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Indirect spectrophotometric determination of bisoprolol and losartan potassium in pure form and pharmaceutical formulation using silver nanoparticles

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Abstract

An indirect spectrophotometric method was developed for determination ofbisoprololeither base or its salt and losartan potassium in pure form and in pharmaceutical formulations. The method was based on precipitation of the studied drugs with silver nitrate solution followed by its reduction by sodium citrate to yield silver nanoparticles .The formed band of silver nanoparticles was measured at 444, 429 nm for bisoprolol and losartan respectively. Different experimental factors were optimized to achieve the highest and stable absorbance. The calibration curves were linear with concentrations of(10.0-30.0 µg/ml), (4.0-20.0 µg/ml) and (5.0-40.0µg/ml) forbisoprololhemifumarate,bisoprolol base and losartan potassium respectively.Validation of the analytical performance of the method was carefully investigated, and results were satisfactory.

Keywords: silver nanoparticles,indirect spectrophotometric, bisoprolol and losartan potassium.

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1.INTRODUCTION

Bisoprololhemifumarate is (RS)-1-[4-[[2-(1-Methylethoxy) ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]propan-2-ol fumarate. It is a cardioselective beta blocker that given in the management of hypertension and angina pectoris. It is also used as an adjunct to standard therapy in patients with stable chronic heart failure. [1]

It is official and can be determined in BP [2] by non-aqueous titration using perchloric acid and determine end-point potentiometrically and in USP [3] by HPLC method. Different techniques were reported for its determination including spectrophotometry [4-11], chromatographic methods [12-17] and electrochemical methods. [18-19]

Losartan potassium is 2-Butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl) benzyl] imidazole-5-methanol potassium. [1] It is used in the management of hypertension, particularly in patients who develop cough with ACE inhibitors and to reduce the risk of stroke in patients with left ventricular hypertrophy, and in the treatment of diabetic nephropathy. Many analytical methods like HPLC [20-22], spectrophotometric [23-25], HPTLC [26], capillary electrophoresis [27], electrochemical [28,29] were reported for determination of losartan potassium in alone and in combination with other antihypertensive drugs.

2.EXPERIMENTAL

Instrumentation

- A single cell holder JENWAY 6715 UV/ Visible spectrophotometer equipped with 10 mm matched quartz cells was employed for all absorbance measurements.
- HettichZentrifugen universal 320/320 R centrifuge, Germany.
- Materials and reagents

All solvents and reagents used were of the highest purity.

- Bisoprololhemifumarate (obtained from Amoun Pharm, Egypt). Its purity was found to be 99.9% as reported from company and 100.02% according to the comparison method
- Losartan potassium (was obtained from SIGMA pharmaceutical industries). Its purity was found to be100.32% according to comparison methods
- Silver nitrate (AgNO3) (obtained from Morgan Speciality Chemicals Company)
- Its purity was found to be 99.5% as reported from company, Batch No 572070216
- Sodium citrate (obtained from Fischer chemical, Fischer scientific UK limited, U.K.)
- Sodium hydroxide (obtained from Alpha Chemicals for laboratory use). Its purity was found to be 98% as reported from company.
- Water (obtained from Fisher chemical® laboratory reagent grade)

Pharmaceutical preparations

- Concorcor® tablets (Amoun Pharm, Egypt, under the licence of Merk –Kga-Darmstadt-Germany) batch number 151513 labelled to contain 2.5mg bisoprololfumarate per tablet.
- Losar® tablets containing 50 mg losartan potassium per tablet (obtained from UniPharma Al-Obour city, Cairo, Egypt) Batch No. 0024

Standard solutions

Stock standard solutions of 1.0 mg /ml of the cited drugs were prepared by dissolving 10 mg of pure drugs in10 ml volumetric flaskwith distilled water.

Preparation of bisoprolol base:

Weigh accurately the appropriate amount of the drug salt, dissolve the powder in 10ml water, transfer into 125 ml

separating funnel, render alkaline with sodium hydroxide and extract with 3 x10 ml chloroform, the chloroformic extract was filtered through anhydrous sodium sulphate, evaporated then dissolvedin 10 ml volumetric flask with distilled water.

General procedure

Precipitation of the studied drugs with silver nitrate solution:

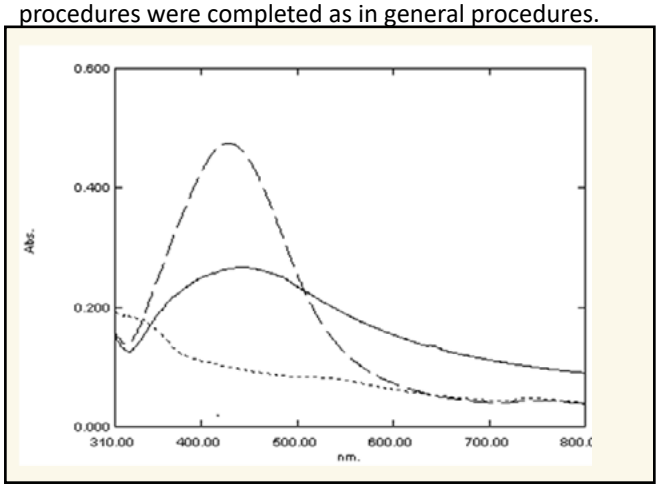
Aliquots containing 1.0 mg ofbisoprololhemifumarate and losartan potassium were transferred into centrifuge tubes followed by 1.0 ml of 1.0 M silver nitrate solution.The mixture was centrifuged for10 min , the supernatant was discarded , the precipitate was washed with distilled water then dissolved and completed to 10 ml with 60 % NH4OH solution.

Indirect spectrophotometric determination of studied drugs using silver nanoparticles:

An aliquot of the 60 % NH4OH solution containing appropriate amounts of the studied drugs (in the range of 4.0–40.0 µg/mL),0.9 ml of 0.5 M NaOH and 1.5 ml of 0.1gm % sodium citratewere transferred to 5 ml volumetric flask.The mixture washeated at boiling water bath for 10 minutes,cooled then diluted to 5 ml with distilled water.Absorbance was measured at the suitable wavelength against reagent blank treated similarly.

A-Assay of pharmaceutical preparations

10 tablets were accurately weighed and grounded to fine powder.In 10 ml volumetric flask, specific quantity of powdered drugs equivalent to 10 mg pure drug were dissolved and diluted to the mark with distilled water.Solutions were filtered then 1.0ml, equivalent to 1.0 mg, was taken and the procedures were completed as in general procedures.



2.Results and Discussion

Herein, we report an indirect spectrophotometric method for the determination of some pharmaceutically interesting compounds in their dosage forms.The present method involves 2 steps. First step is quantitative precipitation of the studied drugs with silver nitrate solution. Second step is the reduction of silver nitrate solution (released with 60%NH4OH from its adduct) by sodium citrate to yield silver nanoparticles that was measured at the specific λ max fig.1.

Fig1: Absorbance spectra of Ag NPs of 10 µg/ml Bisoprolol (–) , 40 µg/ml losartan potassium(- - -) and blank (.....)

The suggested mechanism of the reactions proposed for the current method is given in the following Scheme

•Drug + Ag^+ → Drug-Ag (precipitate was dissolved with NH_4OH).

•$4Ag^+ + Na3C_6H_5O_7 \rightarrow 4Ag^\circ + C_6H_5O7H_3 + 3Na^+ + H^+ + O_2$

Optimization of Experimental Factors

To achieve highly stable and reproducible response, different experimental parameters affecting the reaction were studied.

3.Effect of concentration of silver nitrate:

Different concentrations of silver nitrate solutions were tried ranging from 1x10-3 to 1M Molar solution. The optimum concentration of the reagent (1M) was chosen to achieve high absorbancefig 2.

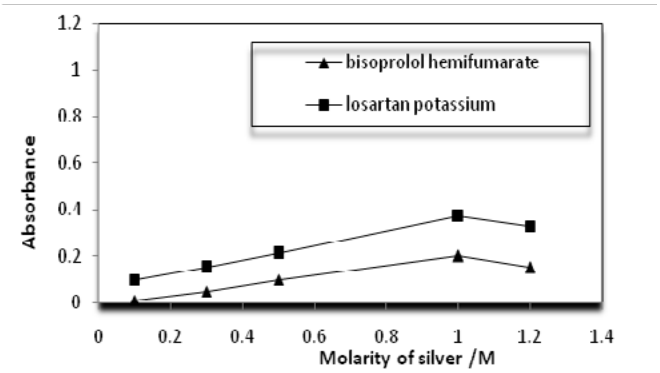


Fig.2: Effect of concentration of silver nitrate solution on the absorbance of silver nanoparticles formed through reaction of sodium citrate and NaOH solution in presence of 30µg/ml of both bisoprololhemifumarate and losartan potassium

Effect of NH4OH Concentration

NH4OH solution plays a key role, as it converts the silver precipitate to[Ag(NH3)2]+ which acts as the silver source insynthesis of silver nanoparticles.In order to find optimum concentration ofNH4OH solution, different concentrations from 60% to100 % at constant volume of 10 ml were examined. The results showed that the maximum absorbance was obtained using 60 % of ammonia solution and lower concentration of ammonia solution gives insufficient dissolving of the precipitate (fig 3).

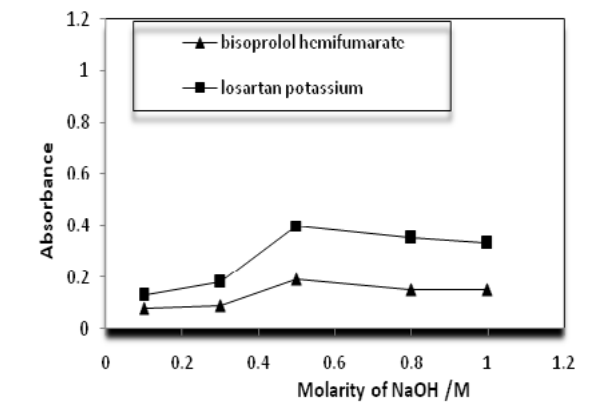


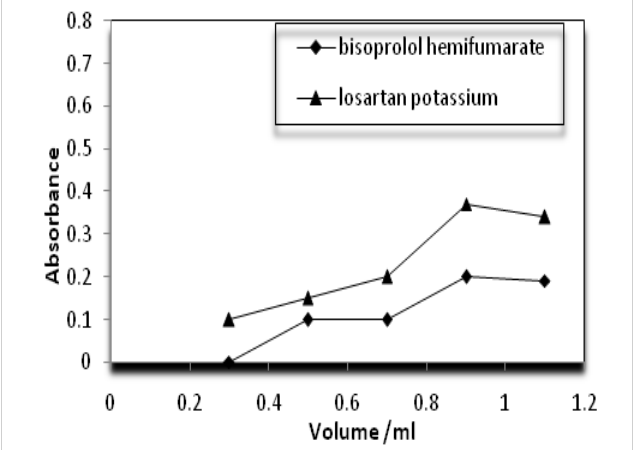
Fig.4: Effect of concentration of NaOH solution on the absorbance of silver nanoparticles formed through reaction

of sodium citrate solution in presence of 30µg/ml of both bisoprololhemifumarate and losartan potassium

Fig.5: Effect of volume of NaOH solution on the absorbance of silver nanoparticles formed through reaction of sodium citrate in presence of 30µg/ml of both bisoprololhemifumarate and losartan potassium

Effect of sodium citrate concentration:

Sodium citrate acts as reducing and stabilizing agent hence its concentration has a crucial role in synthesis and stability of silver nanoparticles. Adsorption of sodium citrate ions on the nanoparticle surface creates repulsion between nanoparticles preventing their aggregation. Low or high concentration of sodium citrate results in silver aggregation. The explanation of this observation can be as follow; at low concentration insufficient stabilization occurred and at high concentration destabilization occurred leading to silver aggregation. Different concentrations of sodium citrate within the range of 0.01 to 0.25 gm% solution were examined. It was observed that 1.5 ml of 0.10 gm % was sufficient or reduction of silver solution and stabilization of silver nanoparticles(fig 6,7).



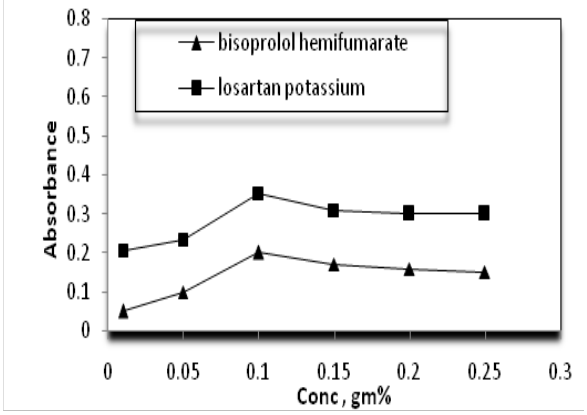


Fig.6: Effect of concentration of sodium citrate solution on the absorbance of silver nanoparticles formed through reaction of NaOH solution in presence of 30µg/ml of both bisoprololhemifumarate and losartan potassium

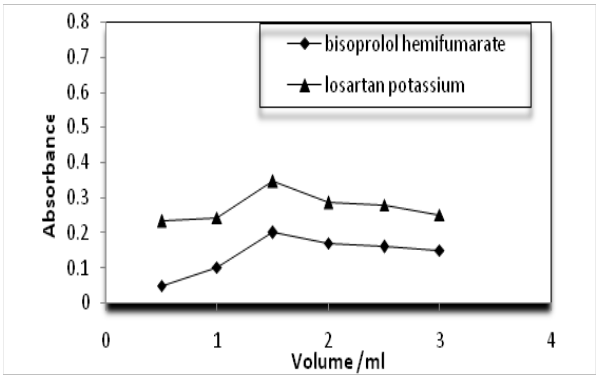


Fig.7: Effect of volume of sodium citrate solution on the absorbance of silver nanoparticles formed through reaction of NaOH solution in presence of 30µg/ml of both bisoprololhemifumarate and losartan potassium

Effect of temperatureand heating time

Change in temperature from 25 to 100°C was studied. It was observed that the reaction rate increased with increasing the temperature till 100°C. Heating for 10 minutes at boiling water bath was sufficient to produce maximum color intensity (fig 8)

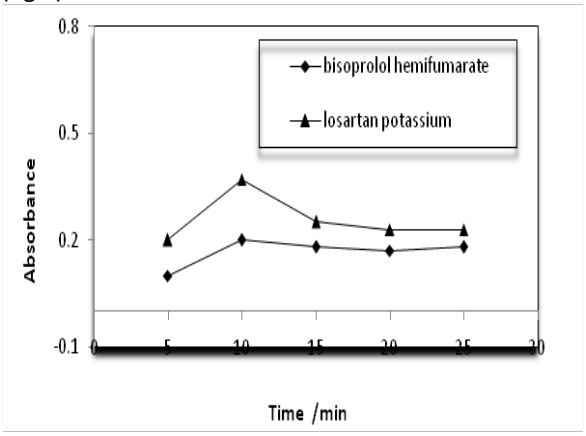


Fig.8: Effect of time of heating on the absorbance of silver nanoparticles formed through reaction of sodium citrate and NaOH solution in presence of 30µg/ml of both bisoprololhemifumarate and losartan potassium

Order of addition

Different orders of components addition were examined and no difference in absorbance was noticed. Addition of the silver solution followed by NaOH then sodium citrate solutions was considered the suitable sequence.

Method validation:

Linearity:

Under the optimum experimental conditions, standard calibration curves for Ag-NPs were constructed by plotting absorbances against concentrations. A linear correlation was found. The ranges of concentration, linear regression equations and correlation coefficients for each drug were calculated indicating good linearity over the working concentration range. (Tables 1, 2).

Sensitivity:

The LODand LOQ were evaluated using the following

Table (1): Spectral data for determination of cited drugs using silver nanoparticles

Parameter	Bisoprololhemifumarate	Bisoprolol base	Losartan potassium
Linearity range (µg/ml)	10.0-30.0	4.0-20.0	5.0-40.0
Limit of detection LOD (µg/ml)	2.946	1.205	1.398
Limit of quantification LOQ (µg/ml)	9.819	4.016	4.661
Regression equation*: Slope (b)	0.0042	0.0225	0.0098
Intercept (a)	0.0632	0.0454	0.0831
Correlation coefficient (r)	0.9998	0.9998	0.9999

Table (2): Assay results for determination of the cited drugs in pure form with silver nanoparticles.

Statistics	Bisoprololhemifumarate		Bisoprolol base		Losartan potassium	
	Taken µg/ ml	Recovery* %	Taken µg/ ml	Recovery* %	Taken µg /ml	Recovery* %
	10	101.90	4	99.56	5	99.80
	15	99.68	6	99.70	10	99.90
	20	100.95	8	99.78	20	100.46
	25	101.71	12	100.96	30	100.99
	30	100.63	14	99.87	40	99.97
			16	101.28		
			20	99.47		
Mean±S.D	100.98±0.894		100.09±0.724		100.22±0.497	
N	5		7		5	
V	0.799		0.523		0.247	
RSD	0.885		0.723		0.496	
SE	0.400		0.273		0.222	

Inter-day precision (intermediate)

The experiment was repeated with the same concentrations on three consecutive days to determine the intermediate precision.The relative standard deviations (RSD %) and percentage relative errors (Er %) were calculated at 95% confidence levels. Results of (table 4) indicate the validity, applicability of theproposed method and the reproducibility of the results.

Selectivity:

Effect of commonly used excipients was studied. Under the experimental condition employed, toknown concentration of the studied drugs, the common excipients lactose, silicon dioxide, starch and magnesiumstearate were added and analyzed. Results showed no interferences from the presence of these excipients (table 5).

*Drug: Excipients, 10 µg /ml Bisoprolol base (2.3x10-3 M) and 20 µg /ml losartan potassium (4.3x10-3 M)
** Mean of three determinations.

Robustness and ruggedness:

Robustness:

Robustness was examined by evaluating the influence of small variations in the experimental parameters on the analytical performance of the proposed method. The studied parameters were NaOH and sodium citrate volumes. The effects of the changes were studied on the absorbance by calculating (recovery±%RSD)and these changeshad negligible influence on results which provided anindication for the reliability of the proposed method. (Table 6)

Ruggedness:

It was tested by applying the proposed method to the assay of the investigated drugs using the same procedures but using two different instruments.

The obtained results were found to be reproducible as shown in Table (6).

Analytical applications:

The proposed method was successfully applied to the assay of thestudied drugs in their pharmaceutical formulations without interferencefrom common excipients. The validity of the developed method was testedby application of the standard addition technique in which the cited drugs wereadded to the analyzed pharmaceutical dosage forms. The recovery study showedthat the proposed method was accurate and reproducible for both drugs (Table7).

Table (7): Application of the proposed method for determination of the cited drugs in their pharmaceutical formulations:

Table (3): Statistical analysis of results obtained by the proposed and the comparison methods.

drug	Bisoprolol base		Losartan potassium	
Items	Proposed method	Comparison method	Proposed method	Comparison method
Mean ± SD	100.09±0.724	100.02±1.04	100.22±0.497	100.32±0.554
Variance	0.523	1.08	0.247	0.307
N	7	8	5	7
Student-t-test	0.149(2.16)*	-----	0.322 (2.228)*	-----
F-test	2.065(3.87)*	-------	1.243(4.53)*	------

Table (4): Precision data for the determination of the cited drugs by the proposed method.

Drug	Added (µg/ml)	Intra-day				Inter-day			
		found±SE (µg/ml)	Recovery %	RSD%	Er%	found±SE (µg/ml)	Recovery %	RSD%	Er%
Bisoprolol base	4	4.012±0.741	100.30	1.279	0.30	3.849±0.642	96.22	1.155	-3.78
	12	12.219±0.653	101.83	1.111	1.83	12.116±0.932	100.96	1.599	0.96
	20	19.834±0.752	99.17	1.313	-0.83	19.834±0.980	99.17	1.711	-0.83
Losartan potassium	10	10.092±0.589	100.92	1.011	0.92	10.092±1.178	100.92	2.022	0.92
	20	20.398±0.295	101.99	0.500	1.99	20.568±0.450	102.84	0.758	2.84
	40	39.276±1.062	98.19	1.874	-1.81	39.344±1.191	98.36	2.096	-1.64

Table (5): Analysis of the cited drugs by the proposed method in presence of some common excipients.

Tolerance Molar ratio (M:M)*	Recovery %**	
	Bisoprolol base (10 µg /ml)	Losartan potassium (20 µg /ml)
	lactose	Silicon dioxide
1:1	99.82	100.46
1:10	99.38	99.95
1:50	98.93	97.91
1:100	98.49	98.42
Other excipients		
Magnesium stearate(40µg/ml)	98.04	101.99
Starch(40µg/ml)	101.16	-----

Table (6): Method robustness and ruggedness expressed as (recovery±%RSD).

Drugs / Variation	Bisoprololhemifumarate (30.0µg/ml)			Losartan potassium (10µg/ml)		
Volume of NaOH solution(ml)	0.80	0.90	1.0	0.80	0.90	1.0
Recovery (%)	99.05	100.63	101.43	97.86	99.90	100.92
Mean Recovery % ±RSD	100.37±1.208			99.56±1.566		
Volume of sodium citrate solution(ml)	1.40	1.50	1.60	1.40	1.50	1.60
Recovery (%)	98.25	100.63	102.22	97.86	99.90	101.94
Mean Recovery % ±RSD	100.37±1.990			99.90±2.043		
Ruggedness						
Instruments	JENWAY6715UV/Vis.			-ShimadzuUV1800 PC		
Drugs / Statistics	Bisoprololhemifumarate (30.0µg/ml)	Losartan potassium (10µg/ml)		Bisoprololhemifumarate (30.0µg/ml)	Losartan potassium (10µg/ml)	
Recovery (%)	100.63	99.90		98.25	98.88	
Mean Recovery %± RSD	99.44±1.693 for bisoprolol 99.39±0.726 for losartan					

Table (7): Application of the proposed method for determination of the cited drugs in their pharmaceutical formulations:

Statistics	Bisoprololhemifumarate		Bisoprolol base		Losartan potassium		
	Taken µg/ ml	Recovery* %	Taken µg/ml	Recovery* %	Taken µg/ml	Added µg/ml	Recovery** %
	10	97.14	5	98.31	5		95.71
	15	96.51	7.5	98.73		5	99.80
	20	96.19	10	98.04		10	98.88
	25	96.95	12.5	98.70		14	99.78
			15	97.96		18	100.28
						22	100.60
Mean±S.D	96.70±0.431		98.35±0.359		99.87±0.653		
N	4		5		5		
V	0.185		0.129		0.427		
RSD	0.445		0.365		0.654		
SE	0.215		0.161		0.292		

Conclusion

An indirect colorimetric method for the determination of bisoprolol and losartan potassium in pure form and pharmaceutical formulations was developed.This assay was based on reduction of silver nitrate to silver nanoparticles resulting in surface plasmon resonance peak that used for quantitative determination of the cited drugs.Statistical analysis of the results has been carried out revealing high accuracy and good precision.

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