

Green Spectrophotometric Estimation of Minor Concentrations of Methyldopa and Terbutaline Sulphate in Pure Forms and Tablets Using Polyvinylpyrrolidone-Capped Silver Nanoparticles

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Abstract

Sensitive and simple colorimetric method was developed for determination of methyldopa and terbutaline sulphate in pure and pharmaceutical dosage forms. The method was based on reduction of silver ions by the cited drugs in basic medium at 90 °C to silver nanoparticles in the presence of stabilizing agent as polyvinylpyrrolidone. The formed silver nanoparticles were distinguished by UV-Vis absorption spectroscopy indicating the characteristic surface plasmon resonance which can be also observed as intense yellow color solution. The plasmon absorbance of the silver nanoparticles was measured at 410 nm for quantitative estimation of methyldopa and terbutaline sulphate over the range of 80-480 and 40-600 ng/mL respectively. Limit of detection was obtained as 26, 13 ng/mL for methyldopa and terbutaline sulphate respectively. The eco-friendly developed method could be successfully applied to the pharmaceutical formulations with studying the interference of different excipients.

Keywords: Methyldopa, Terbutaline sulphate, Silver nanoparticles, Surface plasmon resonance, Colorimetry

Introduction

Methyldopa (MD) is alpha2-adrenergic receptor agonist of (2S)-2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid [1]. MD is broadly indicated for management of hypertension, preferably for hypertension in pregnancy and this effect is mainly owing to its action on the CNS [2]. Several analytical methods have been developed for estimation of MD including official titrimetric methods [1,3], spectrophotometric determinations in pharmaceutical

formulations [4-6] and in presence of other drugs [7,8]. HPLC with fluorescence [9], UV [10,11], electrochemical [12] detections and chiral HPLC for enantiomer separation [13] were applied. Electrochemical analysis [14,15], and NMR spectroscopy [16] were also performed.

Terbutaline sulphate (TER) is an official [1,3], direct-acting sympathomimetic with a chemical definition of bis [(1RS)-1-(3,5-dihydroxyphenyl)-2-[(1,1-dimethylethyl)amino]ethanol] sulphate [1]. TER has a selective action on beta₂ agonists that relax

bronchial smooth muscles producing bronchodilating effect used for obstructive pulmonary diseases. It is also indicated for premature labour because of decreasing uterine contractility [2]. From the literature survey, TER was estimated in different dosage forms using spectrophotometric [17-21], spectrofluorometric [19, 22] and electrochemical methods [23, 24]. Chromatographic analysis of TER were performed using HPTLC [25], gas chromatography [26] as well as HPLC [20] in biological fluids [27] and in combined dosage forms [28] with stability indicating studies [29]. The capillary zone electrophoresis method [30] was also applied for enantioseparation of TER enantiomers.

Metal nanoparticles, compared to their bulk atomic materials, have distinct physico-chemical properties owing to their large surface area and electronic properties utilized in potential applications of biotechnology and biomedical fields [31]. Noble metal nanoparticles of silver and gold have been the nanoparticles of interest in nanoscience and nanotechnology for many decades due to their stability, electric properties and strong optical absorption of electromagnetic radiation in the UV-Vis-NIR region. Upon the excitation of their conducting electrons with incident photon frequency, collective oscillations known as localized surface plasmon resonance (LSPR) will occur and result in extinction spectra. These extinction band depends on the size, shape and dielectric environment of nanoparticles [32]. Thus, silver nanoparticles (Ag-NPs) are considered one of the most vital nanomaterials possessing large degree of commercialization and now widely applicable in the field of surface plasmon resonance spectroscopy for determination of many pharmaceuticals.

Several spectrophotometric determinations using Ag-NPs were reported for catecholamines [33] reducing sugars [34] cannabinoids [35] etilefrine hydrochloride, fenoterol hydrobromide, salbutamol sulphate and estradiol valerate [36], L-cysteine [37] as well as cephalosporin antibiotics [38] and antiviral drugs [39]. Moreover, Ag-NPs were used as a fluorescence probe for assay exofenadine hydrochloride [40], as a nanocomposite modified electrode for voltammetric determination of clonazepam [41] and as a nanocatalyst to enhance chemiluminescence for nitrazepam [42] and isoniazid [43] investigations.

The present work measured peak intensity of surface plasmon resonance of Ag-NPs formed through reduction of Ag^+ ions by the studied drugs

in the presence of polyvinylpyrrolidone (PVP) as a stabilizing agent in alkaline medium. The produced plasmon absorbance enabled highly sensitive and simple colorimetric assay of such commonly used drugs as MD and TER in the nano range, compared with other spectrophotometric methods [4-8, 17-21], without using any hazard chemicals.

Experimental

Instrumentation

Single beam UV and visible spectrophotometer (JENWAY 6715, UK) equipped with 10 mm matched quartz cells was employed for all absorbance measurements.

Jenway 3510 digital pH meter and Wisd water bath (WiseBath[®], Germany) were used.

Materials and Reagents

Pure samples were kindly provided by their respective manufactures; methyldopa (supplied by Pharco Pharmaceuticals Inc., Alexandria, Egypt) and terbutaline sulfate (supplied by AB Draco, Lund, Sweden). Deionized, bi-distilled water and chemicals of analytical grade were used throughout this study. Silver nitrate (0.025 M aqueous solution) from Morgan Speciality Chemicals Co., polyvinylpyrrolidone (0.1 or 0.14% w/v aqueous solution) from Sigma-Aldrich and sodium hydroxide (3 or 2 mM aqueous solution) form El Nasr Chem. Co. were used for MD, TER respectively.

Pharmaceutical preparations

Aironyl[®] tablets (Batch no: 0816314) and syrup (Batch no: 0918155) containing terbutaline sulfate; 2.5 mg per tablet and 1.5 mg per 5 mL syrup (product of Sedico Pharmaceutical Co, 6 October city, Egypt).

Aldomet[®] tablets (Batch no: 1810342) containing 500 mg methyldopa and produced by Kahira pharm., Cairo, Egypt.

Standard stock solutions

Stock solutions (1000 $\mu\text{g}/\text{mL}$) were prepared by dissolving 100 mg of the pure drug in 100 mL methanol and bi-distilled water for MD and TER respectively. Further dilution of each to 4 $\mu\text{g}/\text{mL}$ was made using bi-distilled water.

General procedure

Construction of calibration graphs

Aliquots of working solutions containing different

concentrations of the cited drugs were transferred into 5 mL volumetric flask. Appropriate amounts of 0.025 M silver nitrate, 0.1% PVP, 3 mM NaOH for MD or 2 mM NaOH, 0.14% PVP, 0.025 M silver nitrate for TER were added respectively. Volumes were completed to 5 mL with bi-distilled water and then placed in a water bath at 90 °C. After suitable heating time, absorbance was recorded at 410 nm against reagent blank (Table 1).

Table 1 Analytical performance data for spectrophotometric estimation MD and TER

Parameter	MD	TER
Linearity range ($\mu\text{g/mL}$)	0.08 - 0.48	0.04 - 0.6
λ_{max} (nm)	410	410
Volume of 0.025 M Silver nitrate	0.1 mL	0.1 mL
Conc. and volume of PVP	0.1% (1 mL)	0.14% (0.5 mL)
Conc. and volume of NaOH	3 mM (0.7 mL)	2 mM (1.5 mL)
Temperature	90 °C	90 °C
Time of heating	30 min.	15 min.
Regression equation*		
Intercept (a)	-0.028	0.0583
Slope (b)	2.1508	1.3604
Correlation coefficient (r^2)	0.9998	0.9999

*A = a + bc

Assay of pharmaceutical formulations

For Aldomet[®] or Airony[®] tablets, a weighed amount of ten pulverized tablets equivalent to 100 mg of MD or 10 mg of TER was dissolved in 100 mL methanol or 10 mL bi-distilled water respectively. Solutions were well shaken and filtered then further diluted to 4 $\mu\text{g/mL}$ with bi-distilled water.

For Aironyl syrup[®], 5 mL of syrup and 5 mL of saturated NaOH were added into 60 mL separating funnel and extracted with 30 mL methylene chloride. The organic layer was evaporated till dryness and the residue was dissolved in 10 mL bi-distilled water then further diluted to 4 $\mu\text{g/mL}$.

Procedures were completed as in general procedures using standard addition technique.

Results and Discussion

The proposed method relied on redox reaction between AgNO_3 and the cited drugs which possess a phenolic group giving a reducing property in basic medium. Characteristic LSPR absorption peak observed at 410 nm which referred the formation of Ag-NPs and disappeared in reagent blank due to absence of the cited drugs (Fig. 1). These formed Ag-NPs at high temperature were effectively stabilized in the presence of capping agent as PVP and exhibited more intense absorption spectra with sharp plasmon

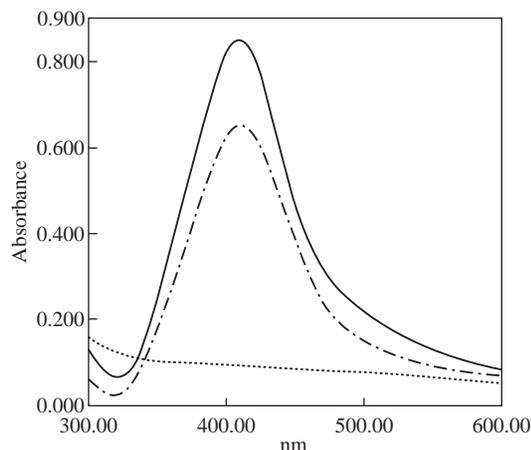


Fig. 1 Absorption spectra of the formed silver nanoparticles after heating 0.1, 0.5 mL of 0.025 M AgNO_3 with 0.32 $\mu\text{g/mL}$ of MD (— · —) and 0.6 $\mu\text{g/mL}$ of TER (—) respectively in the presence of PVP and NaOH under the optimum condition against blank (....).

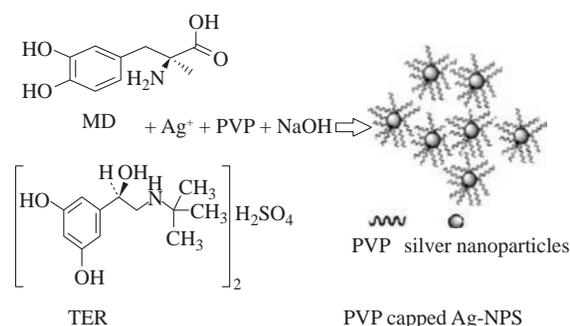
resonance. The proposed method has the merits of being eco-friendly with high sensitivity attributed to the ability of the formed Ag-NPs to absorb UV light even in minor concentrations.

Optimization of the reaction conditions

The formation of Ag-NPS using chemical reduction method employs three essential components; precursors of metal, reductants, and stabilizing/capping agents [44]. The chemical conditions as concentrations of AgNO_3 , PVP, and NaOH, temperature as well as the reaction time were studied and optimized to obtain maximum silver plasmonic response.

Effect of NaOH concentration and volume

The redox reaction relied on reduction of Ag^+ to metallic silver nanoparticles (Ag-NPS) by the cited drugs. These drugs possess dihydroxyphenyl group that could undergo oxidation in basic medium via losing H^+ to form phenolate anion which is more reducible [35] (Scheme 1). NaOH must be added to provide enough alkalinity as buffered condition wasn't enough to form silver nanoparticles. The increase in concentration of



Scheme 1 Reduction of silver ion by the studied drugs.

NaOH affected the plasmon intensity which raised up at the optimum concentration as shown in Fig. 2. At higher NaOH concentrations, the absorbance decreased which might be owing to formation of opaque Ag_2O precipitate. Using 0.7 mL of 3 mM and 1.5 mL of 2 mM NaOH were sufficient to obtain maximum absorbance of the formed silver nanoparticles for MD and TER respectively (Figs. 2 and 3).

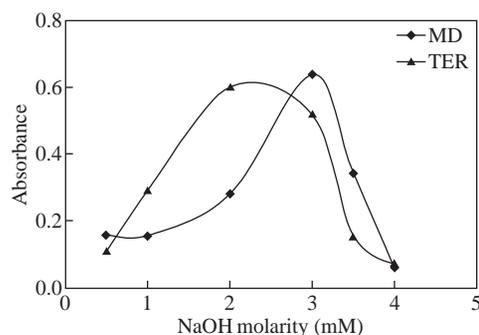


Fig. 2 Effect of NaOH conc. on absorption efficiency of the formed silver nanoparticles through reaction of AgNO_3 with 0.32 $\mu\text{g}/\text{mL}$ MD and 0.4 $\mu\text{g}/\text{mL}$ TER in the presence of PVP.

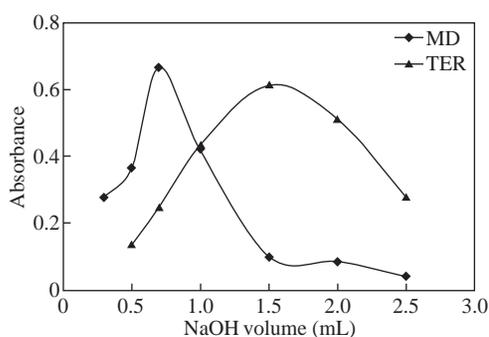


Fig. 3 Effect of 3 and 2 mM NaOH volume on absorption efficiency of the formed silver nanoparticles through reaction of AgNO_3 with 0.32 $\mu\text{g}/\text{mL}$ MD and 0.4 $\mu\text{g}/\text{mL}$ TER respectively in the presence of PVP.

Effect of silver nitrate volume and concentration

It was found that 0.1 mL of 0.025 M silver nitrate was convenient for maximum absorbance values for both drugs as shown in Figs. 4 and 5.

Effect of stabilizer type and concentration

Stabilization of metal nanoparticles is substantial during its synthesis to control particle growth and prevent aggregation. This process occurred through two basic mechanisms; electrostatic and steric stabilization [45]. Electrostatic stabilization is based on adsorbing the stabilizers, as sodium citrate, at the surface of Ag-NPS and forming electrical double layers thus causing columbic repulsion between the particles to prevent agglomeration.

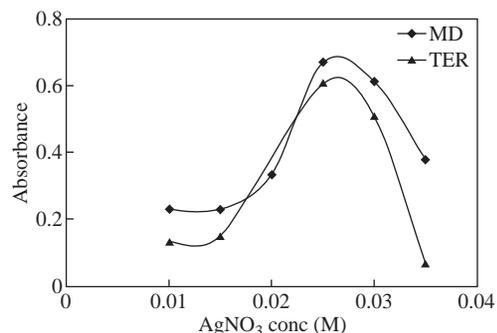


Fig. 4 Effect of AgNO_3 conc. that reacted with 0.32 $\mu\text{g}/\text{mL}$ MD and 0.4 $\mu\text{g}/\text{mL}$ TER on absorption efficiency of the formed silver nanoparticles in the presence of PVP and NaOH.

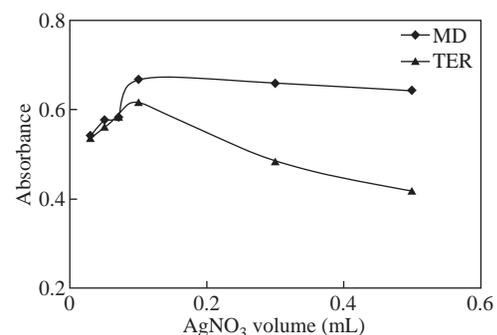


Fig. 5 Effect of 0.025 M AgNO_3 volume reacting with 0.32 $\mu\text{g}/\text{mL}$ MD and 0.4 $\mu\text{g}/\text{mL}$ TER on absorption efficiency of the formed silver nanoparticles in the presence of PVP and NaOH.

On the other hand, steric stabilizers such as PVP make protective shields on the surface of NPS by repulsion forces arise from its hydrophobic carbon chains which extend into solvents causing the steric hindrance effect [46]. In this study, PVP-capped NPS were used to prevent aggregation of Ag-NPS and gave higher absorbance and better linearity rather than those of citrate-stabilized Ag-NPS. Figs. 6 and 7 indicated that 1 mL of 0.1% and 0.5 mL of 0.14% (w/v) PVP were the optimum for MD and TER respectively.

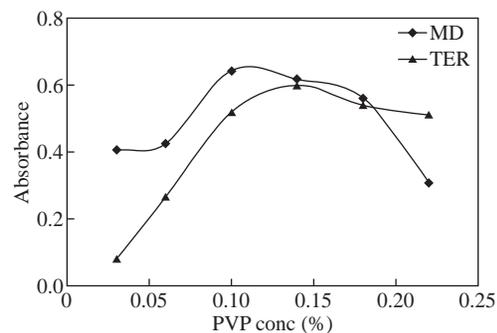


Fig. 6 Effect of PVP conc. on absorption efficiency of the formed silver nanoparticles through reaction of 0.025 M AgNO_3 with 0.32 $\mu\text{g}/\text{mL}$ MD and 0.4 $\mu\text{g}/\text{mL}$ TER in the presence of NaOH.

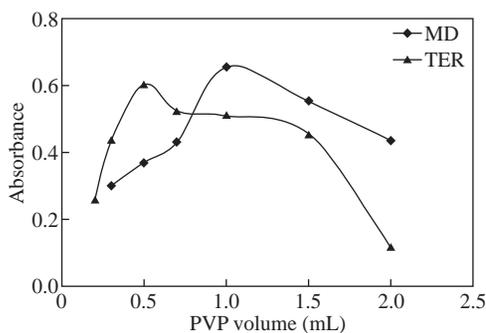


Fig. 7 Effect of 0.1, 0.14% (w/v) PVP on absorption efficiency of the formed silver nanoparticles through reaction of 0.025 M AgNO_3 with 0.32 $\mu\text{g/mL}$ MD and 0.4 $\mu\text{g/mL}$ TER respectively in the presence of NaOH.

Effect of temperature, time of heating and stability

Absorption intensities were monitored at different temperatures for both drugs using a thermostatic water bath. At temperature higher than 60 °C, more intense and sharp peak appeared. Therefore, heating at 90 °C for 30 and 15 min. were the optimal heating time for assay clear solution of the formed Ag-NPS for MD and TER respectively which would be stable up to one hour for measurements.

Effect of order of addition

The sequence of reactants addition was studied to maximize the absorption efficiency of the formed Ag-NPS by the cited drugs, Fig. 8.

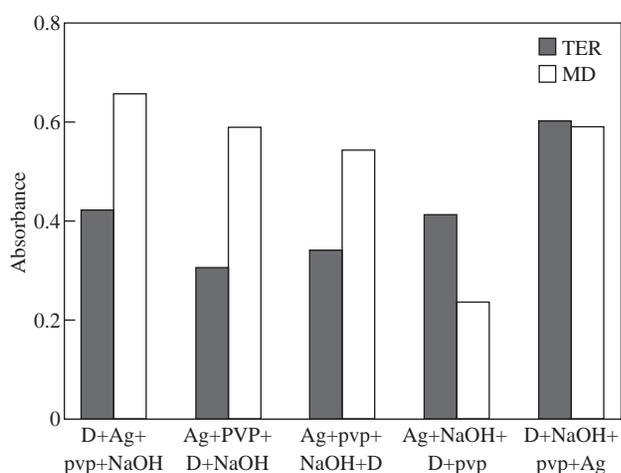


Fig. 8 Order of addition effect of 0.32 $\mu\text{g/mL}$ MD and 0.4 $\mu\text{g/mL}$ TER with 0.025 M AgNO_3 in the presence of PVP and NaOH on the absorbance of the formed silver nanoparticles.

Method validation

Linearity

To obtain the calibration curves for estimation of MD and TER, absorbance of the formed Ag-NPS

was plotted versus concentrations of the drugs. From statistical analysis of data, small intercepts and good correlation coefficients were attained over the working concentration ranges indicating good linearity, Tables 1 and 2.

Sensitivity

According to the ICH guidelines [47], limits of detection and quantification (LOD & LOQ) were calculated and listed in Table 2 using the following equations:

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

where σ = the standard deviation of the replicate blank responses, and S = the slope of the calibration curve.

Accuracy

The accuracy of the proposed method was examined by statistical comparison of the obtained results with those of the potentiometric official methods using non-aqueous titration and perchloric acid as a titrant[1]. It was found that no significant differences between the proposed methods and the official ones using Student's t-test and variance ratio F-test at 95% confidence level, Table 3.

Precision

Intra-day and inter-day precisions of this method were evaluated by analyzing four different concentrations of each pure drug by triplicate determinations in the same day (intra-day) and in three different days (inter-day). The percentage relative standard deviation (RSD%) and percentage relative error (Er%) which was calculated using the following equation:

$$\text{Er}\% = [(\text{founded} - \text{added}) / \text{added}] \times 100,$$

and were evaluated and listed in Table 4 proving acceptable results for the suggested method.

Selectivity

For evaluation selectivity of the proposed method to assay the pharmaceutical dosage forms of the studied drugs, the interference effect of common excipients in the formulations was investigated. Known amounts of MD (0.48 $\mu\text{g/mL}$) and TER (0.6 $\mu\text{g/mL}$) were analyzed under the optimum conditions in the presence of 0.4 $\mu\text{g/mL}$ of each excipient using the general procedures. Results in Table 5 showed no significant interference for MD while magnesium stearate and lactose interfered to some extent with TER.

Table 2 Assay results for determination of MD and TER in pure forms using Ag-NPS

Parameters	MD			TER		
	Taken ($\mu\text{g/mL}$)	Found ($\mu\text{g/mL}$)	Recovery * (%)	Taken ($\mu\text{g/mL}$)	Found ($\mu\text{g/mL}$)	Recovery * (%)
	0.08	0.079	98.80	0.04	0.040	100.52
	0.12	0.118	98.03	0.08	0.079	98.96
	0.2	0.203	101.59	0.28	0.281	100.21
	0.24	0.240	99.96	0.4	0.403	100.65
	0.32	0.322	100.69	0.52	0.516	99.19
	0.48	0.478	99.58	0.6	0.602	100.30
Mean \pm SD		99.77 \pm 1.282			99.97 \pm 0.715	
n		6			6	
RSD		1.285			0.715	
SE		0.484			0.292	
Variance		0.523			0.512	
Slope		2.1508			1.3604	
LOD ($\mu\text{g/mL}$)		0.026			0.013	
LOQ ($\mu\text{g/mL}$)		0.078			0.040	
ϵ ($\times 10^5$) ** $\text{L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$		4.241			9.083	

* Average of three different determinations

** Apparent Molar absorptivity was calculated on the basis of the molecular weight of the drug.

Table 3 Statistical analysis of results obtained by the proposed and the official methods

Parameters	MD		TER	
	Proposed method	BP official method [1]**	Proposed method	BP official method [1]**
Mean \pm SD	99.77 \pm 1.282	99.96 \pm 0.690	99.97 \pm 0.715	99.80 \pm 0.352
Variance	0.523	0.476	0.512	0.124
n	6	3	6	3
Student t-test	0.226 (2.365)*	--	0.387 (2.365)*	--
F-test	3.454 (5.79)*	--	4.140 (5.79)*	--

* The corresponding theoretical values for t and F tests at $p = 0.05$.

** Potentiometric official method for MD and TER.

Table 4 Precision data for determination of the studied drugs through formation of Ag-NPS

	Intra-day					Inter-day				
	Added ($\mu\text{g/mL}$)	Found \pm SE ($\mu\text{g/mL}$)	Recover (%)	RSD (%)	Er (%)	Added ($\mu\text{g/mL}$)	Found \pm SE ($\mu\text{g/mL}$)	Recovery (%)	RSD (%)	Er (%)
MD	0.08	0.078 \pm 0.513	98.03	0.906	-1.97	0.08	0.081 \pm 1.025	100.74	1.763	0.74
	0.12	0.117 \pm 0.129	97.90	0.229	-2.1	0.12	0.119 \pm 1.103	99.32	1.924	-0.68
	0.2	0.203 \pm 0.268	101.59	0.458	1.59	0.2	0.202 \pm 0.205	101.20	0.351	1.20
	0.48	0.477 \pm 1.480	99.38	0.258	-0.62	0.48	0.482 \pm 0.563	100.48	0.970	0.48
TER	0.04	0.039 \pm 1.061	98.68	1.862	-1.32	0.04	0.039 \pm 1.225	98.07	2.164	-1.93
	0.08	0.079 \pm 1.061	98.96	1.857	-1.04	0.08	0.079 \pm 0.810	98.65	1.423	-1.35
	0.28	0.283 \pm 0.381	100.91	0.655	0.91	0.28	0.278 \pm 1.050	99.16	1.834	-0.84
	0.4	0.404 \pm 0.221	101.08	0.378	1.08	0.4	0.400 \pm 1.003	100.04	1.736	0.04

Table 5 Analysis of the cited drugs by the proposed method in the presence of some common excipients

Excipients added (0.4 $\mu\text{g/mL}$)	Recovery (%)*	
	MD (0.48 $\mu\text{g/mL}$)	TER (0.6 $\mu\text{g/mL}$)
Citric acid	97.13	--
Gum acacia	100.66	--
Magnesium stearate	100.43	82.46
Starch	99.96	97.34
Silica	95.08	--
Talc	100.43	--
Lactose	--	135.02
Povidone k30	--	99.55

* Mean of three determinations.

Robustness and ruggedness

The effect of slight variations in one parameter conditions while keeping all the others constant were studied to evaluate robustness of the proposed method performance. The studied variables were the volumes of AgNO_3 (± 0.005 mL), PVP (± 0.05 mL), NaOH (± 0.05 mL) and heating time (± 1 min.) showing negligible influence on the results.

Ruggedness was also examined by performing the same procedures and assay of the studied drugs using

Table 6 Robustness and ruggedness expressed as (*recovery* ±% RSD) for the proposed method

Drugs	Robustness parameters altered							Ruggedness inter-instruments (n=2)		
	Taken (µg/mL)	PVP volume	Taken (µg/mL)	NaOH volume	Taken (µg/mL)	Silver nitrate volume	Taken (µg/mL)	Heating time	Taken (µg/mL)	JENWAY6715UV/Vis. ShimadzuUV-1201
MD	0.12	101.13 ± 1.014	0.28	103.34± 0.825	0.12	100.48 ± 1.460	0.2	97.33 ± 1.728	0.2	96.24 ± 1.025
TER	0.4	97.77 ± 0.760	0.28	102.31 ±1.603	0.52	99.38 ± 1.993	0.08	100.18 ± 1.909	0.52	96.93 ± 1.237

Table 7 Application of standard addition technique for determination of the cited drugs in the dosage forms using Ag-NPS

Parameters	MD			TER					
	Aldomet [®] tablets			Aironyl [®] tablets			Aironyl [®] syrup		
	Taken (µg/mL)	Added (µg/mL)	Recovery* (%)	Taken (µg/mL)	Added (µg/mL)	Recovery* (%)	Taken (µg/mL)	Added (µg/mL)	Recovery* (%)
	0.08		98.22	0.08		98.04	0.08		101.72
		0.12	98.03		0.04	96.85		0.04	102.36
		0.16	99.38		0.28	97.32		0.08	99.88
		0.24	97.64		0.4	99.36		0.2	102.07
		0.32	100.11		0.44	98.52		0.32	99.17
		0.4	99.96		0.52	97.36			
Mean ± SD		99.02 ± 1.129			97.88 ± 1.033			100.87 ± 1.585	
N		5			5			4	
SE		0.505			0.462			0.792	
V		1.276			1.067			2.511	

* Mean of three different experiments.

two different instruments. The obtained results were found to be reproducible and reliable (Table 6).

Analytical applications

Determination of the cited drugs in their commercial dosage forms (tablets and syrup) was successfully developed by the proposed method using standard addition technique. The satisfactory results were summarized in Table 7 showing the recoveries of target analytes and the standard deviations (SD).

Conclusions

The developed method was relied on measuring the formed silver nanoparticles using simple and cost effective spectrophotometry for sensitive assay of MD and TER. Upon heating the cited drugs with silver nitrate and PVP as stabilizer in alkaline medium, Ag⁺ ions would be reduced to yellow in color Ag-NPS. Moreover, the proposed green procedures were validated for routine analysis of these drugs in pharmaceutical preparations with convenient precision, accuracy and no need for elaborate treatments.

Conflict of Interests

The authors declare that no competing interest exists.

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