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Spectrophotometric Determination of Methyl Paraben in Pure and Pharmaceutical Oral Solution

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Abstract

A simple, cheap and sensitive spectrophotometric method for the determination of methyl paraben in pure and dosage form has been described. The Method is based on the diazotization of the drug by sodium nitrite in acidic medium at 5C° followed by coupling with ortho-aminobenzoic acid to form orange color the product was stabilized and measured at 442 nm Beer's law is obeyed in the concentration range of 1-9 μg·ml^{-1} with molar absorptivity of 1.6×10^{6} L·mole^{-1}·cm^{-1}., Sandell's sensitivity were 0.0095 μg·cm^{-1}, The detection limit were 0.0065 μg·ml^{-1}, and The limit of Quantitation were 0.02 μg·ml^{-1}. All variables including the reagent concentration, reaction time, color stability period, and mole ratio were studied in order to optimize the reaction conditions. No interferences were observed Results of analysis were validated statistically and by recovery studies. These methods are successfully employed for the determination of methyl paraben in some oral solution. The developed method is easy to use and accurate for routine studies relative to HPLC and other techniques.

Key words: Determination; Spectrophotometric; Methyl paraben

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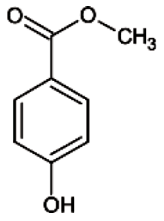
INTRODUCTION

Methylparaben drug is Methyl p-hydroxybenzoate. It is a white or colourless powder crystals, very slightly soluble in water, freely soluble in alcohol and in methanol[1]. The formula structure explain below:



$C_8H_8O_3$
g. mol^{-1} M.wt: 152.15

Methyl paraben, in particular, has been used extensively for more than 50 years due to its most favorable solubility properties compared to the higher chain alkyl hydroxybenzoates (Soni, Taylor, Greenberg, & Burdock, 2002; Giordano et al., 1999). Methyl paraben is none stimulating and nontoxic, and has a broad antibiotic spectrum. The compound is widely used as a preservative for foods, cosmetics and medicines. Those methyl paraben containing products caused contact dermatitis and drug hypersensitivity[2] (Mowad, 2000). Most of the methods for their determination in cosmetics and pharmaceutical preparations are based on gas chromatography (GC) (Mannucci et al., 1992; Aromdee & Rattandon, 2009; Shnmugan, Rajendran, Ralhakrishnan, & Tao, 2010; Han, Jia, Liu, Duan, & Chen, 2010), high-pressure liquid chromatography (HPLC) (Shabir, 2010; Boonleang & Tanthana, 2010; Kamble, Singh, & Singh, 2011; Krishnachaitanya, Israel, & Gowrisankar, 2011; Modi, Vairale, Sherikar, & Nalamothu, 2011) and fluorescence spectrometry (Blanco, Carretero, Peinado, & Guttierrez, 2000).

Spectrophotometric determination of drugs (Saadiyah, Amira, Maha, & Rafah, 2010; Saadiyah, 2011; Dhahir & Hussein, 2012).There has been no spectrophotometric

[1] British Pharmacopoeia Commission 2004.
[2] British Pharmacopoeia Commission 2004.

study determination of methyl paraben in literature. The present investigation is to provide a simple spectrophotometric analytical methods for determining, methyl paraben.

1. EXPERIMENT

1.1 Apparatus

All spectrophotometric measurements were carried out using Computerize UV-Visible, shimadzu; silica glass cell of 1 cm thickness was used throughout this study.

1.2 Materials

❖ Methylparaben stock standard solution 1000 $\mu g \cdot ml^{-1}$ was prepared by dissolving 0.1 g of pure methylparaben (SDI) in distilled water and diluting to the marked in 100 ml volumetric flask. Working standard solution 100 $\mu g \cdot ml^{-1}$ was prepared by diluting 10 ml of this stock standard solution with distilled water in 100 ml volumetric flask.

❖ Sodium nitrite solution 1% w/v was prepared by dissolving 1 g of sodium nitrite in distilled water and diluting to the marked in 100 ml volumetric flask.

❖ Hydrochloric acid solution 1 M was prepared by diluting 43 ml of 11.64 M of concentrated hydrochloric acid (BHD) with distilled water in 500 ml volumetric flask.

❖ Ortho-aminobenzoic 100 $\mu g \cdot ml^{-1}$ was prepared by dissolving 0.01 g of ortho-aminobenzoic in ethanol (BHD) and diluting with distilled water to the marked in 100 ml volumetric flask

❖ Sodium hydroxide solution 1 M was prepared by dissolving 4. g of sodium hydroxide in distilled water and diluting to the marked in 100 ml volumetric flask.

1.3 Recommended Analytical Procedure

The 0.5 ml of Methylparaben standard solution 100 $\mu g \cdot ml^{-1}$ and 0.5 ml of 1M sodium hydroxide solutions were added to 0.5 ml of of ortho-aminobenzoic and 0.5 ml of 1% sodium nitrite and 0.5 ml of 1M HCl were mixed in and completed with distilled water to the mark in 10 ml volumetric flask and shacked for 2 minutes, with shaking and cooling ice bath for 2 minutes, after 5 minutes the orange color is completely developed and the absorbance measurement was carried out at a wavelength at 442 nm, against a blank solution prepared in the same method but without Methylparaben

2. ANALYSIS OF DOSAGE FORM

Oral Solution

a. Ketofen Syrup: 1.25 ml was taken from container containing 0.8 mg of methyl paraben in 100 ml and dissolved with 5ml ethanol and transferred into 100 ml volumetric flasks and diluted up to the mark with distilled water.

b. Cyprodien Syrup: 2 ml was taken from container containing 0.48 mg of methyl paraben was transferred into 100 ml volumetric flasks and diluted up to the mark with distilled water. Working standard solutions was prepared by suitable dilution for Ketofen Syrup and Cyprodien Syrup, the recommended procedure was used to determination methyl paraben.

3. RESULTS & DISCUSSION

3.1 Absorption Spectra

An orange-colored oxidizing coupling product with absorption maximum at 442 nm Figure 1 shows the spectra of orange product

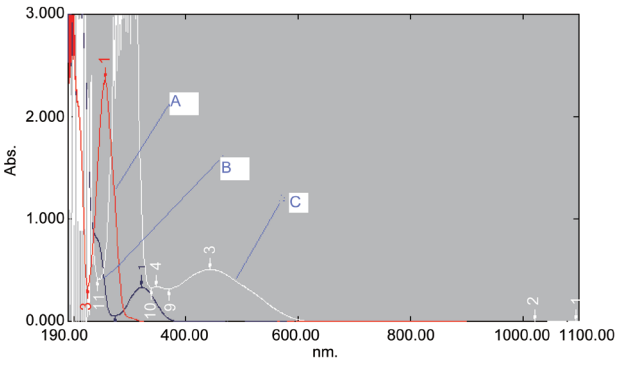


Figure 1
Absorption Spectra of (A) Methyl Paraben Versus Distilled Water, and (B) Reagent Versus Distilled Water (C) Azo Dye Against Reagent Blank

3.1.1 Optimization of the Experimental Conditions

The effect of various variables on the color development was studied to get the optimum conditions for the determination of methyl paraben. In the subsequent experiments, 1ml of (100 $\mu g \cdot ml^{-1}$) methyl paraben solution with varies volumes 0.1% of sodium nitrite solution The optimum concentration of 0.1% sodium nitrite solution that gave maximum absorption at 442 nm versus reagents blanks was found to be 0.5 ml. Figure 2 explained these results. The effect of different volumes (0.1-1.0) ml of 1 M Hydrochloric acid solution, (0.1-1.0 ml) of 100 $\mu g \cdot ml^{-1}$ of ortho-aminobenzoic acid and (0.1-1) ml of 1 M sodium hydroxide solution were examined on the maximum absorbance of the azo dye.

It was found that 0.5 ml of (1 M) hydrochloric acid solution, 0.6 ml of (100 $\mu g \cdot ml^{-1}$) ortho-aminobenzoic acid solution and 0.6 ml of (1 M) sodium hydroxide solution were enough to obtain the maximum absorbance. The azo dye color was only formed in alkaline medium. Therefore, the effects of different alkaline solutions were studied such as potassium hydroxide, sodium hydroxide sodium carbonate, and ammonium hydroxide. It was found that sodium hydroxide is the most suitable alkaline medium to produce a maximum absorbance and was used in all subsequent experiments.

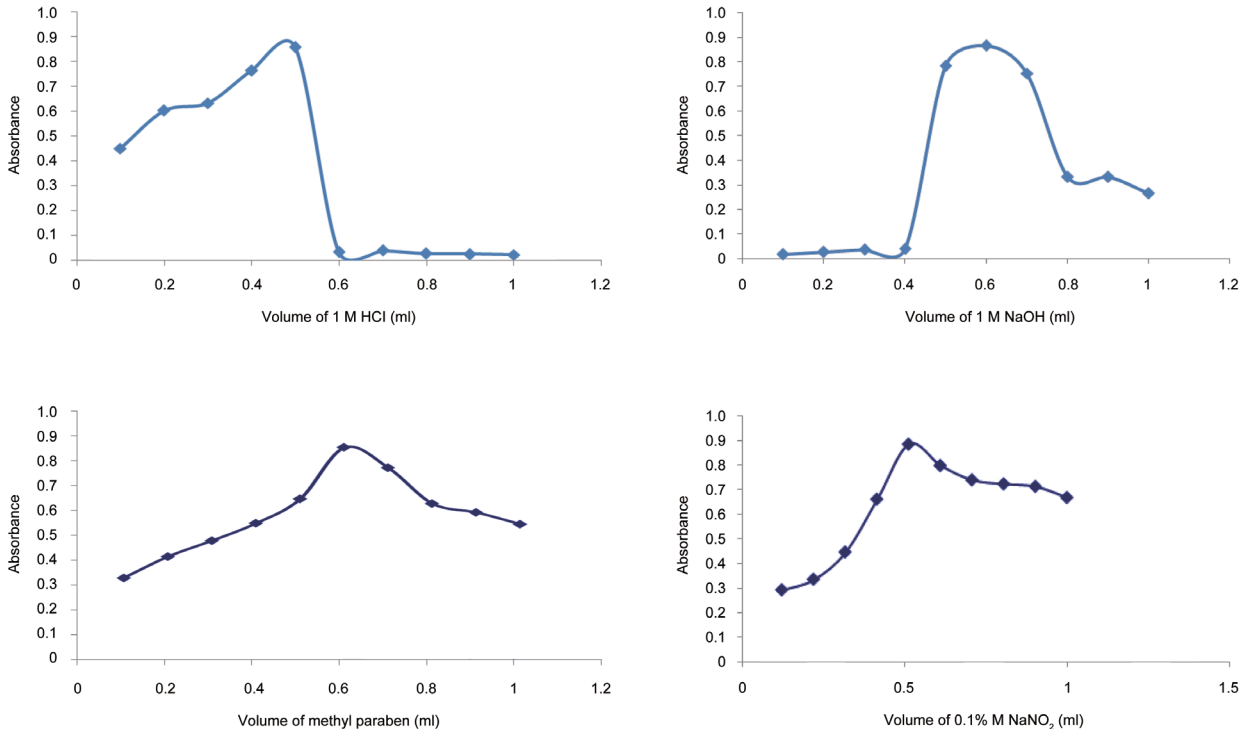


Figure 2
Optimum Conditions for Determination of Methyl Paraben

The stability of the dye was studied for 1 h following the mixing of the reagents. The colored azo dye developed rapidly after mixing and attained maximum absorbance about 4 min at room temperature. The color was stable for a period of 24 h. The effect of temperature on the diazotization and coupling reaction show that the absorbance of the azo dye remains constant in the range 0-40ºC and decreases up to 30 ºC. Therefore, it has been recommended to carry out reaction at zero temperature.

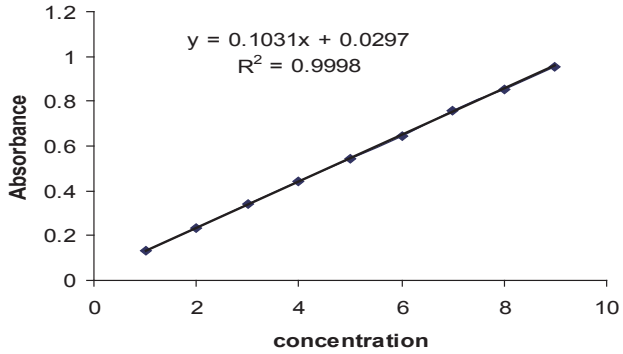


Figure 3
Calibration Graph of Methyl Paraben

3.2 Calibration Graph

Employing the conditions described in the procedure, a linear calibration graph of methyl paraben is obtained (Figure 3), which shows that Beer's law is obeyed over the concentration range of 1-9 $\mu g \cdot ml^{-1}$ with correlation coefficient of 0.9998 and an intercept of 0.0297. The conditional molar absorptivity of the orange product formed was found to be $1.6x10^6$ $L \cdot mol^{-1} \cdot cm^{-1}$. Sandell's sensitivity were 0,0095 $\mu g \cdot cm^{-1}$, detection limit were 0,0065 $\mu g \cdot ml^{-1}$ and The limit of quantitation were 0,02 $\mu g \cdot ml^{-1}$.

3.2.1 Effect of Interference

The effects of some foreign ions which often accompany this drug in pharmaceutical products were studied by adding different amounts of foreign ions to 10µg/ml of methyl paraben. The color was developed following the recommended procedure described earlier. It was observed that the Arabic Gum, glucose, Fructose, sodium acetate, Urea, NaCl, and O-Cresol were not interfering with the determination at levels found in dosage form.

3.2.2 Structure of the Dye

The stoicheiometry of the reaction between Methyl paraben and ortho-aminobenzoic acid was investigated using Job method (Skoog, Holler, & Crouch, 2007); the results obtained Figure 4 show that 1:1 drug to reagent was formed at 442 nm.

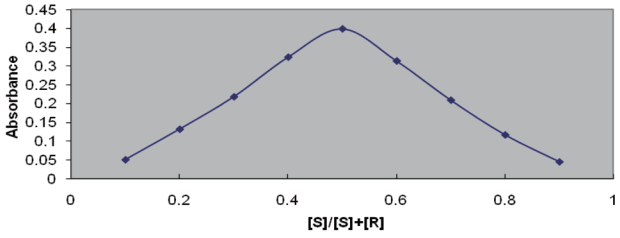


Figure 4
Jop Method of Methyl Paraben (S) **and Ortho–Aminobenzoic Acid** (R)

Therefore the formation of the product probably occurs as follows Figure 5.

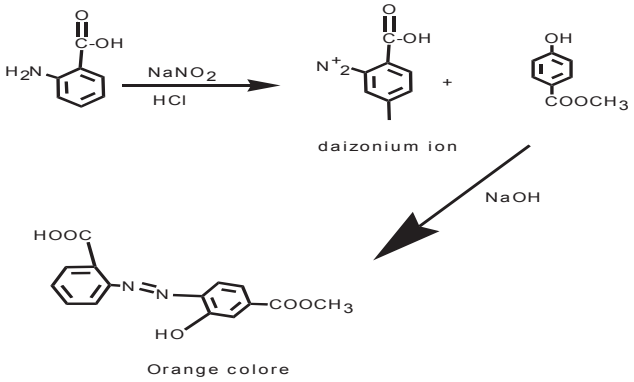


Figure 5
Probable Product Formation Pathway

The product formed was water soluble, the stability constant was calculated by comparing the absorbance of a solution containing stoicheiometric amount of Methyl paraben and ortho-aminobenzoic. The average conditional stability constant of the dye in water under the described experimental conditions was $4.85 \times 10^4\ M^{-2} \cdot L^2$.

4. PRECISION AND ACCURACY

Methyl paraben was determined at three different concentrations. The results are shown in Table 1. A satisfactory precision and accuracy could be obtained with the proposed method.

Table 1
Accuracy and Precision of the Proposed Method

Methyl paraben taken	Methyl paraben found	*Recovery% rec%	Average recovery% rec%	Relative standard deviation* RSD%
5	4.8	96.5	99	0.55
7	6.8	98.5		0.64
9	9.2	102		1.28

* Average of five determinations.

4.1 Analytical Application

Oral solution of drug containing methyl paraben has been analyzed and it gave good accuracy and precision, the results obtained were demonstrated in Table 2.

Table 2
Application of the Proposed Method and Pharmaceutical Preparations for Determination of Methyl Paraben Drug

Oral Solution	Methyl paraben ppm		Recovery% Rec%	* Average recovery% Rec%	Relative standard deviation* % RSD%
	Taken	Found			
	5	4.9	97.8		0.65±
[a]Ketofen Syrup	7	7.1	102.2	99.7	1.212±
	9	8.9	99.3		1.23±
	5	4.9	99		0.76±
[a]Cyprodien Syrup	7	6.8	98.4	98.7	0.85±
	9	8.8	98.8		1.28±

* Mean of three determinations.
[a] Marketed by S.D.I, Iraq.

4.2 Evaluate the Results of the Proposed Method

For the evaluating the results of the proposed method comparing with the standard method (Kebbekus & Mitra, 1998, pp.23-24) to determine the efficiency and success in the estimate Due to unavailable of the standard method in the British Pharmacopoeia, there for Standard addition method was used for determination of methyl paraben in Ketofen Syrup and. Cyprodien Syrup preparation The results shown in Figures 6-7 shows that the results of standard addition method agree well with the proposed method, indicating that the method is selective and free from interference.

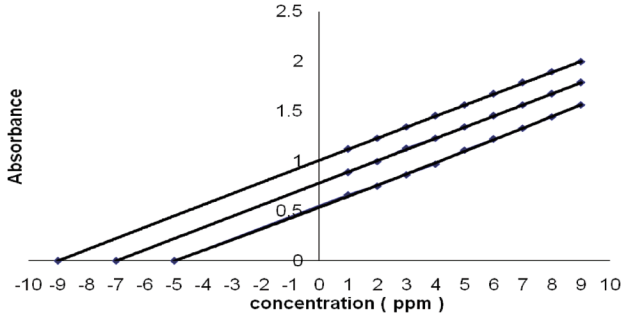


Figure 6
Standard Addition Method for Determination of Methyl Paraben in Ketofen Syrup

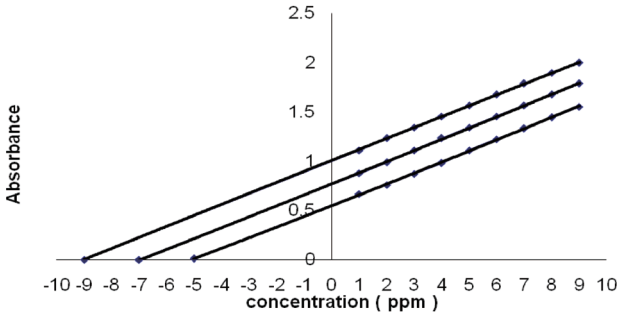


Figure 7
Standard Addition Method for Determination of Methyl Paraben in Cyprodien Syrup

The comparison sensitivity determination of Methyl paraben in the proposed method than other methods in literature as showed in Table 3.

Table 3
Comparison of Methyl Paraben Determination in the Proposed Method and Other Literature Methods

Analytical parameters	Present method	**Literature** (Blanco, Carretero, Peinado, & Guttierrez, 2000) **method**	**Literature** (Boonleang & Tanthana, 2010) **method**	**Literature** (Krishnachaitanya, Israel, & Gowrisankar, 2011) **method**	**Literature** (Dhahir & Hussein, 2012) **method**
Type of method	Azo coupling	fluorescence	HPLC	HPLC	Azo coupling
Reagent	Diazotized anthralic acid	Dansyl clouride	___	___	Diazotized ortho-aminobenzoic acid
λ_{max}	442	482	275	275	390
Colour of the dye	Orange	___	___	___	yellow
Beer's law range (ppm)	0.1-9	0.1-5	8-100	2-6	1-10
Molar Absorptivity ($l \cdot mol^{-1} \cdot cm^{-1}$)	1.6×10^{6}	___	___	___	$1.4x10^{5}$
pH	10.34	___	___	2.5	10.76
Temperature (^{o}C)	R.T	___	___	___	25
LOD (μg)	0.0065	0.001	___	___	0.0082
Recovery (%)	99	___	99.9	99.6	99
RSD (%)	>1	>3	>1.5	___	<1
Analytical application	Mouth wash	Oral solution	___	Cosmetic products	Lesterine antiseptic

CONCLUSION

The proposed methods were found to be simple, economical, selective and sensitive. The statistical parameters and recovery study data clearly indicate no interference. Hence, these methods could be considered for the determination of methyl paraben in the quality control laboratories

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