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Spectrophotometric Determination Of Lisinopril In Pharmaceutical Preparations Assisted By Microwave Oven

Corresponding Author

Asad Raza
Analytical Laboratory,
Bio Fine Pharmaceuticals (Pvt.) Ltd.,
Multan (PAKISTAN)
E-mail: asadbzu@yahoo.com

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ABSTRACT

In this work, two effective and low-cost spectrophotometric methods (A and B) for the determination of lisinopril are proposed in its pure and pharmaceutical preparations. The both methods depend on the charge-transfer reaction between lisinopril as n-electron donor with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol medium and 7,7,8,8-tetracyanoquinodimethane (TCNQ)) in methanol-acetonitrile medium as p-acceptor to give a colored complex, which absorb maximally at 475 nm and 740 nm respectively. These reactions were accelerated by irradiating the reaction mixtures with microwave energy (1100 W) during 45 seconds in method A and two minutes in method B. Beer's law is obeyed in the concentration ranges 0.5-60 μ mg/mL with molar absorptivity of 1.2×10^5 L $mole^{-1}$ cm^{-1} and 0.5-15 μ mg/mL with molar absorptivity of 8.3×10^4 L $mole^{-1}$ cm^{-1} respectively. The optimal reaction conditions values such as reagent concentration, heating time and stability of the reaction product were determined. The analytical results obtained by applying the proposed method compare very favorably with those given by the British Pharmacopoeia standard procedure.

KEYWORDS

Lisinopril;
Spectrophotometry;
Microwave oven;
Pharmaceutical preparations;
Charge-transfer reactions.

INTRODUCTION

Lisinopril (2*S*)-1-[(2*S*)-6-amino-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]hexanoyl] pyrrole-2-carboxylic acid, is a lysine analog of enalaprilat, the active metabolite of enalapril. It is a long-acting, nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor that is used for the treatment of hypertension and congestive heart failure in daily dosages of 10-80 mg[1]. Pharmacological activity of lisinopril has

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been proved in previous experimental and clinical studies[2,3].

Owing to the importance of lisinopril salt in pharmaceuticals and its widespread use, efforts have been made towards the development of simple and reliable analytical methods. Several analytical methods are reported for the determination of lisinopril in dosage forms including spectrophotometric measurements[4-12], U.V.[13], liquid chromatography[6,14-15], gas chromatography[16], spectrofluorimetry[6,7,17,18] derivative Spectrophotometry[19], and polarography[21,22]. The official methods for the assay of lisinopril in the pure form and dosage forms are potentiometric acid base titration[22] and high performance liquid chromatography[23]. On the other hand more sensitive fluoroimmunoassay[24], radioimmunoassay[25] and GC with mass detection[26] methods have been reported for the pharmacological and pharmacokinetic studies of lisinopril. Plasma level of lisinopril can be estimated by these methods. Furthermore, HPLC method with UV detection[27] and with fluorimetric detection[28] has been developed for the determination of the drug in urine samples and liquid chromatographic-mass spectrometric (LC/MS) method[29] for the determination of lisinopril in human plasma is also reported. However, most of these methods are costly, tedious and time consuming.

It is well known that electron donors and electron acceptors can interact in solution to form intensively colored charge-transfer complexes. These complexes are usually characterized by absorption bands, not present in either reagents, assigned to an intermolecular charge-transfer transition[30-32]. Therefore, charge-transfer complexation reactions have been extensively applied to the spectrophotometric determination of several important drugs such as methyldopa[33], fluoxetine[34], sertraline[34], famotidine [35], perindopril[36] and some â-adrenergic blocking agents[37].

During the systematic method development study of lisinopril[11] it was found that lisinopril reacts with certain p-acceptors (DDQ and TCNQ) to give colored complex. Although near recently Nafis-ur-Reahman *et al* reported the spectrophotometric method[12] for the determination of lisinopril in pharmaceutical preparations using TCNQ. But the formation of complex was slow and the sensitivity of the method is low.

The use of microwave oven for analytical procedures was first demonstrated three decades ago[38]. Since that time several papers have described the applications of microwave ovens for sample dissolution[39-42] and more recently for organic synthesis[43]. The purpose of this study was to develop a simple, rapid, sensitive, precise, accurate and low cost method for determination of lisinopril in pure form and in pharmaceutical preparations assisted by microwave. The proposed method was successfully applied to the determination of lisinopril in bulk pharmaceutical formulations. The results obtained by the proposed method were in excellent agreement with those given by the official method[21], proving that the methods are a reliable alternative for the analysis of lisinopril in pure form and in pharmaceutical preparations.

EXPERIMENTAL

Apparatus

A UV-Visible spectrophotometer (U 1100 Hitachi, Japan) with 1.00 cm glass cells was used. All absorbance measurements were carried out at 25 ± 1 °C. Officially calibrated Pyrex glassware was used throughout this study. For lisinopril tablets, the standard procedure of British Pharmacopoeia[21] is based on a potentiometric titration in glacial acetic acid media was used. All potentiometric measurements were carried out using a pH meter (Orion). A domestic microwave oven, Panasonic 1100 watts was used for heating. The distribution of radiation in the oven cavity was performed similarly to the literature procedure[44,45].

Materials, reagents and solutions

All reagents used were of analytical reagent grade. For the preparation of the solutions and samples, double distilled water was used throughout. Pure sample of lisinopril was supplied by Werrick pharmaceuticals (Pvt.) Ltd. Islamabad, Pakistan. Lisinopril tablets were purchased from the local market. For method A stock solution of lisinopril was prepared by dissolving 100 mg powder in sufficient

amount of methanol then diluted with same solvent up to 100 ml. Standard lisinopril solutions were prepared from stock solution by appropriate dilution with methanol. 5 mg mL^{-1} solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), Fluka, Hong Kong , was also prepared in methanol. For method B Stock solution of lisinopril was prepared by dissolving 100 mg powder in sufficient amount of methanol then diluted with acetonitrile solvent up to 100 ml. Standard lisinopril solutions were prepared from stock solution by appropriate dilution with acetonitrile. 1 $mgml^{-1}$ solution of 7, 7, 8, 8-tetracyano quinodimethane (TCNQ), Fluka, Austria, was also prepared acetonitrile.

Proposed procedure

Method A: General procedure and analytical curve

To different aliquots of lisinopril (0.5-60 mg/ml) in 10 ml measuring flask, add 1.5 ml 5 mg ml^{-1} solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Heat the mixture in the microwave oven for 15 seconds at "low" power output (1100 W). Afterwards, the beakers were cooled at room temperature. The working solutions were prepared transferring quantitatively the content inside the beaker in 10 ml volumetric flask and completing to volume with methanol. Finally, the absorbance was measured at 475 nm (b=1cm) against corresponding reagent blank. The analytical curve was obtained by plotting absorbance against lisinopril concentration and the corresponding linear least square equation was used to convert absorbance into lisinopril concentration, for all analyzed samples.

Procedure for the assay of lisinopril in pharmaceutical formulations

Twenty tablets were accurately weighed and powdered. A portion equivalent to 100 mg of lisinopril was stirred with 30 ml methanol. The residue was filtered with Whatman filter paper # 1 and washed with methanol. The filtrate and washings were diluted to 100 ml using methanol and an aliquot from this filtered solution was analyzed using the recommended procedure.

Method B: General procedure and analytical curve

To different aliquots of lisinopril (0.5-15 mg ml^{-1}) in 10 ml measuring flask, add 2 ml 1 mg ml^{-1} solution of 7,7,8,8-tetracyanoquinodimethane (TCNQ). Heat the mixture in the microwave oven for 25 seconds at "low" power output (1100 W). Afterwards, the beakers were cooled at room temperature. The working solutions were prepared transferring quantitatively the content inside the beaker in 10 ml volumetric flask and completing to volume with methanol. Finally, the absorbance was measured at 740 nm (b=1cm) against corresponding reagent blank. The analytical curve was obtained by plotting absorbance against lisinopril concentration and the corresponding linear least square equation was used to convert absorbance into lisinopril concentration, for all analyzed samples.

Procedure for the assay of lisinopril in pharmaceutical formulations

Twenty tablets were accurately weighed and powdered. A portion equivalent to 100 mg of lisinopril was stirred with 30 ml methanol. The residue was filtered with Whatman filter paper # 1 and washed with acetonitrile. The filtrate and washings were diluted to 100 ml using acetonitrile and an aliquot from this filtered solution was analyzed using the recommended procedure.

RESULT AND DISCUSSION

DDQ is π-electron acceptors as a result of the strong electron withdrawing halo and cyano groups conjugated with the π-system[46]. DDQ reacts instantaneously with basic nitrogenous compounds to form charge-transfer complexes of n-π type. The absorption spectrum of DDQ in methanol shows a characteristic band peaking at 360 nm. The addition of lisinopril solution to this solution causes an immediate change in the absorption spectrum, with a new characteristic band peaking at 470 nm. This band may be attributed to the formation of DDQ radical anions, which probably resulted from the dissociation of the donor-acceptor complex in a highly polar solvent like methanol. The mole ratio method suggested a donor to acceptor ration 1:2 confirming the

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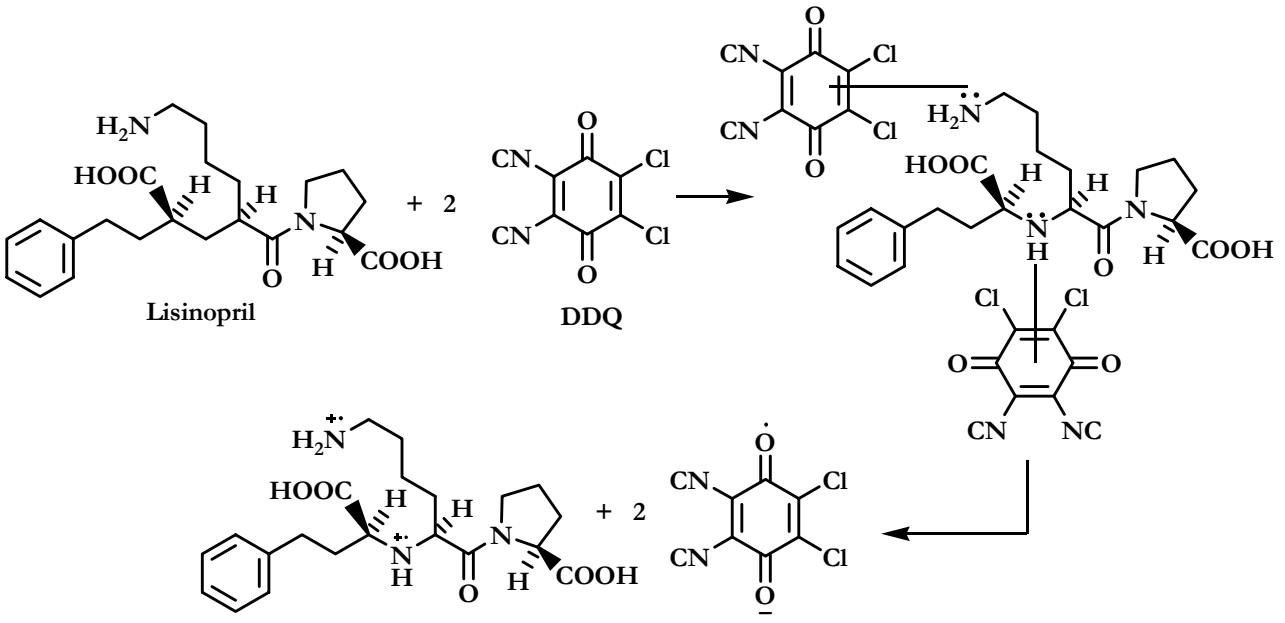

SCHEME 1

presence of two n-donating center in the lisinopril molecule (SCHEME 1).

TCNQ is also used for quantitative determination of pharmaceutical drugs in dosage forms by charge-transfer complex formation[48, 49]. Interaction with TCNQ in acetonitrile solution was found to yield a deep color causing characteristic long wavelength absorption band. The predominant chromagen with TCNQ is blue colored radical anion, which probably resulted through the dissociation of an original donor-acceptor complex with the drug. This complex is formed by the lone pair of electron donated by the lisinopril as n-donor and the charge-transfer reagent as an electron acceptor, which a partial ionic bond (D+ A-) is assumed to be formed.

$$\underset{\text{Donor}}{D} + \underset{\text{Acceptor}}{A} \longrightarrow \underset{\text{Donor-accptor complex}}{[D \longrightarrow A]} \qquad \underset{\text{Donor}}{D^+} + \underset{\text{Anion}}{A^{\cdot}}$$

The dissociation of the complex was promoted by the high ionizing power of acetonitrile solvent[50].

Optimization of variables

The spectrophotometric properties of the colored species formed with DDQ and TCNQ as well as different parameters affecting the color development, were extensively studied. The optimum conditions for the assay procedures (Method A and B) have been established by studying the reaction as function of the concentration of the reagent, the nature of the solvent, heating time and stability of the colored species.

Effect of color producing reagent and time

For method A, the effect of volume of 5 mg/mL DDQ solution was studied over the range of 0.2-2.0 mL, in a solution containing 5.0 mg/mL lisinopril. The results revealed the fact that 1.5 mL of DDQ solution was required to achieve the maximum intensity of the color. Therefore 1.5 mL was the optimum value and maintained throughout the experiment. The reaction gets stabilized with in the 15 seconds of heating the reaction mixture at low power output (1100 W) in microwave oven.

For method B, the effective variables are the concentration of TCNQ and temperature. To study the influence of the volume of 1mg/mL TCNQ solution, we pipetted an aliquot of the drug solution containing 5.0 mg/mL into a series of 10 mL volumetric flasks, followed by varying volumes of 1mg/mL TCNQ solution (0.2-2.0 mL). The contents were diluted to the volume with acetonitrile. The highest absorbance was obtained with volume 2 mL of 1mg/mL TCNQ solution. Further addition of TCNQ solution cause no change in the absorbance, so 2 mL was selected the optimum volume for all determina-

tions. The intensity of the color formed on mixing the reagent reached maximum with in 25 seconds heating the mixture at low power output (1100 W) in microwave oven.

Effect of solvent

The polarity of the solvent used in the reaction between p-acceptors with n-donors can influence on the formation of charge transfer complexes. Therefore, investigations were carried out to establish the most favorable solvent for the formation of the colored product. The solvents studied were: ethanol, methanol, acetonitrile and isopropanol.Lisinopril was found to yield a colored product with DDQ and TCNQ when all these solvents were used. However, methanol was the choice solvent since that it gave maximum intensity and stability of color faster than the others in method A and acetonitrile in method B.

Microwave oven settings and effect of heating time

Radiation absorbed by samples in the oven depends on their position in its cavity. The distribution of microwave radiation was determined as described in the literature[44,45] and the samples were strategically positioned on the center of the oven cavity, point where the microwave energy is more intense. Different heating times and power settings on the microwave oven were investigated to determine the optimal reactions conditions. In this study were used "low", "medium" and "high" power and the best results were obtained using a "low" power output setting on the microwave because when higher powers were used occurred boiling and loss of the solution. Since set up the "low" power different heating times were studied (from 5 to 30 seconds) and 27 seconds of heating provided a temperature around 40 °C, which was sufficient for the complete color development without boiling start.

Optical stability of reaction product

The stability of the colored product in methanol reaction medium was verified by the absorbance measurements (470 nm) to each 5 min and it was observed that the colored product obtained was stable for 90 min. While in acetonitrile medium it was stable for two hours.

Analytical evaluation

DDQ and TCNQ were evaluated as a chromogenic reagent for spectrophotometric determination of lisinopril. Under the proposed experimental conditions a linear response between absorbance and lisinopril concentration was verified. For method A, Beer's law was obeyed in a concentration range from 0.5-60 mg/mL with correlation coefficient 0.998. The spectrophotometric method showed a molar absorptivity of 1.2×10^5 L mole^{-1} cm^{-1}, indicating a good sensitivity for the samples analyzed.

While for method B, Beer's law was obeyed in a concentration range from 0.5-15 mg/mL with correlation coefficient 0.9997 and molar absorptivity of $8.3' 10^4$ L mole^{-1} cm^{-1}.The regression equations for

TABLE 1: Optical characteristics and statistical data for the regression equation of the proposed method

Parameter	Values for Method A	Values for Method B
λ_{max} (nm)	475	740
Beer's law verification range (μg/mL)	0.5-60	0.5-15
Molar absorptivity (L mole^{-1} cm^{-1})	1.2×10^5	8.3×10^4
Sandell's sensitivity (μgml^{-1} per 0.001 A)	3.4×10^{-3}	5.3×10^{-3}
Regression equation (Y*)		
Slope (b)	2.278×10^{-3}	1.8×10^{-1}
Intercept (a)	1.238×10^{-4}	-9.9×10^{-3}
Correlation coefficient (r)	0.998	0.9997
RSD** (%)	0.846	0.56
Limit of Detection (μg/mL)	0.142	0.26
Limit of Quantification (μg/mL)	0.486	0.88

Y* = a + bC; Where C is the concentration of analyte (mg/mL) and Y is absorbance unit

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the described procedures were derived using the least-square method. The limit of detection ($3.SD^{blank}$/ slope of analytical curve) and limit of quantification ($10.SD^{blank}$/slope of analytical curve) are shown in TABLE 1. The analytical parameters and the optical characteristics for the spectrophotometric determinations of lisinopril by the proposed method are given in TABLE1.

Interference study

To study the potential interference problems from the commonly used excipients and other additives such as microcrystalline cellulose, talc, lactose, sodium starch glycolate, povidone, gelatin, starch and magnesium stearate, recovery studies were carried out. Under the experimental conditions employed, to a known amount of drug (lisinopril 5.0 mg/mL), excipients in different concentrations were added and analyzed. Results of the recovery analysis are presented in TABLE 2. Excipients up to the concentrations shown in the TABLE 2 do not interfere with the assay. In addition recoveries in most cases were around 100% and the lower values of the RSD indicate the good precision of the method.

TABLE 2: Determination of lisinopril in the presence of excipients (5 mg/mL) of lisinopril was taken for interferences studies)

	Excipient	Amount Taken (μg/mL)	% Recovery ± RSD (N =5)Method A	% Recovery ± RSD (N =5)Method B
1	Talc	50	99.7 ± 0.30	99.7 ± 0.30
2	Microcrystalline cellulose	300	99.6 ± 0.25	99.6 ± 0.25
3	Sodium starch glycolate	100	99.5 ± 0.25	99.5 ± 0.25
4	Hydroxry propyl methyl cellulose	50	100.1 ± 0.30	100.1 ± 0.30
5	Lactose	300	99.8 ± 0.40	99.8 ± 0.40
6	Magnesium Stearate	50	99.4 ± 0.45	99.4 ± 0.45
7	Starch	200	99.9 ± 0.25	99.9 ± 0.25
8	Calcium phosphate	50	99.1 ± 0.30	99.1 ± 0.30

TABLE 3: Determination of lisinopril in pharmaceutical formulations by the proposed and reference[21] method

Formulation	Method A				Method B				Reference method	
	Recovery* (%)	RSD (%)	t- value	F-value	Recovery* (%)	RSD (%)	t- value	F-value	Recovery* (%)	RSD (%)
Zestril	99.70	0.52	0.17	2.98	99.26	0.48	0.13	3.96	99.75	0.30
Lispril	100.07	0.66	0.41	3.02	99.34	0.78	0.33	2.65	99.88	0.45
Lisopril	99.60	0.48	0.32	3.12	101.56	0.39	0.23	2.26	99.23	0.56

*Average of 3 independent analysis

TABLE 4: Comparison of proposed method with existing spectrophotometric methods.

S.No	λ_{max}	Reagent	Beer's law limit	Molar absorptivity ($mol^{-1}cm^{-1}$)	RSD (%)	References
1	356.5	FDNB	$4.5\text{-}27.2 \times 10^{-5}$M	-	0.35	9
2	346	Chloranil	-	-	-	7
3	225	-	3-30 (μg/ml)	-	-	12
4	-	2,4,6- Trinitrobenzoic acid	-	-	-	8
5	485	NQS	-	-	-	10
6	600	Ninhydrin(Basic media)	10-150 (μg/ml)	4.083×10^{-3}	0.868	11
7	743	TCNQ	2-26 (μg/ml)	1.432×10^{4}		12
8 (a)	475	DDQ	0.5-60 (μg/ml)	1.2×10^{5}		This Work
8 (b)	740	TCNQ	0.5-15 (μg/ml)	8.3×10^{4}		This Work

Application

The applicability of the proposed methods for the determination of lisinopril in commercial dosage forms was examined by analyzing marketed products. The results of the proposed methods were statistically compared with reference method [21] and summarized TABLE 3. It is evident from the table that the calculated t and F values [51] are less than the theoretical ones at 95 % confidence level, indicating no significant difference between the methods compared. The proposed methods are sensitive, simple, and accurate and are successfully applied for the quality control of pure lisinopril in pharmaceutical dosage forms. The proposed methods are favorable compared with other existing spectrophotometric methods as shown in TABLE 4.

CONCLUSION

The spectrophotometric methods proposed are simple, sensitive, rapid, low-cost, does not involve any pre-treatment or extraction steps and gives precise and accurate results. Significant improvements in the time of analysis could be attained using the microwave energy (1100 W) for 15 and 25 seconds respectively for method A and B. The proposed methods were successfully applied to analysis of lisinopril in tablets suggesting its use as a reliable and advantageous alternative to other previously reported methods for routine analysis of lisinopril in these samples.

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Full Paper

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