



Research Article

Aggregation of Gold Nanoparticles for Spectrophotometric Determination of Bisoprolol Hemifumarate, Buspirone HCl and Doxazosin Mesylate

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Received: Apr. 2, 2018; **Accepted:** Sep. 11, 2018; **Published:** Jan. 3, 2019.

Citation: Magda Mohamed Ayad, Hisham Ezzat Abdellatef, Mervat Mohamed Hosny, and Naglaa Abdel-Sattar Kabil, Aggregation of Gold Nanoparticles for Spectrophotometric Determination of Bisoprolol Hemifumarate, Buspirone HCl and Doxazosin Mesylate. *Nano Biomed. Eng.*, 2019, 11(1): 1-10.

DOI: 10.5101/nbe.v11i1.p1-10.

Abstract

A simple, rapid and sensitive spectrophotometric method was developed for determination of bisoprolol hemifumarate, buspirone HCl and doxazosin mesylate in pure form and in pharmaceutical formulations. The method was based on aggregation of synthesized gold nanoparticles (Au NPs). Gold nanoparticles showed an absorption band at 520 nm. Upon interaction with the cited drugs, the band at 520 nm disappeared with formation of a new red shifted band at 616, 656 and 670 nm for doxazosin mesylate, bisoprolol hemifumarate and buspirone HCl, respectively. Different experimental factors were optimized for higher sensitivity. The calibration curves were linear with concentrations of 3-14, 0.1-1.2 and 0.2-1.0 µg/mL for bisoprolol hemifumarate, buspirone HCl and doxazosin mesylate, respectively. The method was applied successfully to determine the studied drugs in minor concentrations in pure form and in their pharmaceutical dosage forms.

Keywords: Gold nanoparticles; Bisoprolol hemifumarate; Buspirone HCl; Doxazosin mesylate

Introduction

Bisoprolol hemifumarate 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 is used 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 [1a].

Bisoprolol hemifumarate is official, and can be determined in British Pharmacopoeia (BP) [2a] by non-

aqueous titration using perchloric acid and in United States Pharmacopoeia (USP) [3a] by high performance liquid chromatography (HPLC) method. Different techniques were reported for its determination including spectrophotometry [4-6], chromatographic methods [7, 8] and electrochemical methods [9].

Buspirone HCl is 8-[4-[4-(Pyrimidin-2-yl) piperazin-1-yl] butyl]-8-azaspiro [4.5] decane-7,9-dione hydrochloride. It is an anxiolytic agent from the azapirone class of compounds [1b]. Buspirone hydrochloride is official and can be determined in BP

[2b] by non-aqueous titration with perchloric acid; it is also official in USP [3b] which reports HPLC method for its assay. Various analytical methods have been employed for its determination in raw material, pharmaceuticals and biological fluids. These methods include chromatography [10], spectrofluorimetry [11] and spectrophotometry [12-14].

Doxazosin mesylate is 1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-4-[(2RS)-2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl] piperazine methanesulfonate [1c]. It is used in the management of hypertension, and in benign prostatic hyperplasia to relieve symptoms of urinary obstruction. Doxazosin is official in BP [2c] and can be determined by liquid chromatographic method. Different methods were reported for its determination including spectrophotometry [15-17], liquid chromatography [18-20] and voltammetric method [21].

Colorimetric methods are still attracting attention due to their low cost, simplicity, and practicality. Here we report a new colorimetric method for the determination of bisoprolol hemifumarate, buspirone HCl and doxazosin mesylate in pure form and in pharmaceutical formulations. The method was based on the aggregation of gold nanoparticles (NPs) upon addition of the studied drugs showing high absorption band at 616-670 nm, according to each drug, after the optimization of reaction conditions. The degree of aggregation of gold NPs led to color change from red to violet to dark blue depending on the size of gold NPs. To put this in other words, gold NPs can determine compounds that do not have chromophore groups or whose colored derivatives can hardly be synthesized. Due to these interesting physicochemical properties, gold NPs have wide applications in various areas of chemistry [22-25].

Experimental

Instrumentation

A single cell holder, JENWAY 6715 UV/visible spectrophotometer equipped with 10-mm matched quartz cells, was employed for all absorbance measurements.

Materials and reagents

All solvents and reagents used were of the highest purity:

Bisoprolol hemifumarate, obtained from Amoun

Pharm, Egypt. Its purity was 100.02% according to the comparison method.

Buspirone HCl, obtained from Sigma pharmaceuticals, Kwasna, Egypt. Its purity was found to be 100.20% according to the comparison method.

Doxazosin mesylate, obtained from EIPICO, Egypt. Its purity was found to be 100.40% according to the comparison method.

Chloroauric acid (HAuCl_4), obtained from Fischer chemical, Fischer scientific UK limited, U. K.

Sodium citrate, obtained from Fischer Chemical, Fischer Scientific UK Limited, U.K.

Acetate buffer pH = 5: Dissolve 13.6 g of sodium acetate and 6 mL of glacial acetic acid in sufficient water to produce 1000 mL acetate buffer [2]

Water, obtained from Fisher Chemical®, of laboratory reagent grade.

Pharmaceutical preparations

Concor cor® tablets (Amoun Pharm, Egypt, under the license of Merk Kga, Darmstadt, Germany), batch number 151513, labeled to contain 2.5 mg bisoprolol fumarate per tablet.

Buspar® tablets (SmithKline Beecham, an affiliated company to GlaxoSmithKline), batch number 109736, labeled to contain 10 mg Buspirone HCl per tablet.

Cardura® tablets (Pfizer Egypt S.A.E. Cairo A.R.E. under authority of Pfizer INC., USA), batch number 5202, labeled to contain 4 mg doxazosin mesylate per tablet.

Standard solutions

Solutions of 100 $\mu\text{g}/\text{mL}$ of the cited drugs were prepared by dissolving 10 mg of pure drugs in 100 mL volumetric flask with distilled water for bisoprolol hemifumarate and buspirone HCl, while 100 $\mu\text{g}/\text{mL}$ doxazosin mesylate was prepared by dissolving 10 mg of the pure drug in least amount of methanol; then completed to 100 mL with distilled water and further diluted to 10 $\mu\text{g}/\text{mL}$ for doxazosin and buspirone and 50 $\mu\text{g}/\text{mL}$ for bisoprolol.

General procedure

Procedure for preparation of citrate-stabilized gold nanoparticles

Citrate stabilized gold NPs were prepared by

reduction of chloroauric acid by sodium citrate [26]. To a 150 mL beaker, 2.0 mL of 1% HAuCl_4 and about 90 mL of water were added, and the solution was heated up to 95 °C. 5 mL of 1% sodium citrate solution was added drop by drop while the solution was vigorously stirred. The solution was kept at 95 °C for 10 min. When the color of solution changed to bright red, the solution was allowed to cool to room temperature and transferred into a 100 mL volumetric flask, diluted to the mark with water and mixed completely. The Au NPs were stored in refrigerator at 4 °C before using.

Procedures of determination of bisoprolol hemifumarate, buspirone HCl and doxazosin mesylate

All glassware used in the following procedures was cleaned by aqua regia, rinsed thoroughly in double-deionized water, and dried in air prior to use. In 5 mL volumetric flask, different aliquots of the cited drugs were placed; then appropriate volumes of acetate buffer and Au NPs solution were added, completed to 5 mL with distilled water, and let to stand at room temperature for 5 min. Absorbances were measured at suitable λ max against reagent blank treated similarly (Table 1).

Assay of pharmaceutical preparations

Ten tablets were weighed, pulverized into fine powder, in 100 mL volumetric flask, specific quantity of powdered drugs equivalent to 10 mg pure drug were dissolved and diluted to the mark with methanol for doxazosin mesylate and distilled water for

bisoprolol hemifumarate and buspirone HCl. Solutions were filtered, then further diluted to 10 $\mu\text{g/mL}$ for doxazosin and buspirone, and 50 $\mu\text{g/mL}$ for bisoprolol. Procedures were completed as in general procedures.

Results and Discussion

NPs made of silver and gold are attracting a great deal of attention due to their unique optical properties. Gold NPs influence the absorbance spectra due to the surface plasmon resonance (SPR) that occurs when electron field around NP oscillates due to the light energy being absorbed by the same field. This effect is influenced by the NP size and shapes [25]; hence, the aggregation state of gold NPs has an effect on their optical properties. In the present study, gold NPs were synthesized by chemical reduction of gold solution using sodium citrate as reducing and stabilizing agent. The synthesized NPs exhibited a well-known absorption band at 520 nm. Upon addition of the studied drugs, a red shift in absorption maximum appeared due to the aggregation of gold NPs (Fig. 1). Gold NPs were successfully utilized in the determination of bisoprolol hemifumarate, buspirone HCl and doxazosin mesylate.

Characterization of gold nanoparticles Synthesis of gold nanoparticles:

Gold NPs were synthesized as a result of certain consecutive procedures: Reduction of chloroauric acid and formation of Au atoms, nucleation of these atoms

Table 1 Analytical parameters and spectral data for determination of bisoprolol hemifumarate, buspirone HCl and doxazosin mesylate using gold nanoparticles

Parameter	Bisoprolol hemifumarate	Buspirone HCl	Doxazosin mesylate
λ max (nm)	656	670	616
Volume of gold nanoparticle (mL)	1.5	2	2
Volume of buffer (mL)	0.1	0.1	--
Time (min)	5	5	5
Temperature (°C)	25	25	25
Linearity range ($\mu\text{g/mL}$)	3-14	0.1-1.2	0.20-1.0
Apparent molar absorptivity $^*(\text{mol}^{-1}\text{cm}^{-1})$	3.00×10^4	3.43×10^5	4.51×10^5
Limit of detection, LOD ($\mu\text{g/mL}$)	0.857	0.028	0.058
Limit of quantification, LOQ ($\mu\text{g/mL}$)	2.856	0.095	0.193
Regression equation **: Slope (b)	0.0303	0.558	0.8874
Intercept (a)	0.0549	0.1122	-0.0341
Correlation coefficient (r)	0.9999	0.9999	0.9999

Note: * Calculated on the basis of the molecular weight of the drug; ** $A = a + bc$.

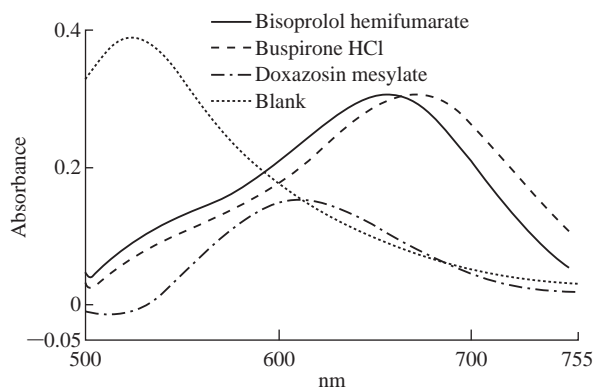
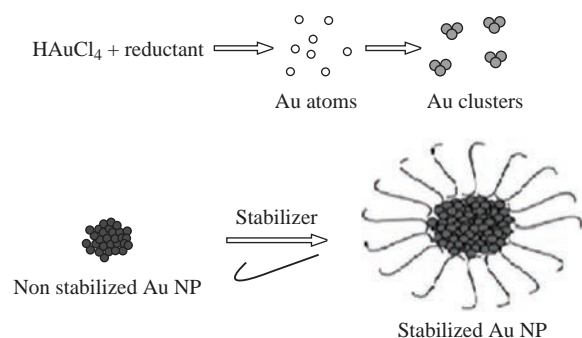


Fig. 1 Absorbance spectra of the reaction between Au NPs and 8 $\mu\text{g/mL}$ bisoprolol hemifumarate, 0.4 $\mu\text{g/mL}$ buspirone HCl, and 0.35 $\mu\text{g/mL}$ doxazosin mesylate.

to form Au cluster, growth of the atomic cluster to certain size, and finally stabilization of these clusters [24]. Schematic 1 shows the synthesis of gold NPs.



Schematic 1 Synthesis of gold nanoparticles.

Reduction of chloroauric acid

Gold NPs were synthesized by reduction of tetrachloroauric acid using sodium citrate as reducing agent according to the following equations [25]:



and



where SADC = sodium acetate dicarboxylate.

Before addition of the reducing agent, the gold was in solution in the Au^{+3} form. When the reducing agent was added, gold atoms were formed in the solution, and their concentration rose rapidly until the solution exceeded saturation. Particles then formed in a process called nucleation [27]. The remaining dissolved gold atoms bound to the nucleation sites and growth occurred as shown in Fig. 2.

Stabilization of nanocluster against aggregation

There are two types of stabilization [28]:

Electrostatic stabilization, and steric stabilization (Fig. 3).

In this method, we depended on the electrostatic stabilization using sodium citrate that acted as reductant and stabilizer. The distance between particles was kept by the balance of two forces, i.e. double layer repulsive force and Van der Waals attractive force [30], as shown in Fig. 4.

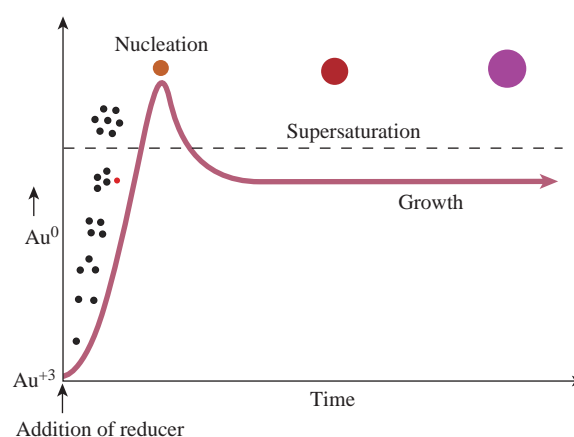
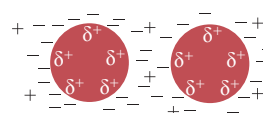


Fig. 2 Nucleation of gold nanoparticles.

Stabilization of Nanoclusters Against Aggregation

1. Electrostatic stabilization

Adsorption of ions to the surface. Creates an electrical double layer which results in a coulombic repulsion force between individual particles



2. Steric stabilization

Surrounding the metal center by layers of material that are sterically bulky. Examples: polymers, surfactants, etc

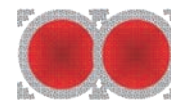


Fig. 3 Types of nanoparticles stabilization.

Colloidal stability

• Citrate stabilized gold nanoparticles

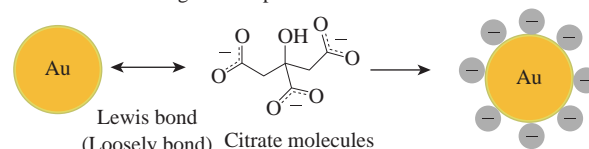


Fig. 4 Electrostatic stabilization.

Effect of sodium citrate concentration

Sodium citrate acts as a reducing and stabilizing agent; hence, its concentration has a crucial role in the synthesis and stability of gold NPs. In the present study, different concentrations were tried to obtain the

ideal NPs solution that won't undergo aggregation. Concentration of 10, 20 and 40 mM sodium citrate were used as reducing agent. The solution using 10 and 20 mM sodium citrate showed signs of aggregation by giving blue color, but the 40 mM solution was stable, giving bright red color. The turbid solution of lower concentration of citrate could result from the binding of NPs with each other in solution due to their increased size, while using the high concentration of sodium citrate led to decreasing of the size of AuNPs and formation of well separated particles. Concerning the quality of the obtained NPs, we chose the concentration of 40 mM.

Colorimetric determination of the cited drugs using gold nanoparticles Optimization of reaction conditions

To optimize sensitivity and selectivity of the method, we investigated several factors:

Effect of buffer pH

The pH of the solution plays an important role not only in the interaction between Au NPs and the studied drugs but also in the stability of the Au NPs. To investigate the effect of pH on the stability of gold NPs, the solution was tested over the pH range of 2-10 using different pH buffer media (acetate buffer, phosphate buffer, chloride buffer and borate buffer). When the pH of the solution was lower than 5, gold NPs would aggregate rapidly because of the positively charged citrate [25]. Above pH 6, a slight decrease in the absorbance of the reaction was observed; hence, acetate buffer at pH 5 was chosen to give stable solution and best sensitivity to bisoprolol hemifumarate and buspirone HCl, while doxazosin mesylate gave the highest absorbance and stability without buffer (Fig. 5 and 6).

Effect of volume of gold nanoparticles solution

The rate of aggregation increased with the increase in the volume of AuNPs till 1.5 mL for bisoprolol hemifumarate, and 2 mL for buspirone HCl and doxazosin mesylate as shown in Fig. 7. It could be seen that absorbance would decrease if the volume of AuNPs was higher or lower than these values. This might be attributed to less binding products, which made the intensity lower; on the contrary, excessive gold NPs would bind with the cited drugs competitively, and so the number of binding drugs for each gold NP would reduce, which resulted in the

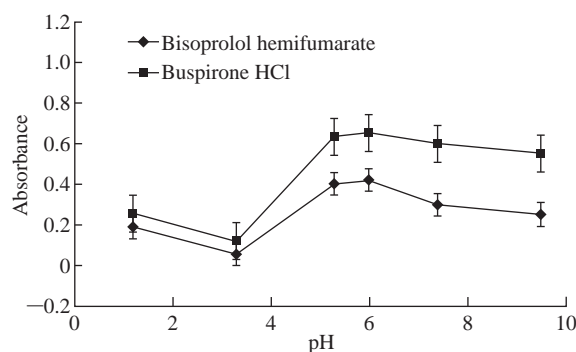


Fig. 5 Effect of pH on aggregation rate in the presence of 14 $\mu\text{g/mL}$ bisoprolol hemifumarate and 1.2 $\mu\text{g/mL}$ buspirone HCl.

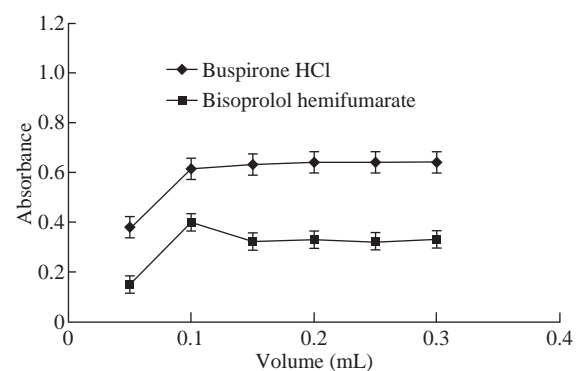


Fig. 6 Effect of volume of the buffer on aggregation rate in the presence of 14 $\mu\text{g/mL}$ bisoprolol hemifumarate and 1.2 $\mu\text{g/mL}$ buspirone HCl.

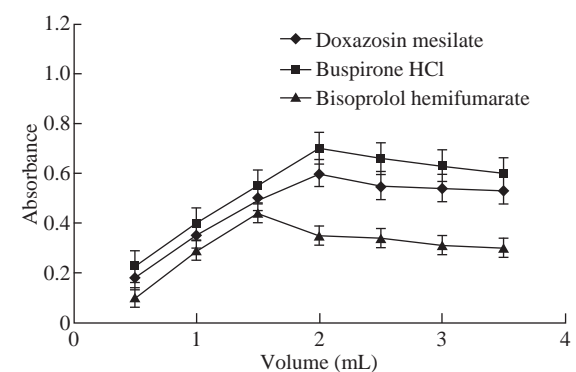


Fig. 7 Effect of volume of gold nanoparticles on aggregation rate in the presence of 14 $\mu\text{g/mL}$ bisoprolol hemifumarate, 1.2 $\mu\text{g/mL}$ buspirone HCl and 0.7 $\mu\text{g/mL}$ doxazosin mesylate.

decrease of intensity.

Effect of temperature

Different temperatures were studied in the range of 25, 40, 60 and 80 $^{\circ}\text{C}$. No absorbance change was recorded; hence, the current reaction was run at room temperature as of 25 $^{\circ}\text{C}$ (Fig. 8).

Effect of time

Maximum color intensity was attained at 5 min for the studied drugs (Fig. 9).

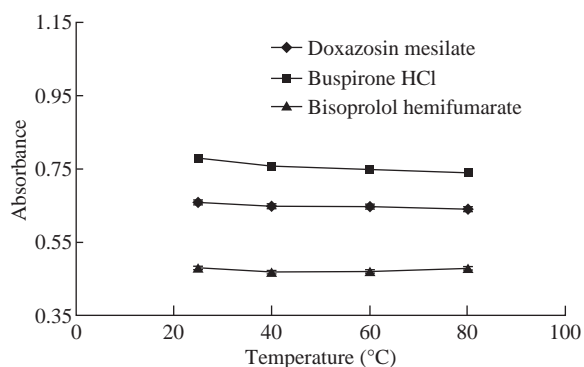


Fig. 8 Effect of temperature on aggregation rate in the presence of 14 µg/mL bisoprolol hemifumarate, 1.2 µg/mL buspirone HCl and 0.7 µg/mL doxazosin mesylate.

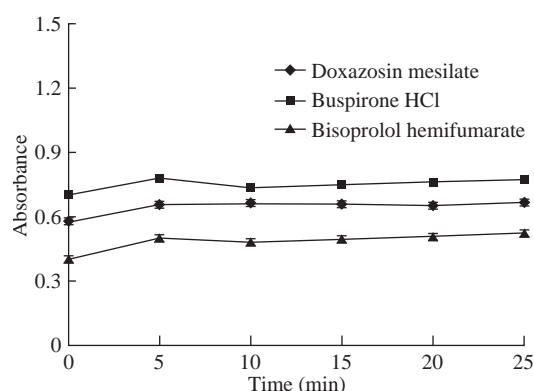


Fig. 9 Effect of time on aggregation rate in the presence of 14 µg/mL bisoprolol hemifumarate, 1.2 µg/mL buspirone HCl and 0.7 µg/mL doxazosin mesylate.

Order of addition

The addition sequence of reactants could influence the aggregation of gold NPs. Different orders of addition of the components were examined. The most suitable sequence was drug, acetate buffer, and then gold NPs for bisoprolol hemifumarate and buspirone

HCl, while because doxazosin mesylate did not need buffer, addition of this drug to gold NPs showed high rate of aggregation (Fig. 10).

Method validation

Linearity

Under the optimum conditions described, calibration curve for determination of the cited drugs by the proposed method was constructed by plotting absorbance against drug concentrations. Beer's law plots were linear over the range of 3-14 µg/mL, 0.1-1.2 µg/mL and 0.2-1.0 µg/mL for bisoprolol hemifumarate, buspirone HCl and doxazosin mesylate, respectively, with small intercepts and good correlation coefficients indicating good linearity over the working concentration ranges. Molar absorptivity, relative standard deviation, analytical standard error, detection and quantification limits were also calculated.

Sensitivity

Limit of detection (LOD) was determined by evaluating the lowest concentration of the analyte which could be detected but not necessarily quantitated as an exact value. Limit of quantification (LOQ) was the lowest concentration of the analyte which could be quantitatively determined with suitable accuracy and precision. LOD and LOQ were evaluated using the following equations according to ICH guidelines [30]:

$$\text{LOD} = 3.3 \sigma/S \text{ and } \text{LOQ} = 10 \sigma/S,$$

where σ is the standard deviation of replicate blank responses (under the same conditions as for sample analysis), and S is the slope of the calibration curve. LODs and LOQs were calculated and listed in Table 1.

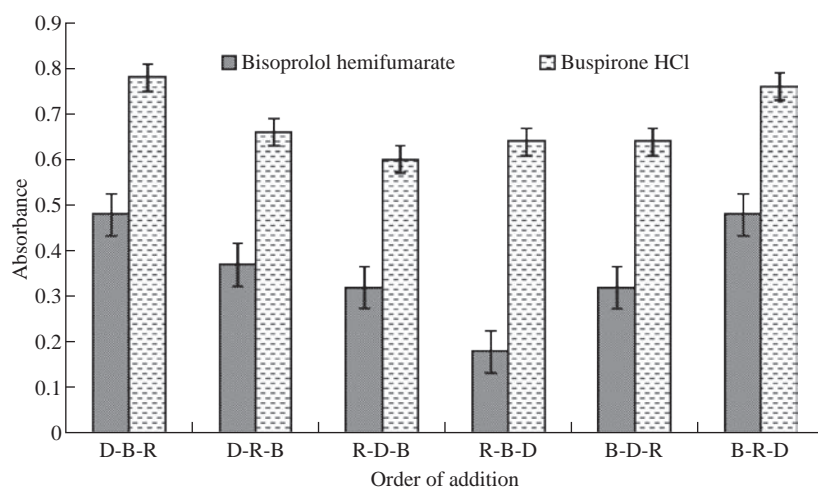


Fig. 10 Effect of order of addition of acetate buffer and gold nanoparticles to 14 µg/mL bisoprolol hemifumarate and 1.2 µg/mL buspirone HCl. (D = drug; B = buffer; R = reagent).

Accuracy

Accuracy of the proposed method was ascertained by determining pure samples of the cited drugs with reported methods. Statistical analysis of the results obtained by the proposed and the comparison methods for the studied drugs showed that the calculated values did not exceed the theoretical ones which indicated no significant differences were found between the proposed and the comparison methods. Statistical comparison [31] of the results was performed using Student's t-test and variance ratio F-test at 95% confidence level.

Intra-day precision (repeatability)

To determine intra-day precision of the proposed method, solutions containing three different concentrations (within the linearity ranges) of each drug in its pure form were prepared and analyzed by the proposed method on three successive times in the same day. The values of relative standard deviation and percentage relative error (Er%) of the suggested method were calculated (Table 6) using the following

equation:

$$\text{Er}\% = (\text{found} - \text{added}) / \text{added} \times 100.$$

Inter-day precision (intermediate)

To establish inter-day precision, three experimental replicates including three different concentrations (within the linearity ranges) of the cited drugs were carried out using the proposed method over a period of three days. Relative standard deviation and percentage relative error (Er%) were calculated (Table 2).

Selectivity

To study the selectivity of the proposed method, interference liabilities were performed to explore the effect of common excipients that might be added during formulations. Under the experimental condition employed, to a known concentration of the studied drugs, the common excipients lactose, sodium dodecylsulphate, starch and magnesium stearate were added and analyzed. Results showed no interferences from the presence of these excipients (Table 3).

Table 2 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 hemifumarate	3	3.029 ± 0.970	100.95	1.665	0.95	3.040 ± 0.635	101.32	1.086	1.32
	8	7.968 ± 0.836	99.60	1.455	-0.40	8.001 ± 0.599	100.01	1.038	0.01
	14	14.162 ± 0.943	101.16	1.615	1.16	13.997 ± 0.981	99.98	1.700	-0.02
Buspirone HCl	0.2	0.198 ± 1.077	98.98	1.884	-1.02	0.199 ± 0.790	99.58	1.374	-0.42
	0.6	0.606 ± 0.797	101.00	1.366	1.00	0.612 ± 0.199	101.99	0.338	1.99
	1.2	1.194 ± 1.085	99.48	1.889	-0.52	1.197 ± 0.863	99.74	1.498	-0.26
Doxazosin mesylate	0.2	0.202 ± 1.142	101.10	1.957	1.10	0.204 ± 0.677	101.85	1.152	1.85
	0.5	0.502 ± 0.941	100.47	1.623	0.47	0.503 ± 0.886	100.62	1.525	0.62
	0.9	0.877 ± 1.013	97.47	1.800	-2.53	0.883 ± 0.796	98.09	1.406	-1.91

Table 3 Analysis of the cited drugs by the proposed method in presence of some common excipients

Tolerance molar ratio (M : M) *	Recovery (%) **			
	Bisoprolol hemifumarate lactose	Buspirone HCl lactose	Doxazosin mesylate	
			Lactose	Sodium dodecylsulphate
1 : 1	101.68	99.40	97.84	104.60
1 : 10	103.99	102.69	103.70	104.60
1 : 50	98.38	97.61	104.60	102.34
1 : 100	103.99	100.90	96.48	104.60
Other excipients	Bisoprolol hemifumarate	Buspirone HCl	Doxazosin mesylate	
Magnesium stearate (40 µg/mL)	101.35	100.90	98.29	
Starch (40 µg/ml)	101.02	98.81	--	

Note: * Drug : Excipients, Bisoprolol hemifumarate 10 µg/mL (2.9×10^{-3} M), Buspirone HCl 0.6 µg/mL (1.5×10^{-4} M) and Doxazosin mesylate 0.5 µg/mL (1.1×10^{-4} M).

** Mean of three determinations.

Table 4 Method robustness and ruggedness expressed as recovery \pm RSD%

Drugs	Robustness			Ruggedness
	Taken ($\mu\text{g/mL}$)	Parameters altered		Inter-instruments (n = 2) JENWAY6715UV/Vis. -ShimadzuUV1800 PC
		Volume of gold solution	Volume of acetate buffer	
Bisoprolol hemifumarate	8	100.70 \pm 1.477	100.98 \pm 1.028	100.08 \pm 1.457
Buspirone HCl	0.6	102.09 \pm 1.755	101.00 \pm 1.629	101.493 \pm 0.832
Doxazosin mesylate	0.5	102.34 \pm 1.375	--	100.65 \pm 1.742

Table 5 Application of the proposed method to determination of the cited drugs in their pharmaceutical formulations

Drug	Bisoprolol hemifumarate			Buspirone HCl			Doxazosin mesylate		
	Taken ($\mu\text{g/mL}$)	Added ($\mu\text{g/mL}$)	Recovery* (%)	Taken ($\mu\text{g/mL}$)	Added ($\mu\text{g/mL}$)	Recovery* (%)	Taken ($\mu\text{g/mL}$)	Added ($\mu\text{g/mL}$)	Recovery* (%)
Statistics	3	--	101.32	0.1	--	98.21	0.2	--	101.48
		3	99.12		0.1	100.00		0.2	100.35
		4	99.92		0.3	99.04		0.3	100.71
		5	97.76		0.5	100.65		0.4	100.88
		6	97.96		0.6	98.81		0.5	100.99
		8	97.81		0.8	98.97		0.6	102.94
Mean \pm S.D.		98.51 \pm 0.962			99.53 \pm 0.718				100.85 \pm 1.015
N		5			6				7
V		0.926			0.515				0.953
S.E		0.430			0.293				0.384

Note: * Mean of three different experiments.

Robustness

Robustness was the measure of capacity of the proposed method to remain unaffected by small variations of the method variables. It was evaluated by making small incremental changes in one parameter while the others were kept unchanged as the volume of gold solution (1.6, 1.5, 1.4 mL for bisoprolol hemifumarate, 2.1, 2.0, 1.9 mL for buspirone HCl and 2.2, 2.0, 1.8 mL for doxazosin mesylate), and acetate buffer volume (0.11, 0.10, 0.09 mL for bisoprolol hemifumarate and buspirone HCl). The effect of the changes was studied on the absorbance by calculating recovery \pm RSD%, and the changes had negligible influence on the results, which provided an indication for the reliability of the proposed method during its routine application to analysis of the investigated drugs (Table 4).

Ruggedness

Ruggedness 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 4.

Analytical applications

The proposed method was successfully applied to the assay of the studied drugs in their pharmaceutical formulations without interference from common excipients. Satisfactory results obtained from the recoveries of the drugs were in good agreement with the label claim and proved the suitability of the proposed method (Table 5).

Conclusions

The authors utilized one of the well-established properties of gold NPs, aggregation, for spectrophotometric determination of bisoprolol hemifumarate, buspirone HCl and doxazosin mesylate. Gold NPs tended to aggregate through electrostatic interaction with the cited cationic drugs which resulted in formation of a new red shifted band at 616-670 nm. The data given previously revealed that the proposed

method was simple, sensitive, inexpensive and easily applicable to analysis of drugs in their pharmaceutical dosage forms with good accuracy and precision.

Acknowledgments

This work was supported by Department of Analytical Chemistry, Faculty of Pharmacy, Zagazig University, Egypt. The authors wish to express their gratitude for the support of this work.

Conflict of Interests

There are no conflicts of interests.

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