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Spectrophotometric determination of methyldopa in pharmaceutical preparation via ion pair formation

Khalaf F Al Samarrai*, Eman Thiab A Al Samarrai, Baidaa Adnan Al Samarrai

Department of Chemistry, College of Education, Samarra University, Samarra, Iraq

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ABSTRACT

A simple, rapid and low-cost spectrophotometric method for determination of Methyldopa (MDA) based on ion-pair formation using Bromothymol blue (BTB) as a reagent in alkaline medium (pH 8.7). The absorbance of the green-blue-coloured product is measured at 616 nm. Beer's Law is obeyed at concentration range up to 5-20µg/ml with molar absorptivity $0.8279x10^4$ L/mol.cm. The correlation coefficient, limit of detection and limit of quantification were 0.9982, 0.4318 µg/ml and 1.4393 µg/ml respectively. The method has been successfully applied to the determination of Methyldopa in pharmaceutical preparations.

* Corresponding Author

Name: Khalaf F Alsamarrai
Phone: +9647734143772
Email: alfarisalsamarrai2013@gmail.com

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INTRODUCTION

The IUPAC name of Methyldopa is (2S)-2-Amino-3-(3, 4-dihydroxyphenyl)-2-methylpropanoic acid. This medicine is used in hypertension therapy. A diuretic is usually added to enhance its effect and reduce fluid retention. It is a white to yellowish white powder; the molecular weight is 211.215 gm/mol. It dissolves in alcohol and slightly dissolves in water. Figure 1 shows the chemical structure of the drug (Rona, K. *et al*., 1996).

Several analytical methods have been proposed for determination of Methyldopa in pure and in pharmaceutical formulations. These methods including; Ultra violet (Sawant, R. L., and S. M. Mhaske, 2014, Khan, H. N *et al*., 2017), Visible spectrophotometry (Thomas, O, E, and Abdulsamad, K, M, 2016, Fiaz, Tehmina *et al*., 2015, Iolanda, V, and Fatibello-Filho, O, 1998, Rashid, Q, N, *et al*, 2016), High-performance liquid chromatography (HPLC) (Samy, E, *et al*, 2015, Raut, P, P, and Shrikant, Y, C, 2014), Flow injection analysis (FIA) (Haddi, H *et al*., 2009, Berzas, J, J *et al*., 1997), Titrimetry (Pathak, V, N *et al*., 1982), Voltammetry (Rezaei, B *et al*., 2013, Molaakbari, E *et al*., 2014, Gupta, V, K, 2015, Movlaee, K, 2017), Fluorimetry (Salem, F, B, 1993) Potentiometry (Badawy, S, S *et al*., 1996, Athanasiou-Malaki, E, M, and Koupparis, M, A, 1984), Chemiluminescence (He, S *et al*., 2006, He, S-H, 2004). Some of these methods are difficult to be applied in a routine analysis because they need expensive and sophisticated instruments or rigorous control procedures on the experimental conditions.

The aim of the present study is developing a simple and economical method for determination of MDA in pure and in pharmaceutical form. This method is based on the ion pair formation.

EXPERIMENTAL

Instrumentals

A Shimadzu UV-Visible-1650–Japan double beam spectrophotometer with 1cm matched quartz cells was used for all spectral measurements. pH meter, Jenway-3310- England. Water bath, Lab tech, Korea.

Chemicals and Standard Solutions

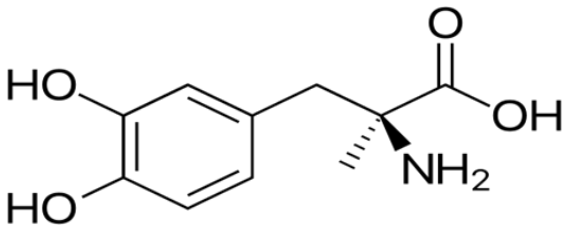

Figure 1: chemical structure of methyldopa

The chemicals used were of analytical grade, the SDI Samarra-Iraq furnished an MDA and BTB, while NaOH from GCC. The standard solution of MAD 1000µg/ml was prepared by dissolving 0.1gm accurately of pure material in 1.5 ml NaOH 0.25M, and the volume was complete to 100ml with distilled water. The standard solution of BTB 100µg/ml was prepared by dissolving accurately weigh 0.01gm of pure material in distilled water and complete the volume to 100ml in a volumetric flask with the same solvent.

Procedure

Aliquots volumes of standard MDA solution 0.5–3.0 ml; 100µg/ml were put in a series of 10 ml calibrated volumetric flasks. Then 1 ml; 100µg/ml of BTB and 0.25 ml of 0.01N NaOH were added, made up to the mark with distilled water and kept aside for 5 min at 25°C. The absorbance was measured at 616 nm against a suitable blank.

RESULTS AND DISCUSSION

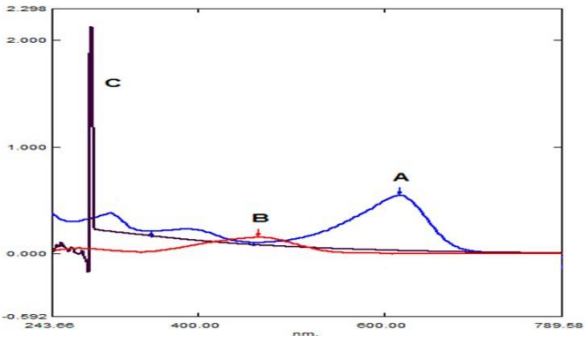

Figure 2: Absorption spectrum of A: ion pair of Methyldopa and Bromothymol blue; B: Bromothymol blue and C: Methyldopa against the blank

The absorption spectrum of ion pair formation shown in Figure 2. It gave maximum absorbance at 616 nm while the MAD and blank didn't give any absorbance at this wavelength.

Study of Optimum Conditions

The rapid formation and stability of the green-blue colored product need to establish the optimum experimental conditions as follows.

Effect of Time

Table 1: show the Effect of time

Time (min)	A
1	0.187
5	0.197
10	0.208
20	0.198
30	0.195
40	0.191

The absorbance with increasing time for the reaction of Methyldopa with Bromothymol blue in alkaline medium was recorded. The product shows a maximum absorbance after 10 min. The result is shown in Table 1.

Effect of temperature

The effect of temperature on the green-blue color intensity was studied between 10-40°C at 616 nm. It was found that the maximum absorbance was between 25-30°C. The result is shown in Table 2.

Table 2: Effect of temperature

Temperature C°	A
10	0.219
15	0.224
20	0.231
25	0.235
30	0.235
35	0.231
40	0.221

Effect of pH

The effect of pH on the reaction of MDA with BTB was studied in acidic and in basic medium. The results of experiments showed that Methyldopa doesn't react with Bromothymol blue in acidic medium. While the reaction occurred in basic medium. The maximum absorbance was when 0.25 mL of 0.01M of NaOH were added, equivalent to pH 8.7, the results shown in Table 3.

Table 3: showing the effect of pH

V (ml)		A	pH
HCl (0.01M)	0.05	0.084	5.5
	0.1	0.041	3.5
	0.15	0.033	2.5
	0.2	0.028	1.3
Without any addition		0.169	7.6
NaOH (0.01M)	0.05	0.212	7.8
	0.1	0.258	8.0
	0.15	0.401	8.2
	0.2	0.578	8.5
	0.25	0.866	8.7
	0.3	0.721	8.9
	0.35	0.701	9.3
	0.4	0.688	9.7

Order of addition

The effect of the order of addition on the absorption of ion pair forming was studied to obtain the optimum results. Table 4 shows the order of addition should be followed, MDA: BTB: NaOH due to give the highest absorption.

Table 4: Order of addition

Order of addition	Absorbance at λmax(616)nm
MDA: NaOH: BTB	0.674
MDA: BTB: NaOH	0.752
BTB : NaOH: MDA	0.663

Calibration curve

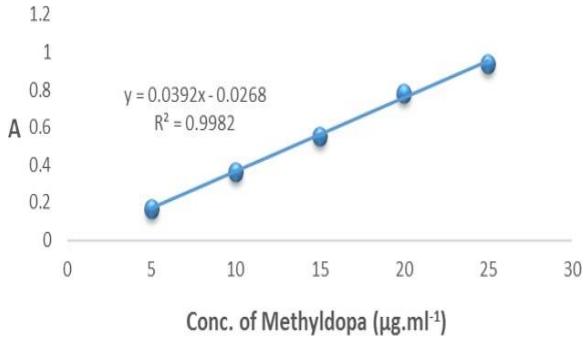

Figure 3: Calibration curve of methyldopa

The calibration curve of MDA with Bromothymol blue showed good linearity at a concentration up to 5-25 µg/ml. The Molar absorptivity, Sandell's index and R^2 were 8279.628 $L.mol^{-1}.cm^{-1}$, 0.255 $\mu g.cm^{-2}$ and 0.9982 respectively. This method was compared with another method (Hussein, A, F *et al.,* 2013). The optical characteristics were shown in Table 5.

Limit of detection and Limit of quantification (Miller, J. and Miller, J.C., 2018)

The Limit of Detection (LOD) is the smallest concentration of the analyte that gives a measurable response. LOD was calculated using equation (1).

$$LOD = 3.3 \times S \times Conc. / X^{-} \quad (1)$$

The Limit of Quantification (LOQ) is the smallest concentration of the analyte, which gives a response that can be accurately quantified. LOQ was calculated using equation (2).

$$LOQ = 10 \times S \times Conc / X^{-} \quad (2)$$

Where, S = standard deviation, Conc = the lowest concentration in calibration curve X^{-}= The arithmetic mean for a series of readings

The results are shown in Table 5.

Accuracy and Precision

The accuracy and precision of the method were tested according to (ICH, Q2B, 1996) since the recovery percentage (Rec%) and relative standard deviation (RSD%) values were 100.021-98.971% and 0.1276-0.3215% respectively. These values revealed to good accuracy and precision.

Stoichiometry of the reaction

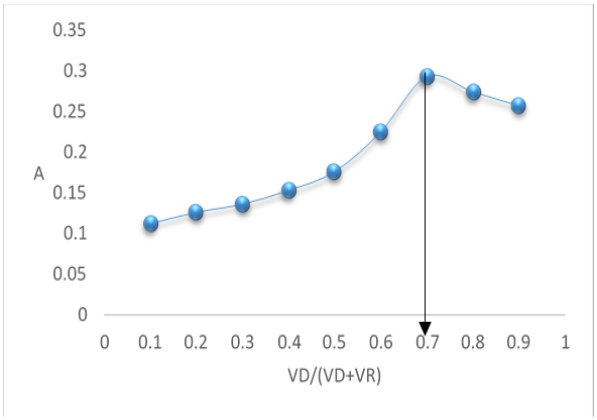

Figure 4: Continuous variations method of Methyldopa: Bromothymol blue ion pair

Under the optimum conditions, the stoichiometry of the reaction between MDA and BTB were investigated by continuous variations methods. The ratio was found to be 2 MDA:1 BTB, as shown in Figure 7.

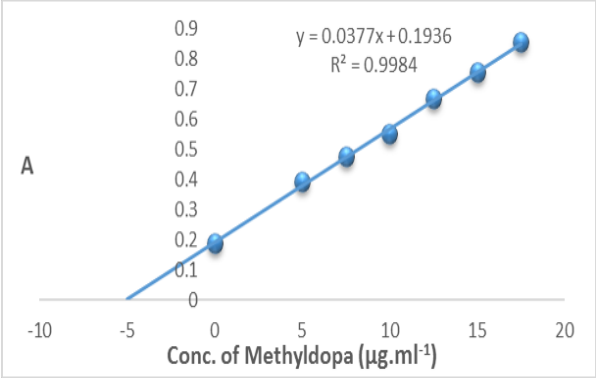

Figure 5: Standard additions curve

Method Application

Two methods were used in the determination of MDA in pharmaceutical preparation. There are direct method and standard additions method.

Direct method

Ten tablets of a pharmaceutical preparation (Aldosam 250 mg) were weighed and crushed to a fine powder. A quantity of powder equivalent to 250 mg of Methyldopa accurately weighed, transferred into a beaker, dissolved in 100 ml of distilled water and filtered. The filtrated solution was collected in a 250 ml volumetric flask, and the volume was completed to the mark with distilled water. The proposed method was successfully applied for the determination of Methyldopa in tablets, the values of the Rec.% and RSD% are summarised in Table 8. These values indicate that the proposed method has high accuracy and precision.

Table 5: Optical characteristics of the suggested method compared with another method

Method	λ_{max}(nm)	Linearity (μg.ml^{-1})	L.O.D (μg.ml^{-1})	L.O.Q (μg.ml^{-1})	RSD%	Rec%	R^2
suggested method	616	5-25	0.4318	1.4393	0.1276-0.3215	100.021-98.971	0.9982
Another method [23]	480	0.5-20	0.1500	--------	1.3800	101.200	0.9996

Table 6: Determination of Methyldopa in Aldosam (250mg) tablets by spectrophotometric method

Direct method	Pharmaceutical	Taken (μg ml^{-1})	Found (μg.ml^{-1})	Rec%	RSD % *
Standard addition method	Aldosam (250mg)	10	10.1377	101.377	1.097
		20	19.7946	98.973	0.780
		10	9.7814	97.814	0.2411
		15	15.0389	100.293	0.4852

* six replicate measurements

Standard additions method

The drug has been estimated in pharmaceutical preparation (Aldosam 250 mg) by standard additions method as shown in Figure 8.

CONCLUSION

The developed method described a simple, rapid and low-cost method for determination of Methyldopa in pharmaceutical preparation. This method doesn't need rigorous control procedure on the experimental conditions. The using of distilled water as the solvent encourages the application of this method in routine quality control analysis of Methyldopa in pharmaceutical forms.

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