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التقدير الطيفي للاوكسيميتازولين هيدروكلوريد بشكله الحر وفي مستحضراته الصيدلانية باستخدام تفاعلات الأزوتة والاقتران

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الخلاصة

يشمل هذا البحث اقتراح طريقة طيفية دقيقة وبسيطة لتقديرالاوكسيميتازولين هيدروكلوريد في المحلول المائي تعتمد الطريقة على تفاعل الاوكسيميتازولين هيدروكلوريد مع الكاشف المؤزوت حامض السلفانيلك بوجود هيدروكسيد الصوديوم، لتكوين صبغة آزوية برتقالية ذائبة في الماء ومستقرة وتعطي أعلى امتصاص عند الطول الموجي 496 نانوميتر. كانت حدود قانون بير في مدى 20 – 400 مايكروغرام اوكسيميتازولين في حجم نهائي 25 مللتر(0.8–16جزء/ مليون)، وكان معامل الامتصاص المولاري 2.30×10^4 لتر. مول$^{-1}$. سم$^{-1}$, الخطأ النسبي بين 0.28– و0.97 + %، والانحراف القياسي النسبي في مدى0.27 ± الى 1.57± % اعتماداً على مستوى التركيز. وتم تطبيق الطريقة بنجاح في تقدير الاوكسيميتازولين في مستحضرين دوائيين.

الكلمات المفتاحية: التقدير الطيفي ، الأزوتة والاقتران ، الاوكسيميتازولين هيدروكلوريد ، حامض السلفانيلك.

Spectrophotometric Determination of Oxymetazoline Hydrochloride in Pure and Pharmaceutical Preparations Using Diazo-coupling Reaction

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ABSTRACT

A ccurate and simple spectrophotometric method has been suggested for the determination of oxymetazoline hydrochloride (OMCl) in aqueous solution is developed. The present process included coupling of OMCl with diazotized sulphanilic acid reagent in the presence of sodium hydroxide. The orange colored azo dye formed very stable and soluble in water gives maximum absorption at 496 nm. The lineratey is obeyed over the range 20 – 400 µg / 25 ml (0.8 –16µg.ml^{-1}) the molar absorptivity is equate to 2.30×10^4 l.mol^{-1}cm^{-1}. The proposed method has been used to the determination of OMCl in two formulations with satisfactories results.

Keywords: Spectrophotometric determination , Diazotization , Oxymetazoline hydrochloride, Sulphanilic acid.

Introduction

The hydrochloride salt of oxymetazoline is 3- [(4,5-dihydro-1H-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)-2,4-dimethyl-phenol hydrochloride(OMCl) [1], it is a sympathomimetic agent with marked α- adrenergic activity has been introduced in some nasal solutions [2]. OMCl is applied to treat epistaxis and eye redness according to minor irritation [3,4].

The large doses of OMCl may cause hypotension, presumably because of a central clonidine-like effect[5].

Various procedures have been illusterated in litreture for the determind is: tittrimetric method[6], ion selective membrane electrode[7], chromatography[8-10] and flow injection[11]. Also, spectroscopy techniques have been used for determination of OMCl as pure and in various formulations different reagents such as 2,6-dichloroquinone-chlorimide[12] 2,4,6-tris(2-pyridyl)-5-triazine[13], 1,10-phenanthroline[14], 3,5-dinitrosalicylic acid [15], and 4-aminoantipyrine [16].

Our aim is to evaluate a simple spectrophotometric method for the determination of OMCl as pure and in pharmaceutical drop formulations included coupling with diazotised sulphanilic acid in an alkaline medium of NaOH . The product of orange azo dye formed proves to be intense, water– soluble and stable.

Materials and Methods

Apparatus

Shimadzu UV-Vis.Recording spectrophotometric had been used in measurement of absorbance using 1-cm silica cells.

Reagents

chemical and solvents are chosed with high purity.

Working OMCl solution, 100 μg / ml. A 0.01g of OMCl is dissolved in distilled water and then volume is completed to 100 ml in a calibrated flask.

Diazotised sulphanilic acid reagent solution, 30mM. A 0.5190 g of sulphanilic acid is dissolved 75 ml of distilled water and the mixture is heated until the clear solution is obtained, then 1 ml of hydrochloric acid (conc.) is added, the mixture is left in ice bath at 0 - 5°C and 0.207g sodium nitrite is added and stirred vigorously and then the volume completed to 100 ml in a volumetric flask using cooled distilled water, and is stored in refrigerator. This solution is prepared freshly each day [17].

Alkaline solution of NaOH(1N),is prepared byThis solution is prepared by appropriate dilution of the concentrated (Fluka) solution with distilled in a plastic container.

Nazodrin drops, (100μg /ml). Three containers of drug (each contains 10 ml of 0.05% OMCl) are mixed, then 20 ml of the above solution was diluted with distilled water to 100 ml in a volumetric flask to prepare a solution of 100 μg /ml OMCl.

Oxymet drops, (100μg/ml). Provided from the Pharaonia pharmaceuticals. Three containers of drug (each contains 15 ml of 0.025% OMCl) are mixed, then 40 ml of the above prepared solution was diluted to 100 ml by adding distilled water in a volumetric flask .

Procedure and calibration graph.

To a series of 25 ml volumetric flasks add 20 – 500 μg (0.8 – 20 ppm) of OMCl, 0.5 ml of diazotised sulphanilic acid (30mM) and 1ml of 1N NaOH are then added and the volumes are diluted to the mark using distilled water as a slovent. After 10 minutes the A are read virsus a reagent blank at 496 nm using 1-cm cell. The linearity is over the range 20 to 400 μg/25ml (0.8–16 ppm) (Fig.1). The molar absorptivity is found to be 2.30×10^4 $l.mol^{-1}.cm^{-1}$

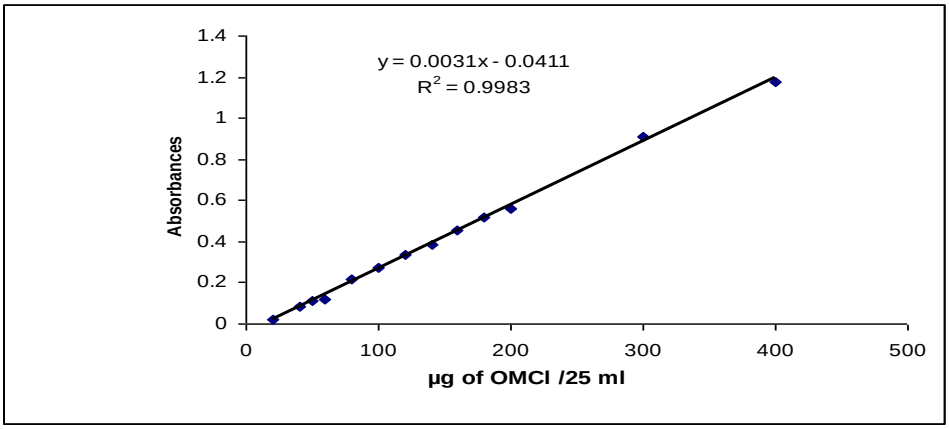

Fig.1. Calibration curve of OMCl determination

Results and Discussion

A 100μg of OMCl has been taken and final volumes are brought to 25 ml with distilled water in subsequent experiment

Absorption spectra.

When OMCl in aqueous solution is treated with diazotized sulphanilic acid reagent solution, an absorption peak is obtained showing an intense orange dye with maximum absorption at 496 nm. The reagent blank shows no absorption at this wavelength (Fig.2).

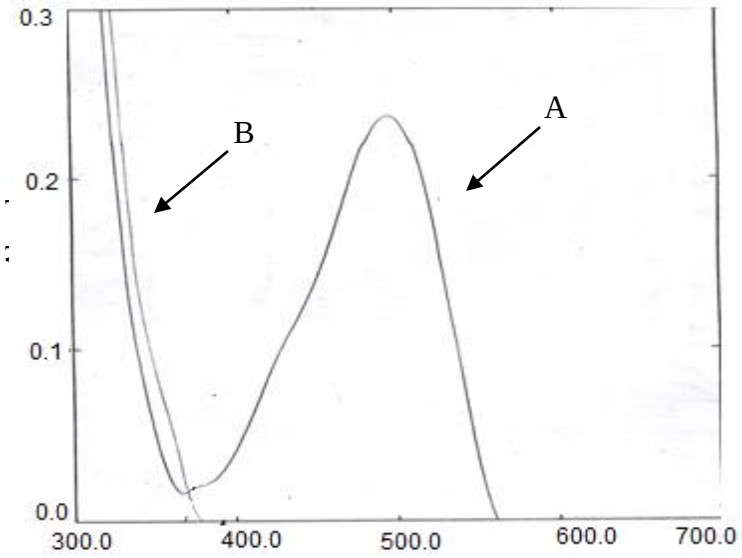

Fig.2:Absorption spectrum of OMCl with diazotized sulphanilic acid at 496 nm (A) the azo dye against blank, (B) blank against distilled water

Study of the optimum reaction conditions. All parameters effecting and related to orange azo dye have been optimized .

Effect of base. The preliminary experiments have shown that the azo dye develops only completely in using base solution . Different amounts of bases (strong and weak) have been used (Table1).

Table 1. Effect of base on the A and color contrast

Alkaline solution (1N)	Variable	A / ml of various base used						
		0.1	**0.3**	**0.5**	**0.7**	**1**	**1.2**	**1.5**
NaOH	A	0.283	0.271	0.259	0.247	0.263	0.199	0.161
	*Δλ, nm	112	113	198	202	202	202	202
KOH	A	0.119	0.127	0.137	0.162	0.206	0.166	0.163
	Δλ, nm	114	114	192	192	196	198	198
Na_2CO_3	A	No color contrast						
	Δλ, nm							
$NaHCO_3$	A	No color contrast						
	Δλ, nm							

*$\Delta\lambda = \lambda_{max}S - \lambda_{max}B$ where S=The azo dye and B= The Blank

The results in Table 1 indicated that 1ml of 1N sodium hydroxide is the more suitable amount which gives a high values of colour contrast.

Effect of diazotized sulphanilic acid reagent amount.

Various volumes of the diazotized sulphanilic acid (30mM) are tested, the results indicate that using 0.5 ml of diazotized sulphanilic acid reagent solution gives maximum A of the complex at 496 nm and the volume is considered as an optimum value (Table 2).

Table 2. The optimize amount of diazotised sulphanilic acid

Ml of diazotised sulphanilic acid reagent solution (30 mM)	Absorbance
0.05	0.144
0.1	0.231
0.25	0.242
0.5	0.272
1.0	0.266
1.5	0.215
2.0	0.122

Effect of surfactant

Three orders by using 1 ml of various types of surfactants have been studied. The effects of different surfactants on the colour intensity are showed that no useful effect and a loss in colour intensity are observed. Therefore, it has been recommended to eliminate the use of surfactants in the subsequent experiments (Table3).

Table 3. Effect of surfactants

Surfactant used	A* / order** of addition					
	I		II		III	
	A	***$\Delta\lambda$	A	$\Delta\lambda$	A	$\Delta\lambda$
CTAB, 1×10^{-3}M	0.075	204	0.080	202	0.098	204
SDS, 1×10^{-3}M	0.258	198	0.269	200	0.262	198
Triton X-100, 1%	0.181	206	0.176	206	0.210	208

* Absorbance without surfactant = 0.273

** I. OMCl (O) + Surfactant (S) + Diazotised sulphanilic acid (R) + NaOH (OH)
II. O + R + S + OH
III. O + R + OH + S

***$\Delta\lambda = \lambda_{max}$ S - λ_{max} B

Stability of formed azo dye

The color development showed that the colour started to form within about five minutes. The formation of azo dye being complete after 15 minutes and the absorbance of the coloured species remained constant for at least 25 minutes, this stability period is sufficient for several measurements (Table4).

Table 4. Effect of time and OMCl amount on A

µg of OMCl present	Absorbance / minute standing time								
	5	10	15	20	25	30	40	50	60
50	0.129	0.187	0.211	0.211	0.207	0.203	0.197	0.178	0.168
100	0.249	0.277	0.307	0.309	0.311	0.310	0.299	0.276	0.255

Accuracy and precision

In order to check the accuracy and precision of the proposed method three various amountes of OMCl where taken and determined. The results illustrated in tables show that suggested method gave satisfactory.

Table 5. Accuracy and precision of the method

Amount of OMCl taken, µg/25ml	Relative error, %*	Relative standard deviation, %*
40	+0.97	±1.57
100	+0.21	±0.32
200	-0.28	±0.27

*Average of 5 determinations.

Nature of the dye.

Job's method indicated that the azo dye has a composition of 1:1 OMCl to diazotized sulphanilic acid [R](Fig.3).

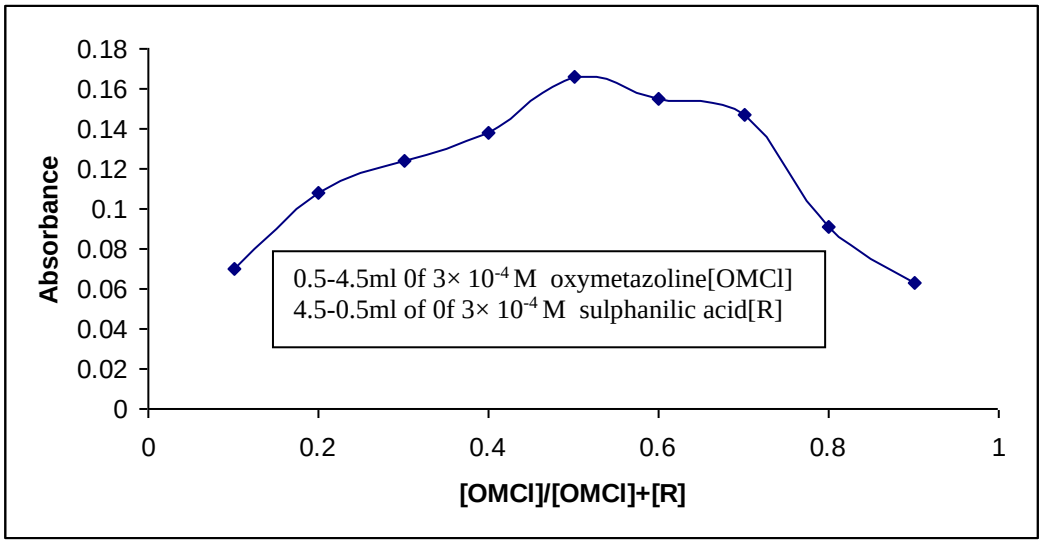

Fig. 3: Job's plot for OMCl – sulphanilic acid

Hence the dye might be the following structure.

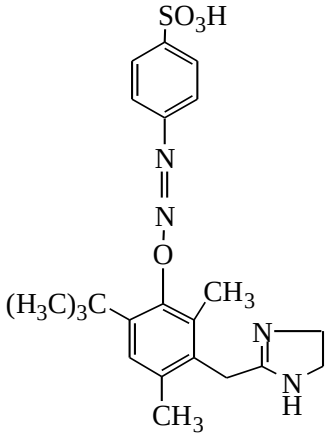

Fig. 5: The possible structure of the orange azo dye

Interference

The excipients which frequently accompany pharmaceutical formulation are studied by adding three various amounts (100, 500 and 1000µg) to 100µg OMCl (Table 6).

Table 6. Effect of foreign compounds for assay of OMCl

Foreign compound	Recovery (%) of 100µg OMCl per µg foreign compound added in 25 ml		
	100	**500**	**1000**
Glucose	105.5	98.5	96.2
Lactose	99.2	95.1	99.6
Starch	98.8	102.9	101.1
Gum Arabic (Acacia)	102.9	105.5	102.6

Table 6 with its results indicated that there is no interference of any excipients added to the determination of OMCl using the suggested procedure.

Applications part

The formulations of OMCl as nasal drops have been selected in our applications part. Good recoveries are obtained (Table 7).

Table7. Result of applications part.

Drug	µg OMCl present/25ml	µg OMCl measured/25ml	Recovery, %
Nazordin 0.05% S.D.I-Iraq	50	52.2	104.5
	100	104.4	104.4
	200	195.3	97.6
Oxymet 0.025% Pharaonia(Egypt)	50	49.5	99.0
	100	105.2	105.2
	200	204.7	102.3

*Average of three determinations.

Evaluation of the proposed method

In order to prove that the suggested method can be applied to the determination of OMCl in formulations without interferences, a standard addition method is applied.

The results in Fig.6 and Table 8 shows that there is no significant different between the amounts taken and experimental results.

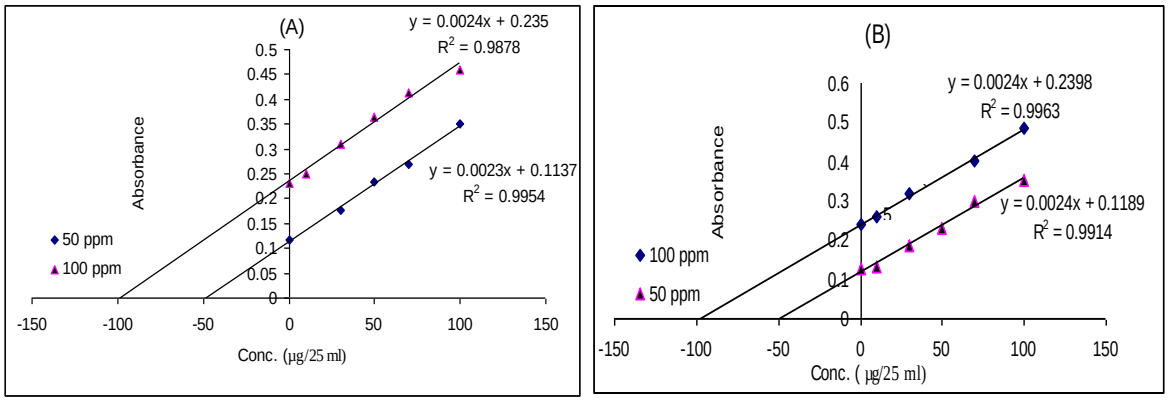

Fig. 6: Calibration standard addition graphs for the determination of OMCl in Nazordin [A] and Oxymet [B]

Table 8. The results of standard addition method

Drug	µg OMCl present/25ml	µg OMCl measured/25ml	Recovery, %
Nazordin 0.05% S.D.I-Iraq	50	49.4	98.8
	100	97.9	97.9
Oxymet 0.025% Pharaonia(Egypt)	50	49.5	99.0
	100	99.9	99.9

* Average of three determinations

Varible Comparison

` The various analytical parameters for our method and the same parameters for other literature methods(14,16) have been calculated and illustrated in Table 9.

Table 9. Comparison of the methods

Anal. Parameters	Present method	Lit. method[16]	Lit. method[14]
pH	11.73	…	…
Temperature (C°)	At room temperature	70	70
$\lambda_{max\ (nm)}$	496	480	510
Medium of reaction	Aqueous	Aqueous	Aqueous
Type of reaction	Diazo coupling	Oxidative coupling	Redox reactions
Reagent	Diazotised sulphanilic acid	4-Amino- antipyrine	1,10-phenathroline
Beer's law range (ppm)	0.8-16	1-20	0.1-7
Molar absorptivity ($l.mol^{-1}.cm^{-1}$)	2.03×10^4	5.34×10^4	5.74×10^4
Nature of the dye	1:1	1:2	1:1
Application of the method	Nazordin 0.05% Oxymet 0.025%	Nazordin 0.05% Oxymet 0.025%	Nazordin 0.05% Oxymet 0.025%

Conclusion

The proposed method is simple, sensitive and there is no previous separation or temperature controlled. The method has been successfully applied to the determination of OMCl in various pharmaceutical preparations.

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