Spectrophotometric method for Determination of oxymetazoline, HCl in a Pharmaceutical formulation using 2,4 - dinitrophenylhydrazine

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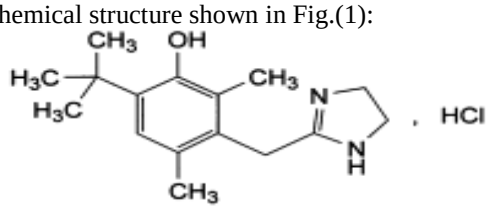
Abstract

Rapid, sensitive and simple spectrophotometric method for the determination of oxymetazoline hydrochloride (OXMZ) is developed. The method is based on an oxidative coupling reaction with 2,4-dinitrophenylhydrazine (2,4-DNPH) in a basic medium (pH 11.2) in the presence of potassium periodate to produce a green colour, soluble in water , stable product and absorbs at 607 nm. Beer's law was in the linear range 2.5-30 µg/ml of OXMZ, the molar absorptivity , Sandell's sensitivity index and detection limit were 7242 liter. $mol^{-1}.cm^{-1}$, 0.0409 $\mu g.cm^{-2}$ and 0.1877 µg/ml respectively. The RSD value was 1.24- 1.39% depending on the concentration. This method was applied successfully to the determination of oxymetazoline in pharmaceutical preparation nazordin drops with recovery of not less than 99.87 % .

Keywords: spectrophotometric, OXMZ, 2,4-DNPH reagent.

Introduction

The scientific name for the oxymetazoline hydrochloride (OXMZ) is[(1)]:
3-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)- 2,4-dimethylphenol hydrochloride. Its chemical structure shown in Fig.(1):



$C_{16}H_{24}N_2O$,HCl
M.Wt = 296.8g/mol

Fig.(1):Chemical structure for Oxymetazoline hydrochloride

Oxymetazoline hydrochloride(OXMZ), is a white or almost white crystalline powder, freely soluble in water and in alcohol[(1)]. It is used to remove the congestion of the mucosa of the nose and pharynx neighboring areas, sinus infections, colds, fever, allergies.[(2)]

Different analytical methods have been used for the determination of OXMZ, such as spectrophotometric methods[(3-7)], high performance liquid chromatographic methods HPLC[(8-16)], electrochemical method[(17-20)] and flow-injection techniques[(21-22)]. In this research a rapid, sensitive and simple spectrophotometric method for determining of OXMZ in pure form as well as in pharmaceutical drops formulations based on the oxidative coupling using 2,4-dinitrophenylhydrazine (2,4-DNPH) in presence of potassium periodate in basic medium.

Experimental

Apparatus

Spectrophotometric measurements have been performed using shimadzu UV-Visible spectrophotometer UV-160, ultrasonic with water bath, UNISONICS, Jenway pH meter 3310, sartorius BL210 S AG and hot plate with magnetic stirrer (BIOSAN MSH 300).

Reagents and chemicals used

All chemicals and analytical reagents used in this research are of high purity.

Preparation of solutions

1-Standard OXMZ solution,250 µg/ml^{-1}

This solution is prepared by dissolving 0.025 g of OXMZ in amount of distilled water and the volume is diluted to 100 ml with distilled water in a volumetric flask.

2- 2,4-dinitro phenylhydrazine reagent solution (1×10^{-2}M)

This solution is prepared by dissolving 0.1981g of 2,4- DNPH in 5 ml of cconcentrated sulphuric acid and the volume is completed to 100 ml in a volumetric flask with distilled water.

3-Potassium periodate solution (1×10^{-2}M)

A 0.1150g of potassium periodate is dissolved in amount of distilled water and the volume is completed to 100 ml in a volumetric flask with distilled water.

4-Sodium hydroxide solution (1.0 M)

This solution is prepared by dissolving 4.000 g of pure sodium hydroxide in100 ml of distilled water.

5-Interference solutions 1000 µg / ml

A 0.1000 g of each foreign compounds is dissolved in distilled water then the volume is completed to 100 ml in a volumetric flask with distilled water.

6-Solution of OXMZ drops formulation (250 µg/ml)

Pharmaceutical formulation of nazordin (production of general company of pharmaceutical industry and medical supplies - Ninawa - Iraq) , 10 ml drop contain 0.05% of oxymetazoline and the solution is prepared as follows: 50 ml of this formulation are transferred to volumetric flask and the volume has been completed to 100 ml with distilled water to obtain a solution with a concentration of 250 µg/ml.

Preliminary Investigations

A 1 ml of 2,4- DNPH reagent is added to 1 ml of standard OXMZ solution in the precence of 1 ml of potassium periodate solution in basic medium using 1

ml of 1.0 M sodium hydroxide then diluted with distilled water in a 25 ml volumetric flask, a green color product. Absorption spectrum of the colored dye against its corresponding blank reagents shows maximum absorption at 607 nm in contrast to blank reagent which shows no absorbance at this wavelength.

Optimization of the experimental conditions

The effect of various variables on the color intensity of 1ml of standard OXMZ solution(250µg/ml) ,1ml of (2,4-DNPH) and 1ml of KIO_4 in alkaline medium (1ml,1.0M NaOH) was studied to establish the optimum conditions.

Selection of the coupling reagent

Different types of coupling reagents are investigated to select the best reagent that gives the highest color intensity, the results are shown in Table(1).

Table (1) Selection of the coupling reagent.

Reagent (1×10^{-2}M)		**Color**	**λ_{max} ,nm**	**λΔ nm**	**Abs.**
2,4-Dinitro phenylhydrazine	**SB**	**Green**	**607**		**0.273**
	BW	**Colourless**	**362**		**1.784**
	BW*	**------**	**607**	**245**	**0.000**
4-Amino antipyrine	SB	Yellow	357		0.064
	BW	Colourless	251		2.126
	BW*	------	357	106	0.000
P-bromoaniline	SB	Yellow	369		0.072
	BW	Yellow	331		2.337
	BW*	------	369	38	0.000
N-(Naphthyl) ethylene diamine dihydrochloride	SB	Brown	468		0.038
	BW	Yellow	354		1.968
	BW*	------	468	114	0.000
P-Amino phenol	SB	Yellow	379		0.165
	BW	Colourless	269		2.126
	BW*	------	379	110	0.000
Sulphanilamide	SB	Colourless	308		0.096
	BW	Colourless	250		2.182
	BW*	------	308	58	0.000

SB : Absorption spectrum of OXMZ solution versus reagent blank.
BW: Absorption of reagent blank versus distilled water.
BW*: Absorption of reagent blank at λ_{max} of OXMZ absorption.

The results illustrated in Table (1) indicate that 2,4-DNPH reagent gives the highest color intensity and a good color contrast Δλ in comparison with other reagents. so this reagent is chosen in subsequent experiments.

Selection of the oxidizing agent

The effect of the oxidizing agent was studied by adding 1 ml of various types of oxidizing agents (1×10^{-2} M) to 1 ml of 2,4-DNPH solution (1×10^{-2}M) and 1ml of sodium hydroxide solution(1M). The results are shown in Table (2).

Table (2) Selection of the oxidizing agent.

Oxidizing agent(1×10^{-2} M)	**Absorbance**	**λ_{max} ,nm**
Potassium periodate	**0.273**	**607**
N-Bromosuccinimde	0.031	412
Ammonium ceric sulphate dihydrate	0.026	368
Sodium nitroprusside	0.117	397
Potassium Hexacynoferrate(III)	0.080	406
Ferric chloride	0.078	389

The potassium periodate solution gives a higher absorption for colored product at a wavelength of 607 nm when compared with other oxidizing agents, so this compound is chosen in subsequent experiments.

Effect of pH

The effect of pH was studied by adding 0.3-3.5ml of 1.0 M sodium hydroxide solution. The best pH is found to be in the range of 10.9–11.5, so the pH of 11.2 and 2.0 ml of sodium hydroxide solution was adopted in subsequent experiments, the results are shown in table (3). It is worth noting that no color was obtained on the addition of any amount of acid indicating that no reaction is occurred.

Table (3) Effect of pH

ml of 1.0M NaOH	Absorbance		pH
	B^{DW}	S^{B}	
0.3	0.010	0.139	3.6
0.5	0.012	0.215	5.8
0.8	0.015	0.246	7.3
1.0	0.013	0.273	9.5
1.5	0.014	0.357	10.9
2.0	**0.013**	**0.389**	**11.2**
2.5	0.012	0.348	11.5
3.0	0.013	0.267	11.6
3.5	0.010	0.211	11.6

S^{B} : Absorption spectrum of OXMZ solution versus reagent blank .

B^{DW}: Absorption of reagent blank versus distilled water.

Effect of the amount of buffer solution

The formed green color product gives the highest absorption at pH 11.2, therefore; the effect of the amount of buffer solution of sodium hydrogen phosphate - sodium hydroxide solution has been studied using increased volumes of the buffer solution ranging from 0.5 - 3.0 ml[23]. The results are shown in Table (4).

Table (4) Effect of the amount of buffer solution.

Buffer solution ml of (Na_2HPO_4+HCl)	Absorbance	
	B^{DW}	S^{B}
0.0	**0.012**	**0.389**
0.5	0.010	0.359
1.0	0.012	0.323
1.5	0.013	0.314
2.0	0.015	0.295
2.5	0.013	0.262
3.0	0.014	0.217

S^{B}: Absorption spectrum of OXMZ solution versus reagent blank .

B^{DW}: Absorption of reagent blank versus distilled water.

The results shown in Table (4) indicate that the addition of different volumes of the buffer solution leads to a decrease in the absorption of colored product, so it is avoided in subsequent experiments.

Effect of the amount of oxidizing agent

This study was conducted to select the best amount of oxidizing agent KIO_4 (1×10^{-2}M) by adding different volumes (0.2-2.5 ml) of oxidizing agent to volumetric flasks containing 1 ml of OXMZ (250 µg/ml) and 1 ml of the reagent solution (1×10^{-2}M), then addition of 2.0 ml of 1.0M sodium hydroxide and the volume was completed to 25ml with distilled water, the results are shown in table (5).

Table (5) Effect of the amount of oxidizing agent.

ml of KIO_4(1×10^{-2}M)	Absorbance	
	B^{DW}	S^{B}
0.2	0.014	0.249
0.5	0.013	0.281
0.8	0.012	0.327
1.0	0.011	0.388
1.2	**0.012**	**0.441**
1.5	0.010	0.395
1.7	0.014	0.328
2.0	0.013	0.306
2.5	0.015	0.246

The results shown in the table (5) indicate that the volume of 1.2ml of potassium periodate solution (1×10^{-2}M) is the optimum amount because of highest absorbance, so it was used in subsequent experiments.

Effect of the amount of coupling reagent

The effect of the amount of coupling reagent was studied by adding different volumes (0.3-2.5ml) of 2,4-DNPH reagent (1×10^{-2} M) to the volumetric flasks containing 1.0 ml of OXMZ (250µg/ml) and 1.2 ml of the potassium periodate (1×10^{-2}M), then the addition of 2.0 ml of 1.0 M sodium hydroxide and the volume is completed to 25ml with distilled water, the results are shown in Table (6).

Table (6) Effect of the amount of coupling reagent.

ml of 2,4-DNPH(1×10^{-2}M)	Absorbance	
	B^{DW}	S^{B}
0.3	0.015	0.277
0.5	0.013	0.331
0.7	0.016	0.353
1.0	0.012	0.389
1.2	0.014	0.439
1.5	0.011	0.443
1.7	**0.013**	**0.455**
2.0	0.015	0.437
2.5	0.012	0.349

It is clear that the volume of 1.7ml of coupling reagent (1×10^{-2}M) is the optimum amount because it gave the highest absorption. So it is adopted in subsequent experiments

Effect of oxidation time

To a series of volumetric flasks, each containing 1 ml of OXMZ (250 µg/ml), 1.2 ml of potassium periodate (1×10^{-2}M) and the solutions were left for different periods of time, then 1.7 ml of 2,4-DNPH reagent (1×10^{-2}M) and 2.0 ml of 1 M sodium hydroxide solution were added. The volume was completed to 25ml with distilled water, and the absorption of solutions was measured at a wavelength of 607 nm versus blank, the results are shown in table (7).

Table (7) Effect of oxidation time.

Time(min)	5	10	15	20	25	30
Absorbance	0.399	0.455	0.454	0.455	0.456	0.455
Time(min)	35	40	45	50	60	70
Absorbance	0.455	0.454	0.453	0.451	0.449	0.441

Table (7) shows that 10 min is sufficient for the oxidation to be completed , so it is adopted in the subsequent experiments**.**

Effect of temperature

The effect of temperature(5-60°C) on the absorption of the formed colored product were studied by using 1 ml of OXMZ solution(250µg/ml) and 1.2 ml of potassium periodate (1×10^{-2}M), then 1.7 ml of 2,4-DNPH reagent (1×10^{-2}M) and 2.0 ml of 1 M sodium hydroxide solution were added, then the volume is completed to 25 ml with distilled water in a volumetric flasks, and the absorption was measured at a wavelength of 607 nm versus blank reagent, the results are shown in table (8).

Table (8)Effect of temperature.

Temp (°C)	10	15	20	25	30
Absorbance	0.297	0.378	0.409	0.455	0.448
Temp (°C)	35	40	45	50	60
Absorbance	0.376	0.328	0.265	0.205	0.177

The optimum temperature is 25°C , so it is adopted in the subsequent experiments.

Effect of time on stability of the colored product

The stability time of the formed colored product was studied by taking 1 ml of OXMZ (250 µg ml) with addition 1.2 ml of potassium periodate (1×10^{-2}M), then 1.7 of 2,4-DNPH (1×10^{-2} M) and 2.0 ml of 1M sodium hydroxide solution. The volume is completed to 25 ml in a volumetric flasks with distilled water. It was observed the absorption becomes constant directly after dilution and remain unaltered for 60 minutes. The results are shown on table (9).

Table (9) Effect of time on stability of the colored product.

Time (min.)	5	10	15	20	25	30
Absorbance	0.453	0.455	0.456	0.454	0.455	0.453
Time (min.)	35	40	45	50	55	60
Absorbance	0.454	0.453	0.454	0.452	0.451	0.452

Effect of the solvents

The effect of the solvents on the formed colored product was studied, the dilution was carried out by different organic solvents instead of water. The results are shown in table (10).

Table (10) Effect of the solvents.

Solvent	Water	Methanol	Ethanol	n- Propanol
Absorbance	0.456	0.649	0.762	0.455
λ_{max}, nm	607	612	612	598

The results shown in table (10) indicate that the water is a good medium for reaction and gives good absorption value at the wavelength of 607 nm and due to its availability, it has been used as the best solvent in the subsequent experiments.

Final absorption spectrum

The spectrum of the formed colored product by coupling of OXMZ with 2,4-DNPH (1×10^{-2}M) in the presence of potassium periodate (1×10^{-2}M) in basic medium (pH 11.2) and temperature 25°C against its corresponding reagent blank show a maximum absorption at 607 nm in contrast to the blank reagent of zero absorbance at λ_{max}. The spectra are shown on Fig. (2).

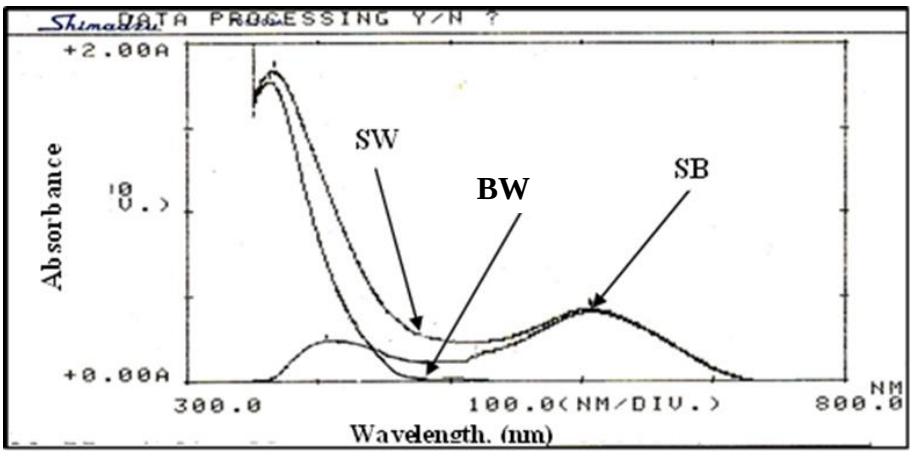


Fig.(2) Final absorption spectrum of the determination OXMZ.

SB :Absorption spectrum of OXMZ solution versus blank reagent.
SW: Absorption spectrum of OXMZ solution versus distilled water.
BW:Absorption of blank reagent versus distilled water.

Procedure for construction of calibration curve

To a series of volumetric flasks (25ml), 0.25-3.0ml of (250 µg/ml) of OXMZ were transferred, 1.2ml of potassium periodate (1×10^{-2}M) and 1.7ml of 2,4-DNPH reagent (1×10^{-2}M), 2.0 ml of 1.0M sodium hydroxide solution (pH 11.2) were added at 25°C . After that the solutions were left for 10 min to complete the reaction, then the volumes were completed to the mark with distilled water. The absorbance was measured at 607 nm against the blank reagent. Fig. (3)

illustrates that the calibration curve is linear over the concentration range of 2.5-30 µg /ml while higher concentrations show a negative deviation from Beer's law. The molar absorptivity value is 7242 liter. $mol^{-1}.cm^{-1}$and the Sandell's sensitivity index 0.0409 $\mu g/cm^2$.

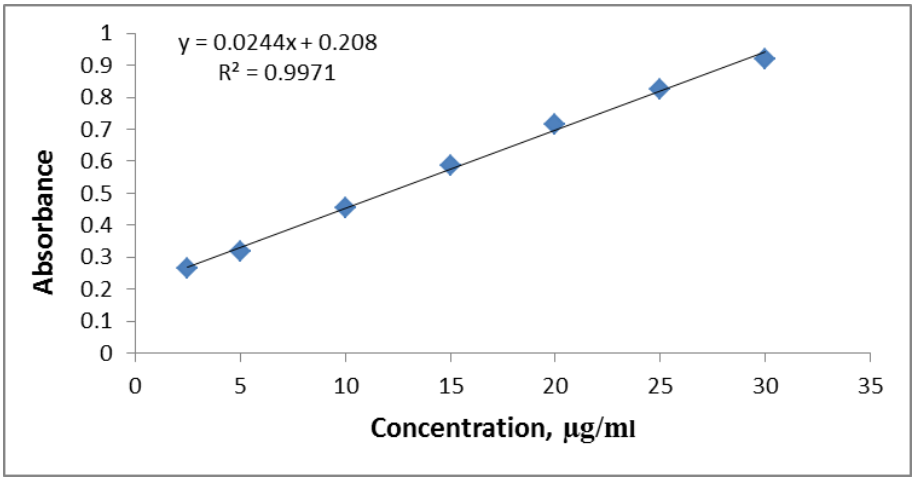


Fig. (3) Calibration curve for determination OXMZ by oxidative coupling with 2,4-DNPH reagent.

Accuracy and precision

Accuracy and precision were studied by measuring absorption (five times) at 607 nm for two different concentrations of the drug within the limits of Beer's law, the average recovery (99.75 %) and the relative standard deviation (<1.39%) indicate that the method is of high accuracy and precision . The results are shown in table (11).

Table (11) Results of accuracy and precision.

Conc. of OXMZ ppm	RSD %	Recovery *%	Average recovery %	RE %
5	1.39	99.94	99.75	-0.06
10	1.24	99.56		-0.44

* Average of five determinations

Detection limit

Detection limit was calculated by measuring the absorption for the lower concentration 2.5 µg/ml at optimal conditions (ten times) at 607 nm. The results are shown in table (12).

Table (12) Detection limit.

Concentration µg/ ml	$\overline{X}$	S.D	D.L µg/ ml
2.5	0.265	0.0023	0.1877

* Average of ten determinations

The nature of the formed product

To know the nature of the formed green color product (stoichiometry of drug with the reagent), Job's method and molar ratio method were applied. In both methods, the concentration of each of the standard OXMZ solution and 2,4-DNPH reagent solution is equal to 8.423×10^{-4} M. In Job's method, in a series of volumetric flasks (25 ml), different volumes of the drug solution ranging from 1-9 ml and different volumes (9-1 ml) of reagent solution were mixed. A 1.2 ml of potassium periodate (1×10^{-2} M) and 2.0 ml 1 M of sodium hydroxide solution were added and volumes were completed to the mark with distilled water. The absorbance was measured at 607 nm against the blank reagent. The results Fig. (4) show that the ratio is 1:1

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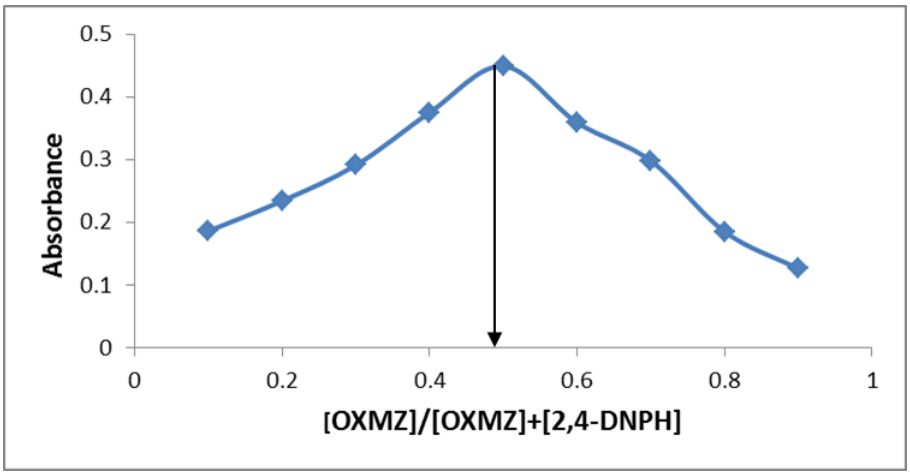


Fig. (4) Job's method of formed product by oxidative coupling of OXMZ with 2,4-DNPH reagent.

In molar ratio method, 1 ml of the standard drug solution in a series of volumetric flasks (25 ml) were transferred and different volumes 0.3-3.5 ml of 2,4-DNPH reagent solution, 1.2 ml of potassium periodate (1×10^{-2}M) and 2.0 ml 1.0 M of sodium hydroxide solution were added. The volumes were completed to the mark with distilled water and the absorbance was measured at 607 nm against the blank reagent. Molar ratio was found to be 1:1. The results are shown in Fig.(5) which is in agreement with the Job's method results.

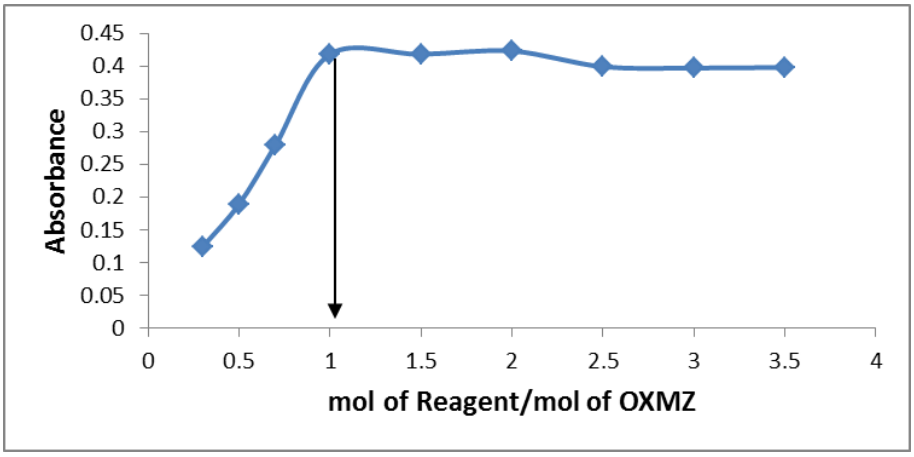
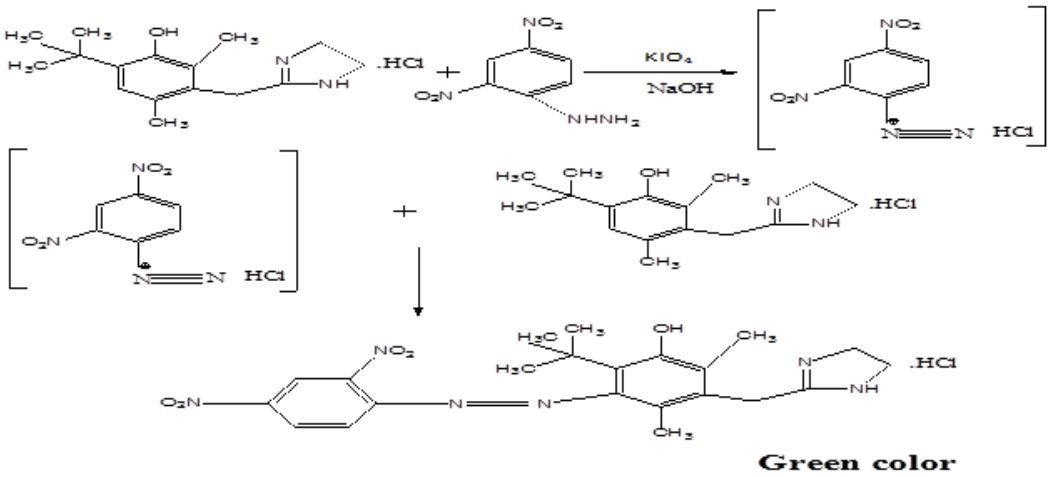


Fig. (5) Molar ratio method for the product formed by oxidative coupling of OXMZ with 2,4-DNPH reagent.

The proposed equation for reaction can be written as follows:



Effect of interferences

In order to test the efficiency and selectivity of the proposed method, the effect of some foreign substances (starch, glucose, fructose and maltose) that usually present in dosage forms are studied by taking volumetric flasks (25 ml) containing 1.0 ml of OXMZ (250 µg /ml), then different volumes (2.5, 5.0 ,7.5 ml) of foreign substances (1000 µg/ml) have been added resulting in a final concentration of (100, 200 ,300 µg/ml). The optimum conditions have been applied and the volumes have been completed to the mark with distilled water.The absorbance was measured at 607 nm versus blank reagent and recovery is calculated. The results showed that there is no interferences (13).

Table (13) Effect of interferences.

Foriegn compound	**Recovery (%) of 10 µg/ml of OXMZ per µg /ml foreign compound added**		
	100	200	300
Starch	99.85	99.67	98.56
Glucose	100.14	99.58	100.32
Fructose	97.78	99.25	99.72
Maltose	99.64	100.31	99.83

Applications

This method was applied for the determination of OXMZ in its pharmaceutical formulation (nazordin drop).

Direct method

In this method, different volumes (0.5, 0.75ml) of a pharmaceutical formulation solutions (250 µg/ml) were transferred to 25 ml volumetric flasks and the resulting concentrations (5 ,7.5 µg/ml) and were treated as in construction of calibration curve. The absorbance was measured at 607 nm for five times. Recovery and RSD were calculated and the results are shown in table (14).

Table (14) Direct method for determination of OXMZ in nazordin drops.

OXMZ present µg/ml	OXMZ measured µg/ml	RE, %	RSD, %	Recovery*, %
5.0	4.98	-0.40	1.47	99.60
7.5	7.51	0.13	1.22	100.13

* Average of five determinations

Table (14) shows the efficiency and success of the developed method for the determination of OMZX in its pharmaceutical formulation, the average recovery is 99.87 %.

standard additions method

To prove that the developed method is free from interferences , method of standard additions is applied for determining of OXMZ in its pharmaceuticals. Different volumes (0.5, 0.75ml) of a pharmaceutical formulation solutions (250 µg/ml) were transferred to seven volumetric flasks (25 ml) for each volume, then increasing volumes (0.25-2.0 ml) of 250 µg/ml of OXMZ standard solution were added with leaving the seventh flask without addition. The solution was treated as in construction of calibration curve. The absorbance were measured at 607 nm (Fig.6) the measured concentration was calculated from the equation of the straight line and the results of Recovery and RE shown in the table (15).

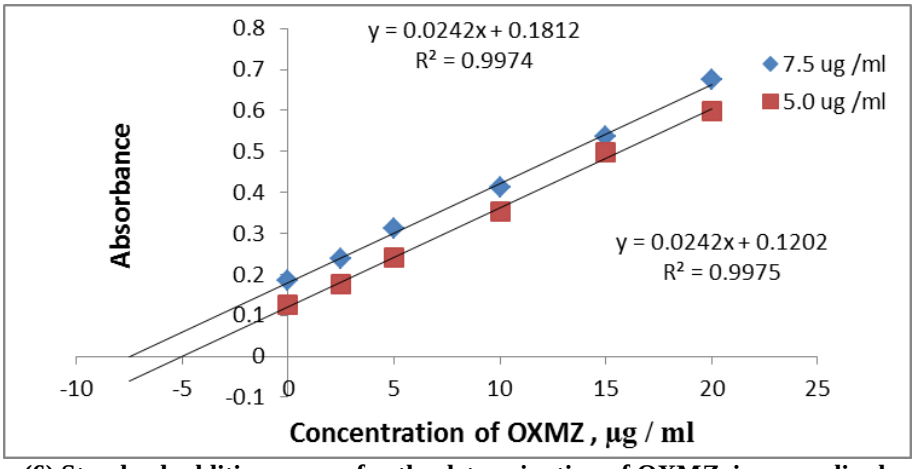


Fig. (6) Standard additions curve for the determination of OXMZ in nazordin drops.

Table (15) Results of standard additions method.

Type of Drug	OXMZ present µg/ml	OXMZ measurd µg/ml	RE%	Recovery, (%)
Nazordin drops	5.0	4.97	-0.6	99.40
	7.5	7.49	-0.13	99.87

The results shown in table (15) indicate that method of standard additions is in agreement with the direct method within the acceptable range of error, indicating that the method is satisfactory and free from interferences.

Conclusions

The results obtained confirm that the proposed method is simple, rapid and of good sensitivity for the determination of OXMZ. The method is based on oxidative coupling between OXMZ and 2,4-dinitrophenylhydrazine reagent in presence of potassium periodate in basic medium to form green colored dye which is water soluble, stable and shows a maximum absorption at 607 nm. This method does not require temperature control, nor use of organic solvents, or solvent extraction and it can be applied successfully for determination of OXMZ in pharmaceuticals formulation with recovery of not less than 99.87%.

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التقدير الطيفي للاوكسيميتازولين هيدروكلوريد في مستحضراته الصيدلانية باستخدام 2،4- ثنائي نيتروفنيل هيدرازين

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الملخص

يتضمن البحث تطوير طريقة طيفية بسيطة وسريعة وحساسة لتقدير عقار الاوكسيميتازولين باستخدام تفاعل الاقتران التأكسدي مع الكاشف 4,2- ثنائي نيتروفنيل هيدرازين في وسط قاعدي بوجود العامل المؤكسد بيريودات البوتاسيوم لتكوين ناتج اخضر اللون ذائب في الماء ويعطي أعلى امتصاص عند الطول الموجي 607 نانوميتر. كانت حدود قانون بير في مدى التراكيز 2.5- 30 مايكروغرام/مل من الاوكسيميتازولين. والامتصاصية المولارية 7242 لتر.مول-1 .سم-1 ودلالة ساندل 0.0409 مايكروغرام .سم-2. وتراوحت قيمة الانحراف القياسي النسبي 1.24- 1.39% ، وحد كشف 0.1877 مايكروغرام/مل. تمّ تطبيق هذه الطريقة بنجاح لتقدير الاوكسيميتازولين في المستحضر الصيدلاني قطرات النازوردين وباسترجاعية ليست اقل من 99.87%.