2011**;2(1):86-91.
28. Ramu BK Raghubabu K.Visible spectrophotometric determination of sumatriptan succinate in tablet dosage forms using folin reagent , *Int .J.Pharm.Biomed . Sci.*,**2010**;1(3):49-52.
29. Satyanarayane KVV, Rao PN. Sensitive bromatometric methods for the determination of sumatriptan succinate in pharmaceutical formulations , E- *Journal of chemistry*, **2011** ;8(1):269-275.
30. 30.Suhagia BN, Patel JR, Patel MM, Patel BH. HPLC analysis for simultaneous determination of rabeprazole and domperidone in pharmaceutical formulation, *Journal of Liquid Chromatography & Related Technologies*,**2007**;30(3):439-445.
31. Patel JR, Patel MM, Suhagia BN, Patel BH. HPTLC determination of rabeprazole and domperidone in capsules and its validation, *Journal of Chromatographic science*.**2008;**46(4):304-307.
32. 32.Garcia CV, Paim CS, Steppe M. New Liquid Chromatographic method for determination of rabeprazole sodium in coated tablets, *Journal of AOAC International*,**2004**;87(4):842-846.
33. 33.Khan NA, Chaudhary AB, Patro B, Rani AD. Analytical study of charge transfer complexation of rabeprazole with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, *ScienceAsia*,**2009**;35:365-371.
34. 34.Pillai S, Singhvi I. Application of orange G dye for quantitation of citalopram hydrobromide, donepezil hydrochloride and rabeprazole sodium

from tablet formulation,*Indian J. Pharm Sci*.,**2006**;8:682-684.
35. 35.Syed AA, Syeda A. Spectrophotometric determination of certain benzimidazole proton pump inhibitors, *Indian J Pharm Sci*.,**2008**;70:507-510.
36. Mohamed GG, Nour el-Din FA, Khalil SM, El-Tantawy ASM. Spectrophotometric determination of peptic ulcer sulfur-containing drugs in bulk form and in tablets, *Drug Testing and Analysis*,**2010**;2(1):28-36.
37. 37.Sreenu D, Sunil K. A new validated spectrophotometric method for the estimation of rabeprazole sodium in tablet dosage forms. *International Journal of Bio-Pharma Research*, **2012**; 1 (1):1-6.
38. 38.Carlucci G. Analysis of fluoroquinolones in biological fluids by high-performance liquid chromatography, *J-Chromatogr,-A*, **1998**;812(1-2):343-367.
39. 39.Chitlang SS, Ranjane M, Wankhede SB, Sakarkar DM . Stability-indicating HPTLC method for estimation of lomefloxacine hydrochloride in pharmaceutical dosage form, .*Int.J.Pharm.Tech*, **2009**;1(3):844-851.
40. 40.Sun H, Li L, Su M. Simultaneous determination of lidocaine,proline and lomefloxacine in human urine by capillary electrophoresis with electrochemiluminescence detection,*Chromatographia*, **2008**;67(5-6):399-405.
41. 41.Vilchez JL, Araujo L, Prieto A, Navalon A. Differential-pulse adsorptive stripping voltammetric determination of the anti bacterial lomefloxacin,*J.Pharm.Biomed.Anal*.**,2001**;26(1):23-29.
42. 42.Limig D, Qingqin X, Jianmei Y.Fluorescence spectroscopy determination of fluoroquinolones by charge-transfer reaction,*J.Pharm.Biomed.Anal*,**2003**;33:693-698.
43. 43.Geffken D, Salem H.Spectrofluorimetric study of charge transfer complexation of certain fluoroquinolones with 2,3,5,6-tetrafluro-p-benzoquinone,*American J of applied science*.,**2006**;3(8):1952-1960.
44. 44.Kaur K, Singh B, Malik AK.Micelle enhanced spectrofluorimetric method for the determination of ofloxacine and lomefloxacine in human urine and serum,*Thai J. Pharm. Sci*.,**2010**;34:58-66.
45. 45.Gomes GC, Salgado HRN. Validation of UV spectrophotometric method for determination of lomefloxacine in pharmaceutical dosage form, *Acta Farm.Bonaerense*,.**2005**;24(3):406-408.
46. 46.Askal H, Refaat I, Darwish I,Marzouq M. Evaluation of N-bromosuccinimide as anew analytical reagent for the spectrophotometric determination of fluoroquinolone antibiotics, *Chem.Pharm.Bull***.2007**;55(11):1551-1556.
47. 47-Amin AS, Dessouki HA, Agwa IA.Spectrophotometric determination of enrofloxacine,lomefloxacine and ofloxacine in pure form and in dosage forms through ion-pair complex formation,*Arabian J. Chem*.**2008**;1(2):209-215.
48. 48.Darwish IA,Sultan MA, Al-Arfaj HA.Kinetic spectrophotometric method for determination of ciprofloxacin and lomefloxacin in their pharmaceutical dosage forms,*Int.J.Res.Pharm.Sci.*,**2010**;1(1):43-50.
49. Lingane JJ. Electroanalytical Chemistry, 2nd Edition, Interscience, New York,**1958;** 90,