Chemistry and Materials Research
ISSN 2224- 3224 (Print) ISSN 2225- 0956 (Online)
Vol.3 No.5, 2013

Spectrophotometric Determination of Methyl Dopa in Pharmaceutical Preparation via Oxidative Coupling Organic Reaction

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Abstract :
A simple, accurate and sensitive colorimetric method for the determination of Methyldopa in pure and pharmaceutical preparations has been developed .The proposed method uses ortho–Tolidine as anew chromogenic reagent .The method is based on the oxidative coupling reaction of Methyldopa with ortho–Tolidine with potassium periodate in neutral media to form orange water soluble dye product , that has a maximum absorption at λmax 480 nm . Linear calibration graph was in the range of (0.50–20.00) $\mu g.ml^{-1}$ with molar absorptivity of (1.37×10^4 $L.mol^{-1}.cm^{-1}$) ,a sandall sensitivity of (1.73×10^{-5} $\mu g.cm^{-2}$) , correlation coefficient of 0.9996 , detection limit (0.15 $\mu g.ml^{-1}$) and the relative standard deviation of RSD% (1.38) . The method was applied successfully for the determination of Methyl dopa in pharmaceutical preparations and the value of recovery% was better than (101.2%) .
Keywords: Spectrophotometric determination , Methyldopa, Pharmaceutical preparations

Introduction

Methyldopa (α-methyl-3,4-dihydroxy phenyl alanine), whose structure is shown in Figure(1), is a catechoamine derivative widely used in the control of moderate and severe arterial hypertension.Methyldopa is considered a prodrug since it acts mainly due to its metabolism in the central nervous system to amethyl norepinephrine, a a2-adrenergic agonist(1).

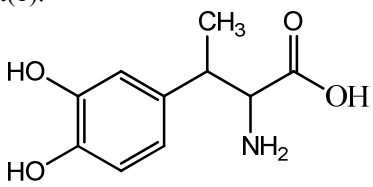


Fig.(1) Chemical structure of methyldopa

The pharmaceutical preparations containing this drug (Aldomate) is available for many years and several analytical procedures have been proposed for their control .These include spectrophotometric(2),chromatographic(3),potentiometric(4) and flow injection method(5,6).
Oxidative coupling organic reactions seems to be one of the most popular spectrophotometric methods for the determination of several drugs such as sulphonamids (7),paracetamol (8), phenylephrine HCL (9), methyl dopa (10) and folic acid (11). The proposed method is based on the reaction of the methyldopa drug with ortho-Tolidine in the presence of potassium periodate in neutral medium to form an orange water soluble dye product which shows an absorption maximum at 480 nm .

Experimental parts

Apparatus:

All spectral and absorbance measurement were carried out in a Double beam UV-Vis spectrophotometer-1800 . Equipped with a 1 cm quarts cell .
- Water bath(Lab. Companion , BS - 11) .
- Electronic balance (Sartorius AG GÖTTINGEN B2 2105 Germany) .

Reagents:

All chemicals used were of analytical-reagent grade .
-Stock solutions (100 $\mu g.ml^{-1}$) of Methyldopa (SDI-Iraq) were prepared by dissolving 0.01gm of Methyldopa in distilled water and diluting to the mark in 100 ml volumetric flask .Working solutions were prepared by diluting the solution in distilled water.
- ortho-Tolidine (0.001M) stock solution was prepared by dissolving 0.0212 gm of ortho-Tolidine in 10 ml of ethanol and completed the volume to 100 ml with distilled water in avolumetric flask of 100 ml .

- potassium periodate (0.005M) was prepared by dissolving 0.115 gm of KIO_4 in distilled water and diluting to the mark in 100 ml volumetric flask .

Recommended procedure :

In to a series of 25 ml volumetric flask ,transfer increasing volume of Methyldopa solution(100.00 µg.ml^{-1}) to cover the range of calibration curve (0.50– 20.00) µg.ml^{-1} .added 0.50 ml from (1.00 x10^{-3}M) of ortho-Tolidine and shake well . Added 2.50 ml from (5.00x10^{-3}M)of KIO_4 ,dilute the solution to the mark with distilled water , and allow the reaction to stand for 10 min., at room temperature (25 ºc) . Measure the absorption at λmax (480 nm) against a reagent blank prepared in the same way but containing no Methyldopa .

Procedure for pharmaceutical preparations :

Aldomate tablets, provided from (SDI) Samara-Iraq and from ASIA - Syria 10 tablets were grinded well and acertain portion of the final powder was accurately weighted to give an equivalent to about 10 mg of Methyldopa was dissolved in distilled water . The prepared solution transferred to 100 ml volumetric flask and made up to the mark with distilled water forming asolution of 100 µg.ml^{-1} concentration . The solution was filtered by using a Whatmann filter paper No. 42 to avoid any suspended particles .These solution were diluted quantitatively to produce a concentrations in the range of calibration curve .

Results and Discussion :

Absorption spectra :

It was found preliminary that the reaction of Methyldopa with ortho-tolidine and potassium periodate in neutral media forming an orange water soluble dye product , that has a maximum absorption at λmax (480 nm) Fig (2) . The above reaction can be utilized for the determination of Methyldopa using spectrophotometric method . Initial studies were directed toward optimization of the experimental conditions , in order to establish the most favorable parameters for the determination of Methyldopa.

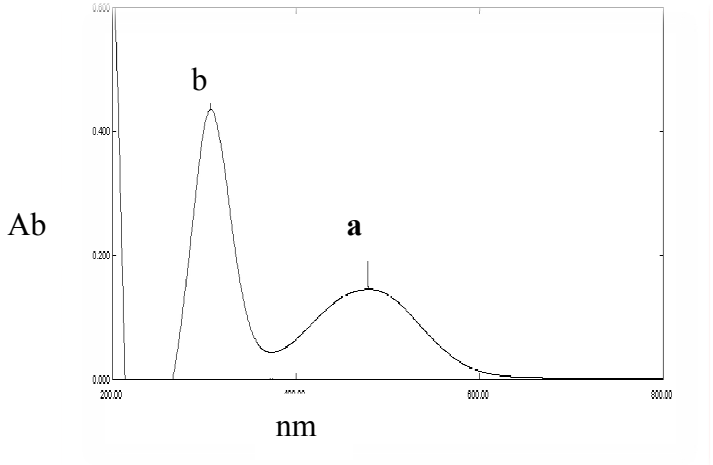


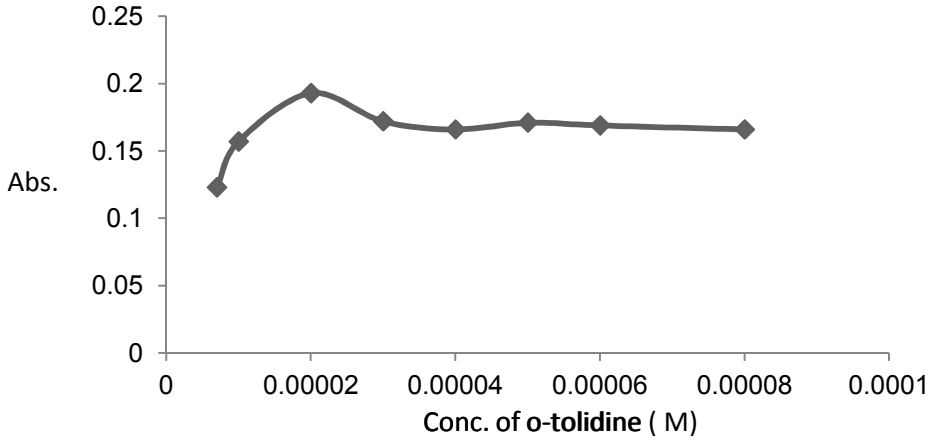
Fig (2) : (a)Absorption spectra of (3.00 µg.ml^{-1}) of Methyldopa with ortho-Tolidin (2.00 x 10^{-5}) M , and KIO_4 (5.00 x 10^{-4}) M at room temperature and measured against blank solution.
(b) blank solution prepared in the same way but containing no Methyldopa measured against distilled water .

Optimization of the Experimental Condition :

The influence of various reaction variables such as concentration of reactants , order of addition ,time and temperature were investigated .

Effect of ortho-Tolidine Concentration :

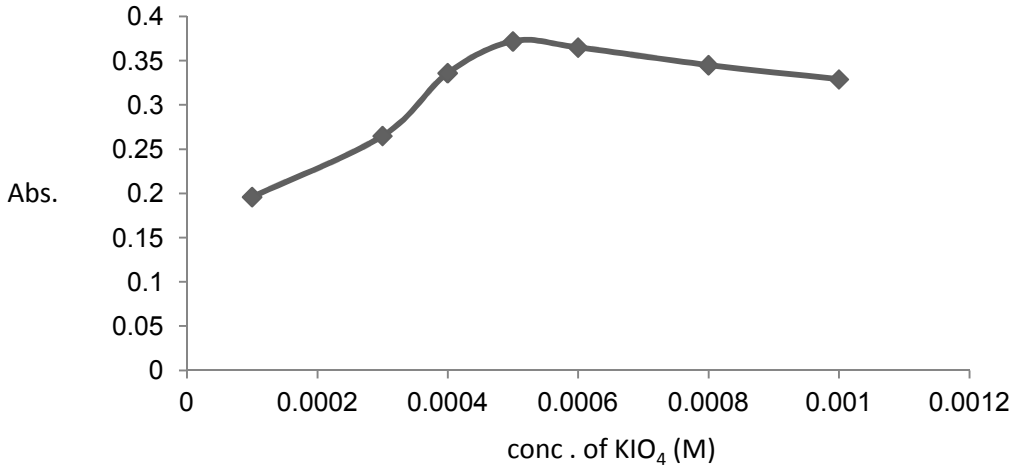
The effects of different concentration of ortho-Tolidine in the range of (7.00 x 10^{-6} – 8.00 x 10^{-5})M were investigated .A Concentration of (2.00 x 10^{-5})M give the higher absorption intensity at λmax 480 nm for (10.00) µg.ml^{-1} of Methyl dopa and (1.00x10^{-4})M of KIO_4
Fig (3) and thus was chosen for further use .



Fig(3) : Effect of ortho-Tolidine Concentration on Absorption spectra of (10.00 µg.ml^{-1}) of Methyl dopa .

Effect of Potassium periodate KIO_4 Concentration :

The effect of KIO_4 Concentration in the range of (1.00 x 10^{-4} - 1 .00 x 10^{-3})M was similarly studied . A Concentration of (5 .00 x 10^{-4})M of KIO_4give the higher absorption intensity at λmax 480 nm for (10.00) µg.ml^{-1} of Methyl dopa and (2.00 x 10^{-5}) M ortho-Tolidine .Fig (4) and thus was chosen for further use .



Fig(4): Effect of potassium periodate KIO_4 Concentration on Absorption spectra of (10.00 µg.ml^{-1}) of Methyl dopa .

Order of addition :

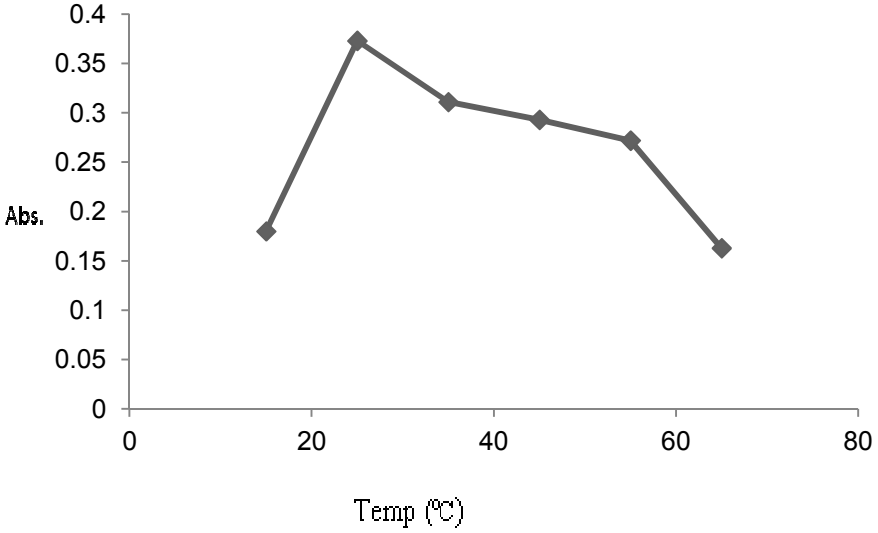
The effect of order of addition on the absorption of orange water soluble day was studied . Table (1) , shows the order of addition could be followed , Drug : ortho-Tolidine : KIO4 . Due to give the higher absorption .

Table (1) Effect of order of addition

Order of addition	Absorbance at λmax(480)nm
Drug : O-Tolidine : KIO4	0.373
Drug: KIO4 : O-Tolidine	0.208
KIO4 : O-Tolidine: Drug	0.254
KIO4: Drug : O-Tolidine	0.196
O-Tolidine : Drug : KIO4	0.365
O-Tolidine: KIO4 : Drug	0.263

Effect of Temperature :

The effect of Temperature on the color intensity of the product was studied in practice the highest absorption was obtained when the colored product was developed at room temperature (25ºc) . as shown in Fig (5)



Fig(5) : Effect of Temperatureon Absorption spectra of (10.00 µg.ml^{-1}) of Methyl dopa .

Effect of Time :

The color intensity reached a maximum absorption after Methyl dopa (10.00 µg.ml^{-1}) has been reacted with o-Tolidine and KIO_4 at 10 min . Therefore 10 min development time was chosen for further use . The results obtained are shown in Fig(6).

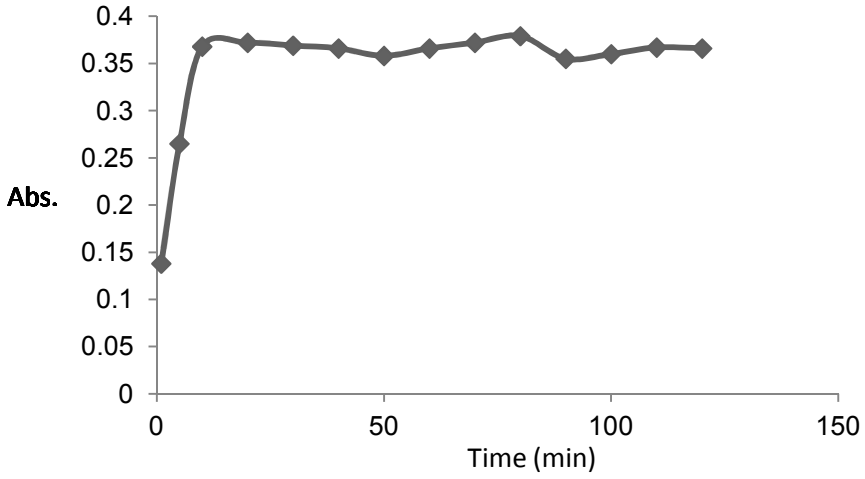


Fig (6): Effect of Time on Absorption intensity of (10.00 µg.ml^{-1}) of Methyl dopa .

Calibration Graph :

Under the optimum conditions , a linear calibration graph for the determination of Methyl dopa was obtained over the concentration range of (0.50 – 20.00) µg.ml^{-1}. The linear regression equation for the range of (0.50–20.00)µg.ml^{-1} Methyldopa is Y=0.0315 X + 0.0477and a correlation coefficient of 0.9996. The linear calibration graph is shown in Fig (7) .

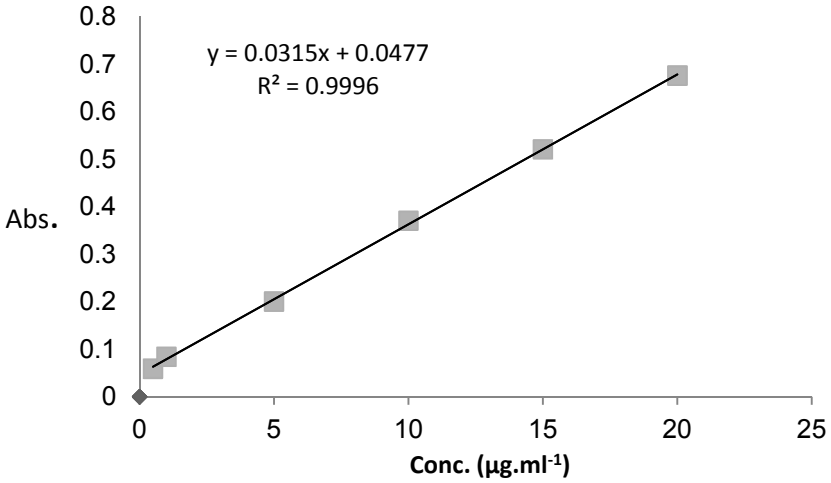
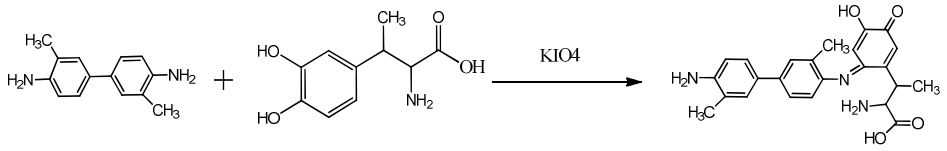


Fig (7) : Calibration graph for the determination of Methyl dopa

Nature of the dye product :

The stoichiometry of the reaction between Methyldopa and ortho-Toidine was investigated using the mole ratio, Job's and Slope ratio method (12-15) under the optimized conditions . The results obtained Fig (8 - 10) , show a 1:1 drugs to reagent product was formed .The formation of the dye may probably be occur as follows (16):



0-tolidine Methyl dopa

(*E*)-2-amino-3-(6-((4'-amino-3,3'-dimethyl-[1,1'-biphenyl]-4yl)imino)4-hydroxy-3-oxocyclohexa-1,4-dien-1-yl)butanoic acid

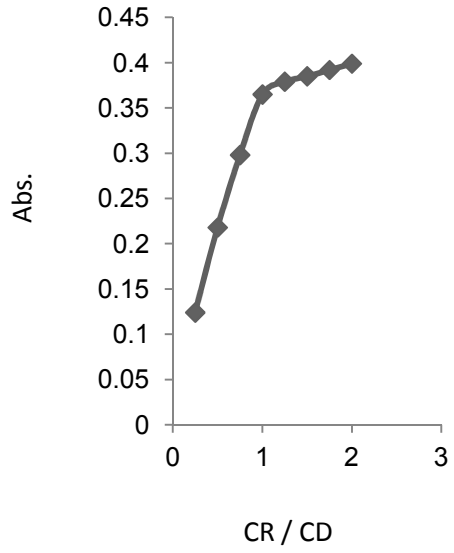


Fig (8) : Mole ratio of reagent to drug

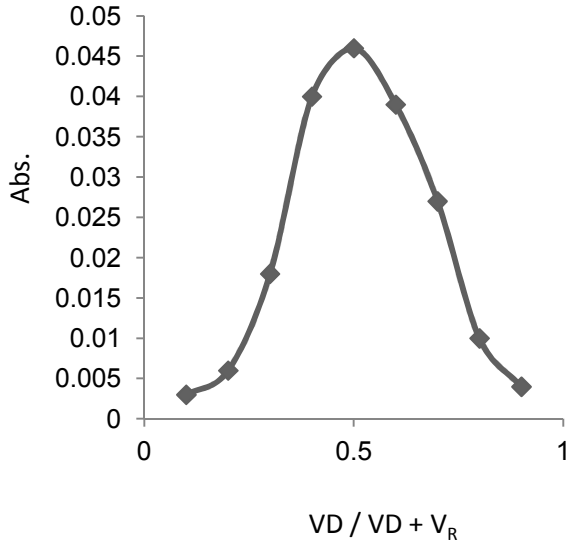
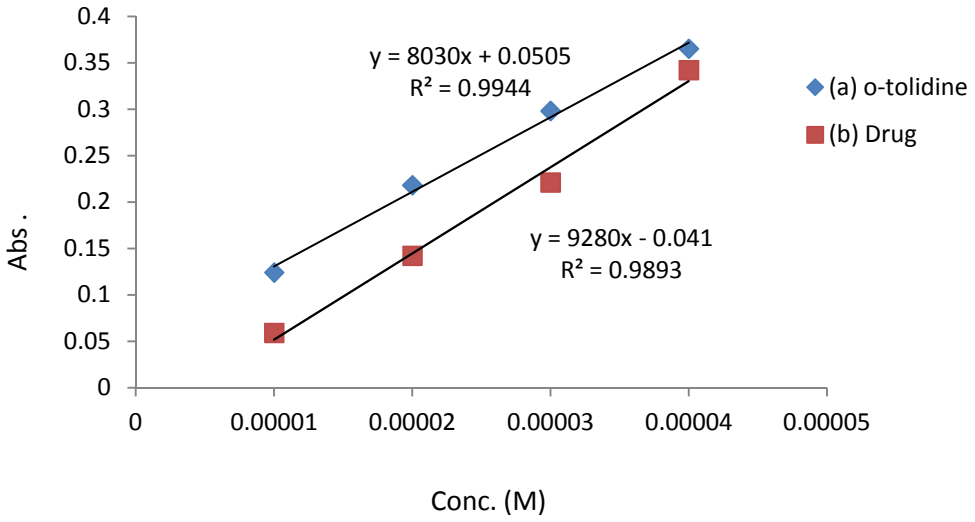


Fig (9) : Job's method



Fig(10) : Slope ratio method

(a) Absorbance vers concentration of o-Tolidine at constant concentration of drug
(b) Absorbance vers concentration of drug at constant concentration of o-Tolidine

Interference :

Several pharmaceutical preparations are associated with flavoring agents, diluents and excipients. Table (2) shows the effect of interfering materials that may be present in pharmaceutical preparations

Table (2) : Influence of excipients and additives as interfering species in the determination of Methyl dopa .

Foreign compound	Recovary (%) of 500 µg Methyl dopa per µg compound added				
	100	500	1000	2000	5000
Glucose	99.82	100.28	98.69	99.64	102.20
Lactose	100.48	101.59	101.91	102.31	101.33
Starch	101.58	102.95	101.74	98.45	102.95
Sucrose	101.91	99.84	102.26	102.33	98.60
Sodium chloride	101.82	101.20	101.54	101.84	102.45
EDTA	100.67	101.77	101.32	101.89	101.60
Citric acid	100.09	100.36	102.55	102.29	101.95
Magnesium setarate	101.36	101.05	102.06	101.58	102.47

Analytical Application :

The proposed method was applied for the determination of Methyl dopa drug in pharmaceutical preparations. Good accuracy and precision were obtained for the studied drugs . The results obtained were given in Tabel 3 which confirm Finally, the proposed method was compared successfully with the standard method Table(3).

Table (3) : Application of the proposed method for the determination of Methyl dopa in pharmaceutical preparations .

Drug sample	Amount of Methyldopa($\mu g.ml^{-1}$)		Proposed Method			Standard Method
	Taken	Found	RSD %*	Error *	Recovery*	Recovery %[17]
Pure Methyldopa	5.00	5.07	0.43	0.07	99.93	98.30
Aldomate(SDI)tablets	5.00	4.75	0.37	0.25	100.25	
	10.00	10.82	0.79	0.82	99.18	
	15.00	14.55	1.32	0.45	100.45	
Aldomate (ASIA) tablets	5.00	5.35	0.57	0.35	99.65	
	10.00	10.74	0.94	0.74	99.26	
	15.00	13.83	1.38	1.17	101.17	

*Average of five determinations .

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