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Research Article

CONDUCTOMETRIC DETERMINATION OF LOSARTAN POTASSIUM USING PHOSPHOTUNGSTIC ACID, BROMOCRESOL PURPLE, MERCURY (II) CHLORIDE, AND CUPRIC CHLORIDE AS REAGENTS

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ABSTRACT

Objectives: In the current study a simple and precise four conductometric methods were introduced for determination of Losartan Potassium (LK) in pure form and tablets.

Methods: Method A is based on titration of LK using phosphotungstic acid, method B is based on titration of LK using bromocresol purple dye, method C is based on titration of LK using mercury (II) chloride, and method D is based on titration of LK using cupric chloride.

Results: LK was found to be linear in the concentration range of 3–20 mg/mL for all methods except for method C, the concentration range was 1–12 mg/mL. The obtained percentage recoveries for the four methods ranged from 99.69% to 100.53%; the relative standard deviation values were not exceeding two for all methods.

Conclusion: The suggested methods were successfully applied for the determination of LK in tablets, with results in close agreement at 95% confidence level with those obtained using the reference spectrophotometric method.

Keywords: the determination of different compounds such as captopril

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INTRODUCTION

Losartan potassium (LK) is an angiotensin II receptor antagonist with antihypertensive activity used in the treatment of hypertension [1]. Its chemical structure is 2-Butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl) benzyl] imidazole-5-methanol potassium [2] as shown in scheme 1.

There are various reported spectrophotometric methods for the analysis of losartan including ultraviolet (UV) spectrophotometry [3], reaction with bromothymol blue [4], bromophenol blue [5], and charge transfer complex formation with iodine, tetracyanoquinodimethane, p-chloranilic acid, and 2,4,7-trinitro-9-fluorenone [6]. Furthermore, fluorescence spectroscopic method has been reported for the determination of LK [7]. Furthermore, different chromatographic methods such as HPLC with UV detection [8,9], mass detection [10], thin-layer chromatography [11], and capillary electrophoresis [12] have been published for determination of LK. Electrochemical methods have also been reported including conductometric methods [13,14] and potentiometric method [15].

The use of phosphotungstic acid (PTA), bromocresol purple (BCP) dye, mercury (II) chloride ($HgCl_2$), and cupric chloride ($CuCl_2$) in conductometric methods introduces several advantages over spectrophotometric ones, being easier, faster, and simpler. The methods determine the cited drug without previous filtration or extraction and therefore avoiding organic solvents using. Precipitimetry conductometric titrations using PTA as titrant are commonly used for the quantitative determination of different compounds such as reproterol HCl, salbutamol sulfate [16], papaverine hydrochloride [17], and dextromethorphan [18]. PTA was also used in the spectrophotometric estimation of Mebikar [19].

Precipitimetry conductometric titrations using BCP dye as a titrant are not commonly used. It has been used for the determination of fexofenadine hydrochloride [20] and candesartan [21]. Furthermore, precipitimetric conductometric titrations using $HgCl_2$ as a titrant are commonly used for the determination of different compounds, especially containing thiol groups such as 1-propanethiol, 2-propanethiol and 2-methyl 2-propanethiol [22]. Furthermore, precipitimetric conductometric titrations using $CuCl_2$ as a titrant are commonly used for the determination of different compounds such as captopril [23] and gabapentin [24].

This paper introduces conductometric determination of LK using four reagents: PTA (method A), BCP dye (method B), $HgCl_2$ (method C), and $CuCl_2$ (method D). The proposed methods are simple, practical, and reproducible and can be easily applied to determine LK in tablets.

METHODS

Materials and reagents

All reagents and chemical used were of analytical grade together with bidistilled water.

- LK was kindly provided from Egyptian Int. Pharmaceutical Industries Co. (10^{th} of Ramadan city, Egypt).
- PTA (PARK Scientific limited, Northampton, UK) 1×10^{-3} M prepared by dissolving 0.288 g in 100 ml bidistilled water.
- BCP dye (Sigma Chem. Company, Milwaukee, USA) 5×10^{-3}M prepared by dissolving 0.27 g in the least amount of methanol then completing to 100 ml with bidistilled water.
- $HgCl_2$ (Universal Fine Chemicals PVT-LTD) stock solution of concentration 1×10^{-2} M prepared by dissolving 0.2715 Gin 100 ml with bidistilled water. Working solution of a concentration of 5×10^{-4}M was prepared by further dilution of the stock solution.
- $CuCl_2$ (Aldrich Chemical Co. Ltd.) was prepared as 1×10^{-3}M solution by dissolving 0.0171 g in 100 ml bidistilled water.

Pharmaceutical preparation

Losartan® tablets (Amriya Pharmaceutical Industries, Alexandria, Egypt) labeled to contain 50 mg LK per tablet.

Instrumentation

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

General procedures

Preparation of stock and standard working solutions

LK standard solution of 1 mg/ml (2.17×10^{-3}M) was prepared by dissolving 100 mg of the pure drug in bidistilled water then completing to 100 ml with bidistilled water.

Construction of calibration curves

Aliquots of drug solution containing(3–20 mg),(3–20 mg), (1–12 mg), and (3–20 mg) for methods A, B, C, and D, respectively, were transferred to a 50 ml calibrated flask; dissolved and completed to volume with bidistilled water. The contents of the calibrated flask were transferred to a beaker, and the conductivity cell was immersed.

PTA, BCP, $HgCl_2$, and $CuCl_2$ were used as titrant; the conductance was measured subsequent to each reagent solution addition after stirring for 1 min, the conductance was corrected for dilution [25] by means of the following equation, assuming that conductivity is a linear function of dilution.

$$\Omega^{-1}\text{correct} = \Omega^{-1}\text{obs}\ [(v1+v2)/v1]$$

Where Ω^{-1}correct is the corrected electrolytic conductivity, Ω^{-1}obs is the observed electrolytic conductivity, v1 is the initial volume, and v2 is the volume of reagent added. A graph of corrected conductivity versus the volume of added titrant was constructed and end-point was detected.

The amount of drugs under study was calculated according to the following equation:

Amount of drug = VMR/N

Where V is the volume of titrant, M is molecular weight of drug, R is molar concentration of titrant, and N is no of moles of titrant consumed by 1 mole of drug.

Procedures for determination of stoichiometric ratio using Job's method [26]

About 6 m of 10^{-3}M LK were transferred to 50 mL volumetric flasks and completed to volume with bidistilled water. The contents were transferred to a beaker and the conductivity cell was immersed. 10^{-3}M PTA, BCP, $HgCl_2$, and $CuCl_2$ were used for titration. The conductance was measured subsequent to each reagent solution addition after thorough stirring for 1 min. A graph of conductivity versus volume was constructed.

Procedure for Losartan® tablets

The contents of 10 tablets were pulverized, an accurately weighed amount equivalent to 100 mg of the studied drug was extracted by shaking with 50 ml bidistilled water in a 100 ml volumetric flask, completed to mark using bidistilled water then filtered.

RESULTS AND DISCUSSION

PTA method

On using PTA as a titrant for the determination of LK, ion associate is formed leading to a regular rise in conductance up to the equivalence point where a sudden change in the slope occurs; a precipitate is formed through replacing K + by H + ion quantitatively forming insoluble losartan parent drug. The representative titration curve is shown in Fig. 1. Two straight lines are obtained, intersecting at the equivalence point. The first segment corresponds to the formed PTA potassium and the second segment represents the excess of PTA added.

The reaction may be represented by the following equations:

3 Losartan potassium+ H_3PTALosartan+3PTAPotassium→Parentdrug↓

BCP method

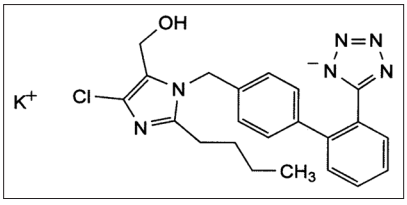
On using BCP as a titrant for the determination of LK, ion associate is formed leading to a regular rise in conductance up to the equivalence point where a sudden change in the slope occurs, a precipitate is formed through replacing K^+ by H^+ ion quantitatively forming insoluble losartan parent drug. A representative titration curve is shown in Fig. 2. Two straight lines are obtained, intersecting at the equivalence point. The first segment corresponds to the formed BCP potassium and the second segment represents the excess of BCP added.

The reaction may be represented by the following equation:

1Losartan potassium+BCPIosartan+BCP potassium→Parent drug↓

$HgCl_2$ method

On using $HgCl_2$ as a titrant for the determination of LK a precipitate is formed through replacing K^+ by Hg^{+2} ion quantitatively forming insoluble mercuric salt with the drug. A representative titration curve is shown in Fig. 3. Two straight lines are obtained, intersecting at the equivalence point. The first segment corresponds to the formed potassium chloride and the second segment represents the excess of $HgCl_2$ added.



Scheme 1: Chemical structure of Losartan K

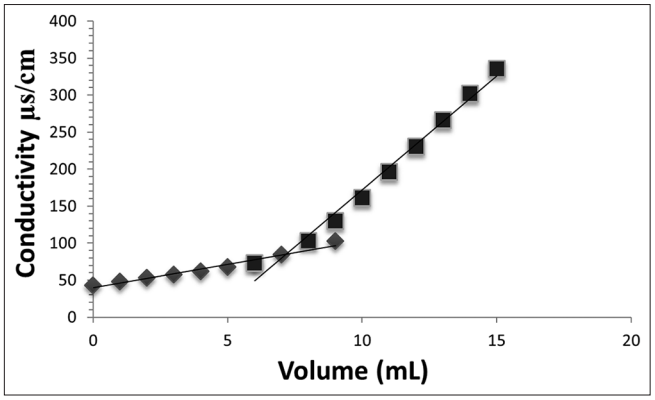


Fig. 1: Conductometric titration of 10 mg of LK using 1×10^{-3}M PTA

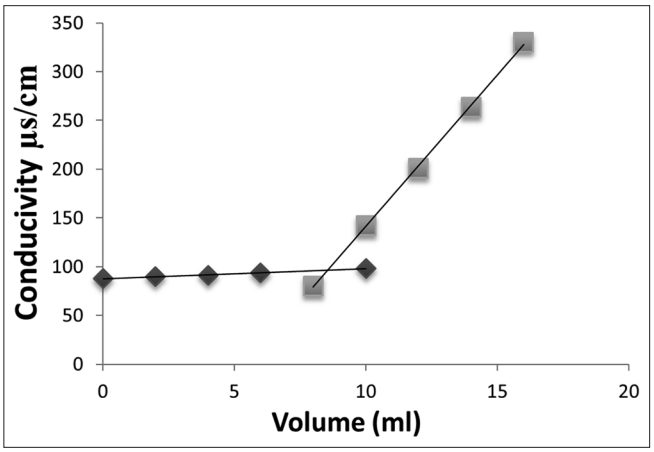


Fig. 2: Conductometric titration of 20 mg of Losartan potassium using 5×10^{-3}M bromocresol purple dye

The reaction may be represented by the following equation:

2 Losartan potassium+$CuCl_2$Losartan cupper+→2KCl↓

$CuCl_2$ method

On using $CuCl_2$ as a titrant for the determination of LK a precipitate is formed through replacing K^+ by Cu^{+2} ion quantitatively forming insoluble cupric salt with the drug. A representative titration curve is shown in Fig. 4. Two straight lines are obtained, intersecting at the equivalence point. The first segment corresponds to the formed potassium chloride and the second segment represents the excess of $CuCl_2$ added.

The reaction may be represented by the following equation:

2 Losartan potassium+$CuCl_2$ Losartan cupper→+2KCl↓

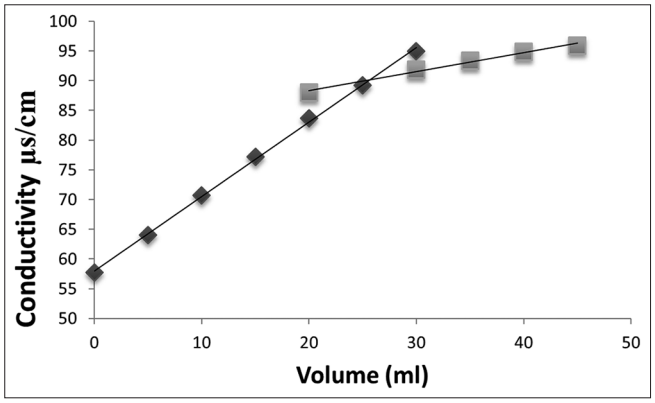


Fig. 3: Conductometric titration of 12 mg of LK using 5 × 10^{-4}M $HgCl_2$

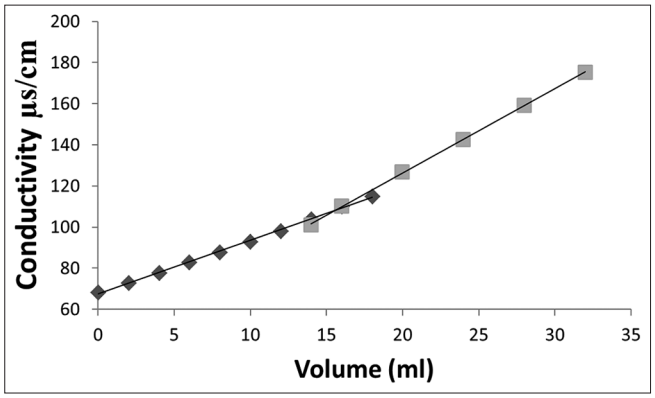


Fig. 4: Conductometric titration of 15 mg of LK using 1 × 10^{-3}M $CuCl_2$

The results from the conductometric titrations are summarized in Table 1.

The data show that accurate results were obtained with good percentage recoveries and low standard deviation values. The optimum concentration ranges for the determination of LK were in the range of 1–20 mg for method C and 3–20 mg for methods A, Bm and Dm respectively. Stable conductance readings and sharp inflections were achieved at such ranges.

Investigations were carried out to establish the most favorable conditions for the reaction to reach the end point. The effects of some variables on the reaction have been examined, and the optimum conditions for performing the titration in a quantitative manner were explained as described below.

Titrations in different media were tried to obtain the best results. Preliminary experiments in

1. Aqueous solutions of both drug and reagent,
2. Drug and reagent solutions in ethanol-water (50%, v/v) mixture,
3. Methanolic solutions of both drug and reagent,
4. Drug and reagent solutions in methanol-water (50% v/v) mixture,
5. 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 for the cited drugs where the highest conductance and the sharpest endpoints were obtained.

Reagent's concentration

The optimum concentrations of PTA, BCP, $HgCl_2$, and $CuCl_2$ were 1×10^{-3}M, 5×10^{-3}M, 5×10^{-4}M, and 1×10^{-3}M, respectively, to achieve a constant and highly stable conductance reading after 1 min mixing. Concentrations less than these gave unstable readings and more time were needed to obtain constant conductance values.

Determination of the drug–titrant ratio

Curve break is observed at drug-reagent molar ratios of 3:1 and 1:1 for methods A and B, respectively, and 2:1 for methods C and D.

Method validation

Linearity range

The developed method was validated according to the ICH guidelines [27]. The linearity range of conductivity as a function of drug concentration (Table 1) provides an accurate measure of the sensitivity of reagents used. Calibration curves have determination coefficients (R^2) >0.999 indicating good linearity.

Accuracy and precision

The accuracy of the method was expressed as the mean recovery percentage (average of four replicates within Beer's law limits) while

Table 1: Conductometric determination of LK in its pure form using PTA, BCP, $HgCl_2$, and $CuCl_2$

$CuCl_2$ method		$HgCl_2$ method		BCP method		PTA method	
Found %*	**Taken (mg)**	**Found %***	**Taken (mg)**	**Found %***	**Taken (mg)**	**Found %***	**Taken (mg)**
100	3	99.12	1	101.53	3	101.38	3
99.57	5	101.54	3	99.12	5	99.58	5
100.13	7	99.57	5	100.46	7	100.27	10
99.58	10	98.81	7	101.38	10	99.12	12
100.8	15	99.12	10	101.54	15	99.58	15
101.43	20	100	12	99.12	20	99.58	20
100.25±0.733		99.69±0.996		100.53±1.159		99.92±0.805	Mean±SD
6		6		6		6	N
0.536		0.991		1.345		0.648	V
0.299		0.407		0.474		0.328	S.E
0.731		0.999		1.153		0.804	R.S.D

*Average of three different experiments. RSD: Relative standard deviation, BCP: Bromocresol purple, $HgCl_2$: Mercury (II) chloride, $CuCl_2$: Cupric chloride, PTA: Phosphotungstic acid, SE: Standard error, SD: Standard deviation, LK: Losartan potassium

Table 2: Evaluation of the interday and intraday precisions and accuracy for LK obtained by the proposed methods

Method	Taken Conc. (mg)	Interday			Intraday		
		Accuracy (Er %)	Precision (RSD %)*	Recovery (%)*	Accuracy (Er %)	Precision (RSD %)*	Recovery (%)*
PTA	5 mg	1.12	1.38	101.12	0.275	1.78	100.275
BCP	5 mg	−0.42	0.757	99.58	0.274	0.88	100.274
$HgCl_2$	3 mg	0.275	1.47	100.275	1.15	0.76	101.15
$CuCl_2$	5 mg	1.42	1.48	101.42	−1.35	1.87	98.65

RSD%: Relative standard deviation percentage, Er%: Relative error percentage, *Mean of five determination, PTA: Phosphotungstic acid, BCP: Bromocresol purple, $HgCl_2$: Mercury (II) chloride, $CuCl_2$: Cupric chloride, LK: Losartan potassium

Table 3: Conductometric determination of LK in Losartan® tablets using PTA, BCP, $HgCl_2$, and $CuCl_2$

$CuCl_2$ method		$HgCl_2$ method		BCP method		PTA method	
Found %*	Taken (mg)	Found %*	Taken (mg)	Found %*	Taken (mg)	Found %*	Taken (mg)
99.69	3	101.43	2	100	3	99.58	5
101.47	5	101.54	3	99.08	5	99.41	7
98.68	7	99.57	5	98.81	7	100.96	10
101.42	10	101.45	7	99.08	10	100.23	12
98.34	15	99.12	10	99.88	12	99.58	15
99.88	20					100.96	20
99.91±1.322		100.62±1.177		99.37±0.533		100.12±0.709	Mean±SD
6		5		5		6	N
1.748		1.385		0.284		0.502	V
0.539		0.526		0.239		0.289	S.E
1.323		1.169		0.537		0.709	R.S.D

BCP: Bromocresol purple, $HgCl_2$: Mercury (II) chloride, $CuCl_2$: Cupric chloride, PTA: Phosphotungstic acid, RSD: Relative standard deviation, SE**:** Standard error, SD: Standard deviation, LK: Losartan potassium

Table 4: Statistical analysis of results obtained by the proposed methods applied on Losartan® tablets compared with the reported method

Parameters	Reported method [6]	PTA method	BCP method	$HgCl_2$ method	$CuCl_2$ method
Mean recovery	99.99	100.12	99.37	100.62	99.91
SD	0.974	0.709	0.533	1.177	1.322
N	6	6	5	5	6
Variance	0.95	0.502	0.284	1.385	1.748
Student-t		0.264 (2.220)*	1.265 (2.262)*	0.972 (2.262)*	1.84 (2.220)*
F-test		1.892 (5.05)*	3.345 (5.19)*	1.458 (5.19)*	0.119 (5.05)*

*Theoretical values of t-test and F-test at p=0.05. PTA: Phosphotungstic acid, BCP: Bromocresol purple, $HgCl_2$: Mercury (II) chloride, $CuCl_2$: Cupric chloride, SD: Standard deviation

the precision was expressed as the relative standard deviation (RSD) percentage (Table 2).

Analytical application

The proposed method was successfully applied to the assay of the studied drug in its pharmaceutical formulations using the standard addition technique. Satisfactory results obtained for the recoveries of the drugs were in good agreement with the label claim and proved the suitability of the proposed methods (Table 3).

According to ICH guidelines, the obtained values indicated a high sensitivity of the proposed methods. Statistical comparison of the results obtained from the analysis of the studied drugs by the proposed method to those of reference method [6] using t-and F-tests, showed no significant difference between them (Table 4).

CONCLUSION

The suggested method has the advantages of simplicity and cost affectivity make it an alternative method to the more complex and expensive methods for assay of LK. The proposed method is easy and very useful for the determination of the studied drug in pharmaceutical formulations and can be applied in laboratories for routine analysis.

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