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Spectrophotometric Determination of Salbutamol and Meptazinol in Drug Formulations Using the Berthelot Reaction

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Abstract: A rapid and delicate spectrophotometric tactic was developed and associated with drug betrothal in pharmaceutical definitions for the audacity of a few phenolic enclosures (salbutamol or meptazinol). The way is based on oxidative coupling revulsion of these compromise with sulfapyridine and ethyl p-aminobenzoate in the person of potassium meta periodate as an oxidizing agent. The formed blue indophenol dyes have maximum absorptions at 670, 690, 630, and 650 nm for salbutamol with benzocaine (D1), salbutamol with sulfapyridine (D2), meptazinol with benzocaine (D3) and, meptazinol with sulfapyridine (D4), respectively. The spectrophotometric determination of these phenolic compounds using molar absorptivity are 2.969× 10^3, 5.848× 10^3, 2.724 × 10^3, and 2.172 x 10^3 L mol^{-1}. cm^{-1} for concentrations obeyed Beer's law in the ranges 2-20, 1-16, 2-14, and 1-12 µg ml^{-1} for the above compounds, respectively. The average recovery % was ranged between (99.45% - 100.51%) with a relative standard deviation ≤ 0.111 for all the studied compounds. The method is applied successfully to the assay of salbutamol and meptazinol.

Keywords: indophenols, phenolic compounds, Job's method, Beer's law, Berthelot reaction.

农场实地考察对学生实践管理咖啡行业废物的影响

摘要：一种快速而精细的分光光度计策略被开发出来，并与药物定义中的药物订婚相关联，用于一些酚类物质（沙丁胺醇或美普他嗪）的大胆。该方法是基于这些妥协与磺胺吡啶和对氨基苯甲酸乙酯在人偏高碘酸钾作为氧化剂的氧化偶联排斥。所形成的蓝色吲哚酚染料分别在 670、690、630 和 650 纳米 处对沙丁胺醇与苯佐卡因 (染料 1)、沙丁胺醇与磺胺吡啶 (染料 2)、美普嗪醇与苯佐卡因 (染料 3) 以及美普嗪醇与磺胺吡啶 (染料 4) 具有最大吸收。使用摩尔吸光度法测定这些酚类化合物的分光光度为 2.969×103、5.848×103、2.724×103 和 2.172×103 升摩尔$^{-1}$。对于上述化合物，厘米$^{-1}$ 的浓度分别在 2-20、1-16、2-14 和 1-12 µg ml-1 范围内符合比尔定律。所有研究化合物的平均回收率范围在 (99.45% - 100.51%) 之间，相对标准偏差 ≤ 0.111。该方法成功应用于沙丁胺醇和美菌素的测定。

关键词：吲哚酚、酚类化合物、乔布法、比尔定律、贝特洛 反应。

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1. Introduction

A significant number of studies have focused on the different biological effects of phenolic groups found in medicines. Several attempts have been made to associate this biological activity (antibacterial, analgesic, antipyretic, and fungicidal) with different physicochemical parameters to optimize and ultimately predict drug action, either metal complex stability or persistent ionization [1].

The good antioxidant potential of phenolic compounds should be demonstrated, taking into account their bioavailability and bio-efficacy. Therefore, in vivo experiments must be conducted to determine the antioxidant activities of phenolic compounds and extracts. In addition, in vivo studies have analyzed biological and physiological factors, including metabolic variations (ingestion, digestion, and absorption). In arrange to progress the well-being of individuals within the future, and the bioavailability of phenolic compounds that seem to influence the antioxidant control reaction is fundamental [2].

Several methods for the study of phenolic drugs [3] have been published, such as salbutamol, which is usually used to treat bronchospasm [4] and chronic obstructive pulmonary disease [5]. It is also one of the drugs used most commonly in emergency inhalers. Meptazinol is used for mild to the extreme pain, most widely used in obstetric (childbirth) pain treatment [6].

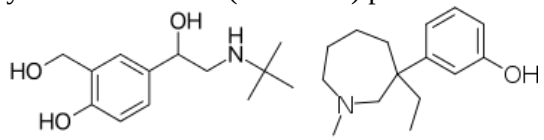


Fig. 1 Salbutamol and meptazinol

The Berthelot reaction (sometimes referred to as the indophenol reaction) is the name given to an ammonium ion and phenol reaction that results in the formation of an indophenol dye under sufficient oxidizing conditions. Indophenol dyes are heavily conjugated and, between 600 and 720 nm, absorb strongly [7]. The pharmaceutical formulations containing the phenolic moieties [8] can be analyzed using this tool. Many medications containing the phenolic part can be estimated using these methods. The methods mentioned in the research make it easier to estimate medicines in various forms of medicine.

This paper proposes basic, fast, delicate, and precise oxidative-coupling strategies for deciding salbutamol and meptazinol in pharmaceutical arrangement utilizing benzocaine and sulfapyridine. The strategy is based on our perception that these compounds create colored species with potassium meta periodate sulfapyridine and benzocaine beneath soluble conditions. The color concentration is specifically relative to the phenol concentration display within the test. Through the study results, we invite researchers in this field to use similar spectral methods to estimate the forms of the drug.

2. Experiment

A Shimadzu UV 2450 double-beam spectrophotometer was used with 1 cm of glass cells for spectral scans and absorption measurements.

2.1. Reagents

By dissolving 1.07 g of the potassium meta periodate analytical reagent (B.D.H. Chemicals) in 500 ml of distilled water, a 0.01 M potassium meta periodate solution was prepared.

2.2. Standard Stock Solutions

Salbutamol and meptazinol were prepared by dissolving 50 mg of each compound separately into 100 ml of distilled water or methanol (if the compound is insoluble in water). By diluting the stock solution with aliquots, lower concentration solutions (100 g ml^{-1}) were developed.

Amines like benzocaine (BZE 0.1%) and sulfapyridine (SFP 0.1%) were prepared separately in 100 ml of distilled water or methanol (if insoluble in water) by dissolving the necessary amount of each compound.

As previously reported, potassium hydrogen phthalate (pH 3.4), borate (pH 6.8), and glycine (pH 8.5) buffer solutions were prepared [9].

2.3. General Procedure

A 25 ml calibrated flask was filled with 15 ml of buffer solution, 2 ml of amines volumes of B.Z.E. or SFP, and a fixed amount of IO4- solutions, then 0.4-5.0 ml of the drugs solution was applied, and the mixture was diluted to the mark with distilled water. During the stability phase, the absorbance of the colored species formed was calculated at max against a reagent blank prepared in the same way. The amount of compound was deduced under similar conditions from a calibration graph prepared from standard solutions.

2.4. Procedure for the Determination of Phenolic Drugs in Pharmaceutical Preparations

The drug composition was diluted correctly with distilled water to bring the concentration of phenolic drugs to 100 μg ml-1, and the general assay protocol was followed. A calibration graph was used to measure the sum of medicines.

3. Results and Discussion

3.1. Optimum Reaction Condition

The influence of various reaction variables was tested to establish the optimum conditions for the proposed procedure and the most suitable values of the variables tested based on absorbance obtained in each case. The two phenolic drugs were used in all reactions.

3.2. The Volume and Type of Oxidizing Agent KIO_4

A series of dyes containing different volumes of reagent IO_4^- were prepared and ranged between (0.5 - 3.5ml) of the reagent with a concentration of (0.01M), and then the absorption was measured for each mixture of the series. Table 1 and Fig. 2 show the results of the effect of the volume of the reagent used on the dyes (D1-D4), where the optimum volume ranges for each reaction are kept, and the variation in the reagent volumes for each amine is noted, and this can be attributed to the nature of the compounds. Various oxidizing agents such as potassium hexacyanoferrate (III), potassium persulfate, ceric ammonium sulfate were tested instead of IO_4^- and found to be less effective [10].

Table 1 Effect of IO_4^- volume on dyes absorption intensity (reagent concentration 0.01 M)

Ml of 0.01M IO_4^-	Dyes	1	1.5	2	2.5	3	3.5
Absorbance	D1	0.125	0.182	0.437	0.533	0.794	0.731
	D2	0.335	0.496	0.499	0.472	0.465	0.402
	D3	0.270	0.555	0.628	0.702	0.614	0.567
	D4	0.261	0.239	0.265	0.245	0.235	0.227

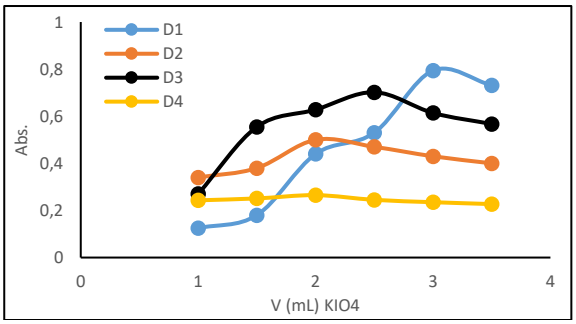


Fig. 2 Effect of volume of potassium meta periodate solution (KIO_4) on absorption spectra of dyes (D1-D4)

It was concluded from the results of the current study that the aromatic compounds containing one group O.H. oxidized by a suitable oxidizing agent to form ortho, meta, and para -benzoquinone, according to group sites O.H. The oxidation product is coupled with aromatic amines. That is due to the NH_2 donor group of electrons, which leads to the formation of indophenol dye [11].

3.3. Effect of B.Z.E. and SFP Concentration

The effect of changing the B.Z.E. and SFP concentration on the absorbance was studied. Table 2 shows that the absorbance increased with increasing B.Z.E. and SFP concentration and reached the maximum when using 2ml of 9 x 10^{-3} and 4 x 10^{-4} M (B.Z.E. and SFP). Therefore, this volume was used in all subsequent experiments.

Table 2 Effect of concentration of B.Z.E. and SFP on the absorption

Amine	Volume (mL)	Absorbance
B.Z.E. 9 x 10^{-3} M	0.5	0.722
	1	0.774
	1.5	0.769
	2	0.803
	2.5	0.755
SFP 4 x 10^{-4} M	0.5	0.362
	1	0.609
	1.5	0.750
	2	0.844
	2.5	0.701

3.4. Effect of Addition Order

In analytical chemistry experiments, including the oxidative coupling reaction, it is recognized that the addition sequence has a significant influence on the strength of the colors of the resulting compounds. Therefore, several experiments were carried out with a series of different additives. The best addition sequence, which gives the highest absorption strength of the resulting compounds, was chosen for all the studied reactions, as shown in Table 3.

To obtain optimum results, the addition of reagents should be followed as given under the recommended procedure. However, any delay in mixing phenolic drugs (R) + B.Z.E. or SFP (A) + IO_4^- agent (O) caused a considerable decrease in absorbance.

Table 3 Effect of order of addition on the absorption (→ = direction of addition, B= buffer; O=oxidizing agent; A= amine; R= reagent)

Order	D1	D2	D3	D4
→ R + O + A + B	0.589	0.379	0.263	0.133
→ R + A + O + B	0.588	0.388	0.277	0.134
→ A + R + O + B	0.672	0.413	0.455	0.189
→ B + A + O + R	0.790	0.530	0.687	0.288

3.5. Stabilization Time

Previous studies have proven the time effect of the oxidative coupling reaction on the absorption of the resulting dye under ideal conditions at time intervals ranging from (5-120) minutes by a normal reality every five minutes. This study discovered that all of the dyes produced require a period ranging from (25-35) minutes to achieve stable absorption values and maximum absorption strength. The absorbance values remain stable for up to about 90 min. After that, the absorption begins to decline. Therefore, studies can be conducted for such type of reactions easily, and Fig. 3 demonstrates this.

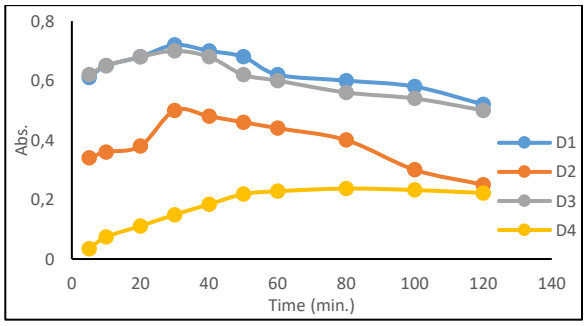


Fig. 3 The settling time for dyes (D1-D4) resulting from the oxidative coupling reaction at the highest wavelengths

3.6. Effect of Medium Reaction

To determine the appropriate medium for this type of coupling reaction, the absorbance of the dye solutions formed at the maximum wavelengths was measured by change pH.

The results shown in Fig. 4 and Table 4 indicated that the basic function corresponding to this coupling and with a lower acid function was observed a decrease in absorption, which indicated the incomplete coupling reaction [12], and by exceeding this value, the appearance of a precipitate and instability of absorption was observed.

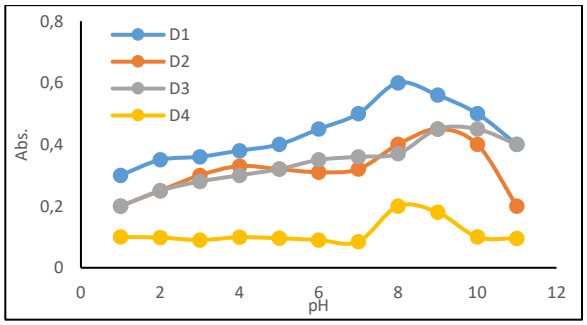


Fig. 4 Absorbance changing by pH effect for indophenol dyes (D1-D4)

After determining the best conditions for each of the oxidative coupling reactions of the studied compounds, a spectroscopic scan of the products was performed in the UV-Visible regions of the spectrum within the range (300-700 nm) against the blank solution, which contains all the components of the reaction except the drugs under study. Also, the absorbance of the blank solution within the same range of wavelengths was measured against distilled water as a reference (Fig. 5). It is noticed through the figure that the blank solution does not have maximum wavelength as it is colorless. Therefore the colors shown are due to the dissolved dyes resulting from the oxidative coupling reaction between the amine and the drugs.

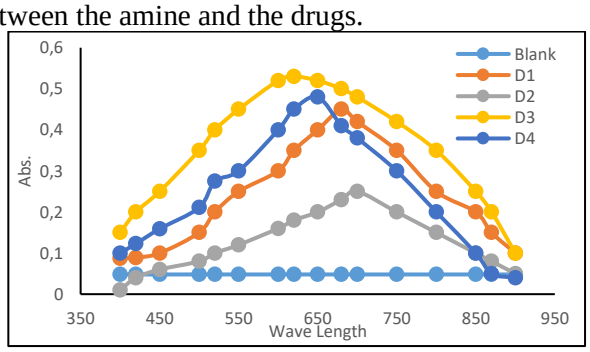


Fig. 5 The absorption spectra of the indophenol dyes and blank

Fig. 5 shows the dyes' characteristic maximum wavelengths, while phenolic compounds or oxidation of B.Z.E. or SFP display no absorbance in these areas. Table 1 displays the Beer's law limits, detection limits (DL), molar absorptivity, and Sandal's sensitivity values (4). Optimum conditions, such as pH adjustment and B.Z.E. or P.S.F. and IO4 concentrations, are important for achieving optimum absorption and color stability using control experiments. These conditions are included in Table 4.

3.7. The Absorption Spectrum of Resulting Dyes

Table 4 Experimental conditions

Comp.	Reagent	λ_{max} (nm)	pH	Stability (min)	ε ($mol^{-1}.L\ cm^{-1}$) x 10^3	Beers law ($\mu g.\ ml^{-1}$)	Sandal's index ($\mu g,cm^{-2}$)	Correlation coefficient	DL $\mu g.ml^{-1}$
D1	BZE-IO_4^-	670	8.6	17-88	2.969	2-20	0.05662	0.9381	0.083
D2	SFP-IO_4^-	690	8.8	20-120	5.848	1-16	0.02875	0.9627	0.045
D3	BZE-IO_4^-	630	9	15-60	2.724	2-14	0.06122	0.9933	0.061
D4	SFP-IO_4^-	650	9.3	20-90	2.172	1-12	0.04877	0.9976	0.075

3.8. Beer's Law and Sensitivity of the Method

The applicability of Beer's law [13] to the dye solutions was studied after fixing all the best experimental conditions. A series of solutions were prepared for each reaction containing increasing volumes ranging from (0.1-6 ml) of the drug solution at a concentration of 100 $\mu g.ml^{-1}$. Then they were treated with the reagent, oxidizing agent, and buffer solution according to the fixed concentrations and volumes when studying the best conditions for each oxidative coupling reaction under study. All volumes were completed to the point of the mark with distilled water, and the absorption of these solutions was measured against the blank solution at the maximum wavelengths of the resulting dye; Fig. 6 shows the calibration curves of the dyes, from which analytical standards were calculated for each coupling reaction.

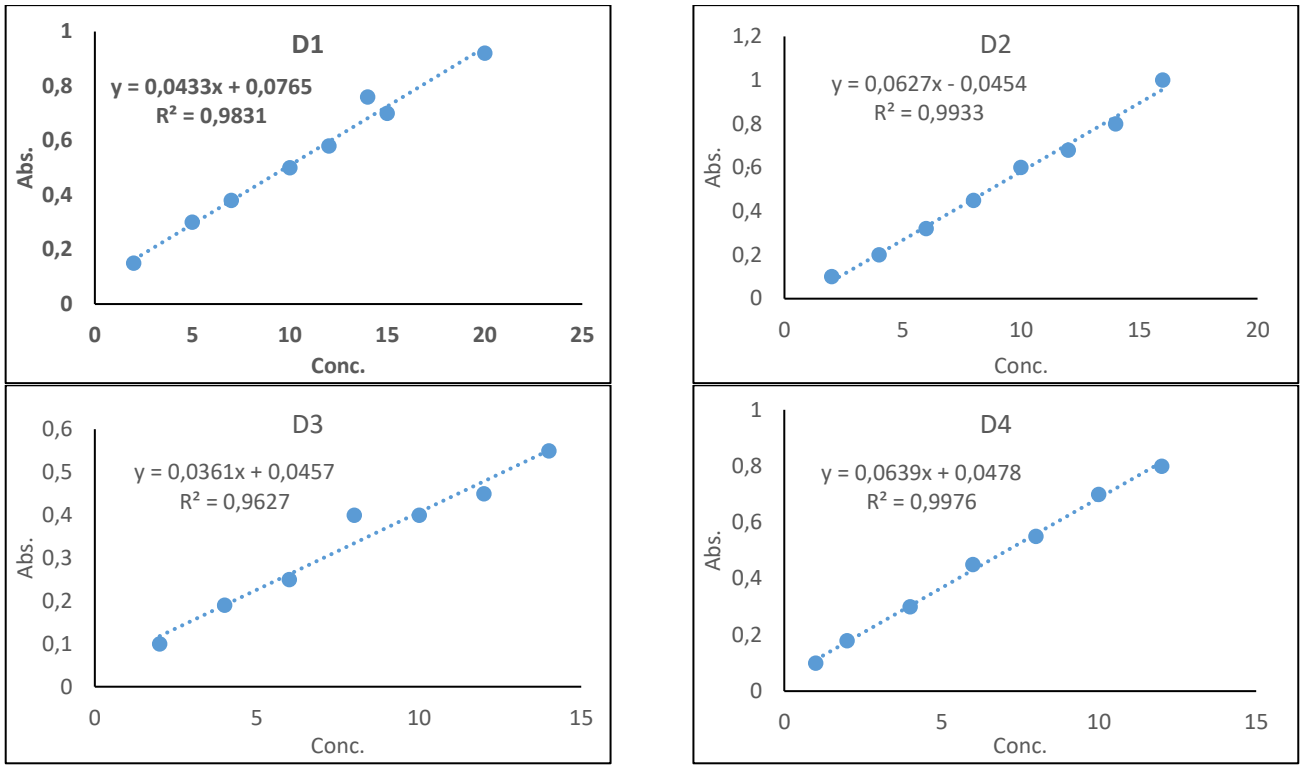


Fig. 6 The calibration curves of the dyes

3.9. Accuracy and Precision

According to the results of molar absorptivity and Sandal's sensitivity, we conclude that this method has a high sensitivity for studying the dye composition using the reagent-potassium meta periodate and can be used to estimate these drugs.

The quality of the methods proposed was studied by assessing the absorbance in each instance of six replicates containing 100 µg of the phenolic compound. Table 5 displays the standard error, relative standard deviation, and error range (95% confidence limit).

Table 5 The results obtained for the analysis of salbutamol and meptazinol formulations

Phenolic compound	Present ppm	Found ppm	% R.S.D.	% Recovery	% Error
D1	10	9.945	0.111	99.45	-0.55
D2	10	10.027	0.105	100.27	0.27
D3	10	10.03	0.126	100.3	0.3
D4	6	6.031	0.108	100.51	0.516

3.10. The Nature of Reaction Product

Job's method [14] was used to identify the nature of the dyes resulting from the oxidative coupling reactions under study. The method included increasing volumes (0-5ml) of the reagent at a concentration of ($1x10^{-4}$ M) to the competing volumes of amines with the same concentration. The total volume of the reagent and the amine is (5ml) with the addition of the oxidizing agent and the buffer, and then complete the volume to (25ml) distilled water under the same best conditions. The absorption at the greatest wavelength was measured for each reaction against the blank solution. The method showed that the ratio of the reagent used with all the studied amines is (1:1) (A:R), as shown in Fig. 7.

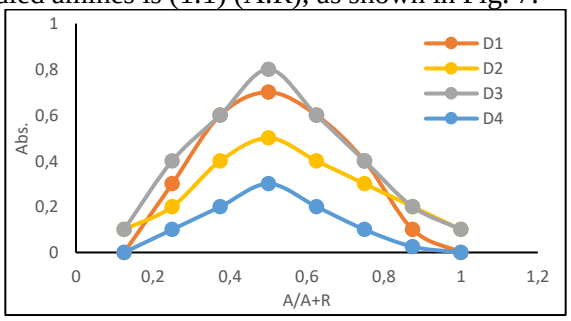
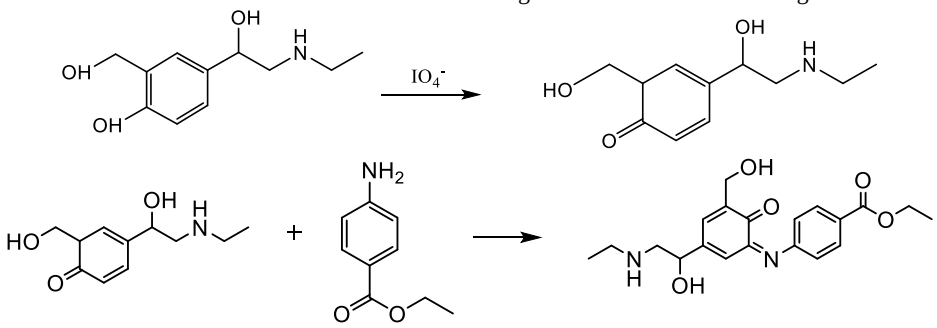


Fig. 7 Mole ratio for amine-reagent solutions at optimum conditions



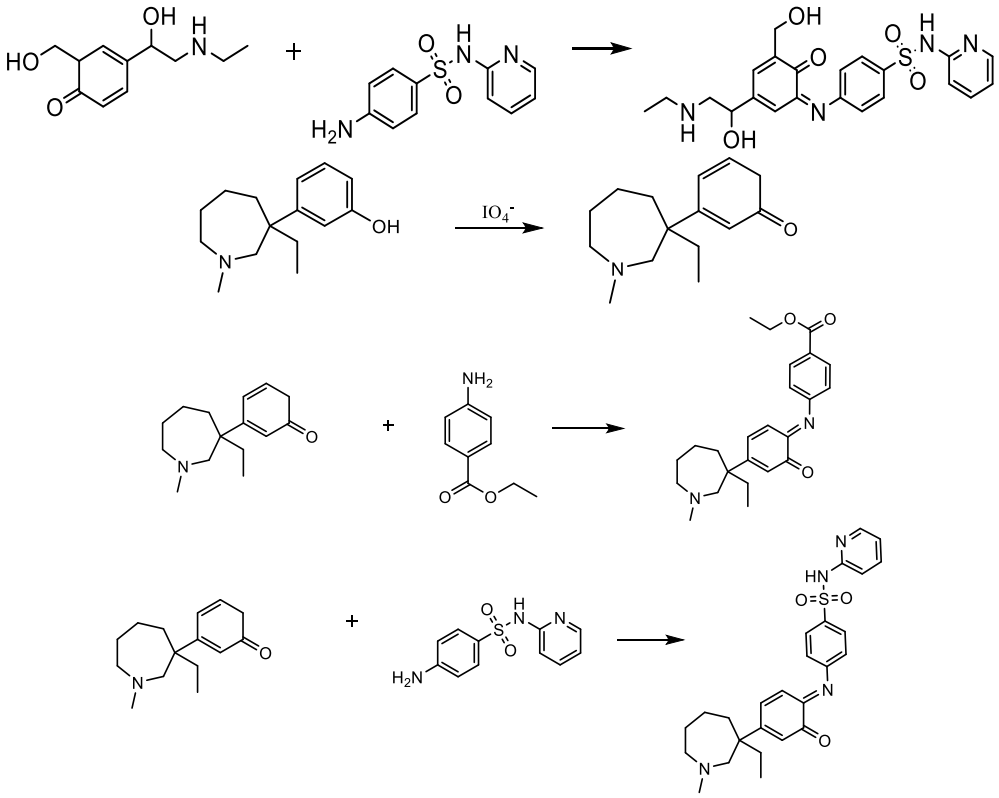


Fig. 8 Coupling reaction between phenolic compounds and amines

3.11. Interference

It is important to study the effect of some negative and positive ions and some excipients (additives) that can interfere and affect the absorption values of colored compounds resulting from the reaction of oxidative coupling of studied drugs. So, according to the selectivity of this method, it may be applying in routine analyzes to various samples, including pharmaceutical preparations [14].

The pure form of additives was added to the studied solutions with a concentration of ten times the concentration of the studied drugs by using the standard method of calibration curves. The solutions containing 10 mg/ml of salbutamol or meptazinol and various amounts of diverse species in a final volume of 10 ml, using the standard method followed in the calibration curve. The results indicated that the effect of additives is considered acceptable if the error rate does not exceed (± 2%) compared to measurements when there are no interferers. Typical results are given in Tables (6 and 7). Through the values of (Error %) and (Recovery %), there is no effect of such additives. The value in the table is an average of three readings.

Table 6 The effect of interferences on the absorption of D1 at 10 ppm

Interferences	Recovery%	Error%	Conc. of (ppm) D1
Lactose	100.11	0.11	10.011
Starch	99.76	- 0.24	9.979
Sucrose	99.93	- 0.07	9.993
Mannitol	99.81	- 0.19	9.981
Magnesium stearate	100.12	- 0.12	10.012
Titanium dioxide	99.78	-0.22	9.978
Benzoic acid	99.86	- 0.14	9.986
Ag^+	99.94	- 0.06	9.994
K^+	100.2	-0.2	10.020
Al^{3+}	99.79	-0.21	9.979
Cl^-	100.15	0.15	10.015

Table 7 The effect of interferences on the absorption of D3 at 10 ppm

Interferences	Recovery%	Error%	Conc. of (ppm) D1
Lactose	100.09	0.09	10.009
Starch	99.69	- 0.31	9.969
Sucrose	99.79	- 0.12	9.979
Mannitol	100.17	0.17	10.017
Magnesium stearate	99.89	- 0.11	9.989
Titanium dioxide	99.96	-0.04	9.996
Benzoic acid	100.18	0.18	10.018
Ag^+	99.81	-0.19	9.981
K^+	99.85	-0.15	9.985
Al^{3+}	99.67	-0.33	9.967
Cl^-	100.21	0.21	10.021

3.12. Analysis of Drugs in Pharmaceutical Formulations

The proposed method has been applied to quantify drugs in dosage forms obtained from the local market. Using a mortar and pestle, twenty tablets of each drug were weighed and powdered finely. For injection, one ml of Meptid (100mg/ml) solution was combined. In a 100mL volumetric flask, a quantity of each substance equal to 10 mg was transferred. The mixture was

mechanically stirred for 5 minutes in a small amount of water, sonicated in an ultrasonic wash, diluted to volume with water, blended, and filtered. The sufficient filtrate aliquot covering the working concentration range referred to in the general procedure was transferred to 10 mL of volumetric flasks. The powders for S.B.M. and M.P.Z. tablets were treated with 1 mL of 1.0 mol L^{-1} HCl before being subjected to the extraction steps mentioned above. The drug quantity in the formulation was evaluated according to the protocol mentioned above. Table 8 shows the role of excipients in the formulations for the assay of two phenolic drugs.

Table 8 Effect of excipients for assay of salbutamol and meptazinol

Preparations containing (S.F.D.)	Conc. of S.F.D. (µg/ml)		% Error	% Recovery	% R.S.D.
	Present	Found			
Butalin 2mg tablet, Julphar company	10	9.992	-0.08	99.92	0.178
Ventolin 2mg tablet, gsk company	10	9.988	-0.12	99.88	0.212
Meptid 100mg/ml Solution for injection (as hydrochloride) Company: Almirall Limited, UK	10	10.012	0.12	100.12	0.183
Meptid 200mg Film-Coated Tablets, meptazinol (as hydrochloride) Company: Almirall Limited, U.K.	10	10.03	0.3	100.3	0.126

4. Conclusion

The proposed methods offer simple, accurate, economical procedures and spectral analyses to estimate trace amounts of salbutamol and meptazinol, based on oxidative coupling reaction with the reagents Benzocaine (BZE 0.1%), and Sulfapyridine (SFP) and the oxidizing agent potassium meta periodate. Using these methods in routine drug estimation in pure and dosage forms justifies the optical parameters and statistical comparison. This method may apply to the blood and urine samples containing the same drugs. According to the structural factor, the limitation of the results indicates the presence of phenolic groups in the drugs that had para or ortho open positions in an aromatic ring.

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