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Spectrophotometric assay of oxymetazoline-HCl in pure form and in its pharmaceutical formulations using potassium permanganate.

Eman B. Basheer, Salim. A. Mohammed*

Department of Chemistry, College of Science, University of Mosul, Mosul, Iraq

Highlights

- **KMnO4 was found to be used as a suitable oxidizing agent to assay oxymetazoline-HCl spectrophotometrically.**
- **Beer's law was found to be linear in the concentration range of 1.0-30 and 0.5-3.5 µg/ml with molar absorptivity $0.64\times10^4$and 3.16×10^4 $l.mol^{-1}cm^{-1}$ for method (A) and (B), respectively.**
- **The two suggested methods were successfully applied to determine oxymetazoline-HCl in drops and spray with accepted results.**

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**Address of correspondence:*

E-mail address: salimsalih813@yahoo.com

S. A. Mohammed

ABSTRACT

This study involves the development of two sensitive and reproducible spectrophotometric methods to determine oxymetazoline- HCl in pure form and its dosage forms. Both spectrophotometric methods were based on the reduction of potassium permanganate with oxymetazoline- HCl.

In method (A), oxymetazoline-HCl was reacted with an excess known amount of potassium permanganate in an acid solution of H_2SO_4 and the absorbance of unreacted potassium permanganate was measured at 545 nm. In method (B) the oxidation reaction of oxymetazoline-HCl was carried out in an alkaline solution of sodium hydroxide and the absorbance of the resulting (MnO^2) was measured at 610 nm. In method (A), the amount of potassium permanganate reacted corresponds to the oxymetazoline-HCl content and the intensity of absorbance decreased linearly with the concentration, while in method (B), the intensity of absorbance was increased linearly with concentration.

Under optimum conditions, Beer's law was found to be linear in the concentration range of 1.0-30 and 0.5-3.5 µg/ml with molar absorptivity 0.64×10^4 and 3.16×10^4 $l.mol^{-1}cm^{-1}$and corresponding to Sandell's sensitivity values of 0.0448 and 0.0090 µg/cm² for both methods (A) and (B), respectively. The detection limit (LOD) and quantification limit (LOQ) have also been estimated. Accuracy for pure OXM was calculated and found in the range -0.7% to 0.8% and-2.68% to 0.614%, while the precision (RSD) was <0.176% and <0.929% for method (A) and method (B), respectively. The two suggested methods (A) and (B) were successfully applied to the determination of oxymetazoline -HCl in bulk and its pharmaceutical preparations (drops and spray) with accurate and accepted results.

1. Introduction

Oxymetazoline–HCl (OXM), [6-tert-butyl-3(2-imidazolin-2-ylmethyl)-2-4-dimeth-ylphenol monohydrochloride] (Fig. 1) (British Pharmacopoeia, 2005), belongs to non-selective adrenergic drugs which have been used as eye and nose drops and acting on adrenergic receptors causing strong vasospasm leading to an increase of blood pressure (Stanszis and Nowinski, 2000).

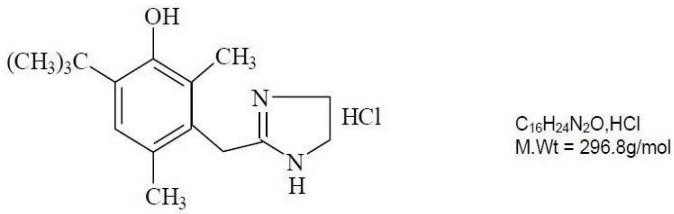

Fig. 1: Oxymetazoline hydrochloride

OXM is used to treat eye redness and epistaxis because of minor irritation (Blessing, 2001). Various analytical methods have been employed for the determination of OXM which included: HPLC (Shaikh and Patil, 2013), liquid-chromatographic mass spectrometry (Hayes *et al.*,1995), chemiluminescence (Wang *et al.*, 2009), ion-selective electrode (Issa and Zayed, 2004) and first derivative spectroscopic (FDSFS) (Abdel-Aziz *et al.*, 2014). These methods require expensive reagents and sophisticated instruments and involve derivatization reactions and several manipulation steps.

Several spectrophotometric methods have also been employed to the assay of OXM in bulk and its pharmaceutical preparations used various reagents for determining OXM, these reagents included: 2,6–dichloroquinone chlorimide with an oxidant reagent (Sankar *et al.*, 1987), potassium ferricyanide – Fe(III) (Othman and Sahar, 2013), 4-chloro-7-nitrobenzo-2-oxa-1, 3-diazole (Salama *et al.*, 2018), 2,4,6-tris(2-pyridyl)-5-triazine (Sankar *et al.*, 1988), 2,4–dinitrophenylhydrazine (Humeidy, 2015), 1,10-phenanthroline – iron(III) (Al-Sabha and Rasheed, 2011), 4-aminoantipyrine (Zakaria, 2011), cobaltinitrite-Na (Shingbal and Naik, 1983), cerium sulphate (IV) (Mohammed and Ikram, 2016) and 2,2-bipyridyl (Basheer and Mohammed, 2018). Some of these

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methods suffer from various limitations, for example, low sensitivity, and a long time to complete the reaction, and low stability of the product. Others required heating, applicable to higher concentrations of OXM.

In the present investigation, potassium permanganate ($KMnO_4$) has been employed to develop simple, fast, and inexpensive two visible spectrophotometric methods for the assay of OXM in pure form and in its pharmaceutical preparations.

2. Experimental

2.1 Apparatus

All absorbance measurements and absorption spectra were carried out by using a double beam UV-visible spectrophotometer (JASCOV-630) with 1.0-cm quartz cells. A professional HANNA pH meter 212 was used for the pH measurements.

2.2 Chemical reagents

All chemical substances used were of the highest purity available and were obtained from Fluka, BDH, and Merk companies. The standard material of OXM was obtained from the state company for drug industries and medical appliances (SDI), Samarra-Iraq

- OXM stock standard solution 100 µg/ ml: A 0.0100 g of pure OXM was dissolved in 10 ml of distilled water and the volume was then completed to 100 ml with the same solvent in 100 ml volumetric flask. Working standard solution was freshly prepared by diluting the stock standard solution with distilled water to obtain the appropriate concentration.

- Potassium permanganate stock solution 0.02 M: A 0.3161 g of potassium permanganate ($KMnO_4$) was dissolved in about 30ml of distilled water. The solution was boiled to 10 min to destroy any residual manganese, cooled, filtered, and diluted to 100 ml with distilled water. This solution was then standardized with a standard solution of sodium oxalate.

Working solutions of $KMnO_4$ were prepared by appropriate dilution of the stock solution with distilled water to get 500 and 1000 µg/ml for methods (A) and (B), respectively.

- Sodium hydroxide solutions of 0.1 M were obtained by diluting 25 ml of the standard concentrated solution of NaOH (1M) to 250ml with distilled water using a volumetric flask.

- Sulphuric acid 5M was also prepared.

2.3 Analysis

2.3.1 Method (A)

An increasing volume of 0.1-5.0 ml of OXM standard solution (100 µg/ml) was transferred into a series of 10 ml volumetric flasks. To each solution 1 ml of 5M sulphuric acid was added and followed by 1.2 ml of 500 µg/ml $KMnO_4$, the latter being measured accurately. The contents were shaken thoroughly for 10 min and then completed to the mark with distilled water andthe absorbance was recorded at 545 nm versus the corresponding blank solution which was prepared by mixing 1.2 ml of 500 µg/ml $KMnO_4$ and 1ml of 5M sulphuric acid into 10 ml volumetric flask.

2.3.2 Method (B)

Into a series of 20 ml volumetric flasks, 0.1-1.2 ml of 100 µg/ml pure OXM solution, 3 ml of 0.1M NaOH, and 1ml of 1000 µg/ml KMnO4 solution were added. The contents were shaken thoroughly and kept constant at room temperature for 15 min andthen completed to the mark with distilled water. The absorbance was recorded at 610 nm against a blank solution that is prepared similarly but without a drug.

2.4 The recommended procedure to assay OXM in drug

Three containers of nasal drops (each one contains 0.05% OXM) were mixed well to get a homogeneous solution. An aliquot volume, equivalent to 10 mg of OXM was pipetted into a 100 ml calibrated flask and with distilled water completed to the mark. Each ml of this solution contains 100 µg of OXM. An aliquot of diluted solution of the drug was then analysed using the procedures described in both methods (A) and (B).

3. Results and Discussions

3.1 Optimum reaction conditions

In method (A), when a fixed concentration of $KMnO_4$ was treated with increasing amounts of OXM in an acid solution of H_2SO_4, a decrease in absorbance at 545 nm occurred, due to the concomitant fall in the $KMnO_4$ concentration (Fig. 2). Thus, the absorbance of the blank solution was measured against colored products and increased with time.

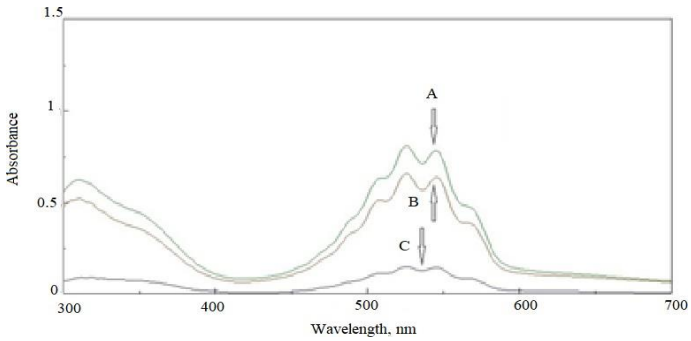

Fig. 2. Absorption spectra of blank solution (KMnO4 + H2SO4) Vs. distilled water (A), sample (50 µg OXM + KMnO4 + H2SO4) Vs. distilled water (B), and sample Vs. blank (C)

To study the effect of KMnO4 on the oxidation of OXM at 545 nm, varying volumes from 0.1 to 2.0 ml of 500 µg/ml KMnO4 in the presence of 1ml of 5M H2SO4 have been investigated. Fig. 3 shows that the absorbance is increased with increasing the volume of KMnO4 solution up to 1.2 ml (60 µg), further increase in volume resulted in a very slight decrease in the absorbance of the product. Thus, 1.2 ml of 500 µg/ml KMnO4 was selected to be the most suitable concentration.

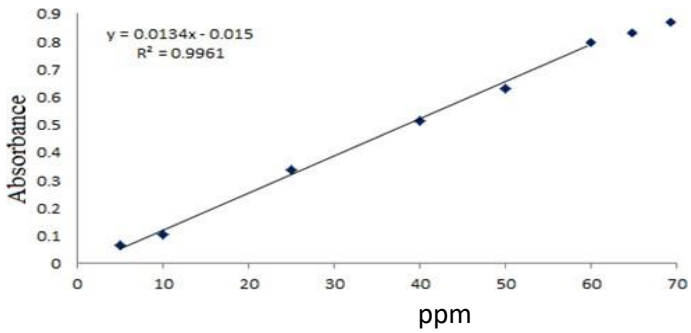

Fig. 3. Linear relation between the absorbance of working KMnO4 solution at 545 nm in 5M H2SO4

The effects of 5M of various acids solutions such as H_2SO_4, HNO_3, and HCOOH have been studied on the oxidation of OXM with $KMnO_4$.The data are summarized in Table 1 and revealed that H_2SO_4 was the most suitable acidic medium for obtaining maximum absorbance.

Table 1

Effect of various acid solutions on absorbance

Acid solution (5M)	Absorbance/ml of acid added					
	0.5	1.0	1.5	2.0	3.0	4.0
H_2SO_4	0.1382	0.1422	0.1415	0.1414	0.1408	0.1405
HNO_3	0.1120	0.1150	0.1148	0.1137	0.0987	0.0989
HCOOH	0.0151	0.0168	0.0179	0.0181	0.0183	0.0177
CH_3COOH	0.1252	0.1279	0.1280	0.1276	0.1248	0.1241

The results in Table 1 show that no change in the absorbance occurred when 1-3 ml of 5M H_2SO_4 were used in 10 ml asa total volume, therefore, 1ml of 5M H_2SO_4 was selected for the reaction. The effect of HCl was not studied since $KMnO_4$ being a strong oxidizing agent would react with HCl to liberate chlorine. The order of addition on the reaction was also investigated and the experimental results show that the order of (OXM + H_2SO_4 + $KMnO_4$) at 545 nm is the optimum (Table 2).

Table 2

Order addition effect on absorbance.

Order No	Order of addition	Absorbance
I	OXM + H2SO4 + KMnO4	0.1427
II	OXM + KMnO4 + H2SO4	0.1289

In order to investigate the range of concentration over which OXM adheres to Beer's law, the intensity of absorbance of theunreacted potassium permanganate was measured at 545 nm after developing the colour by following the proposed procedure for a series of solutions containing increasing concentrations of OXM (Fig. 4).

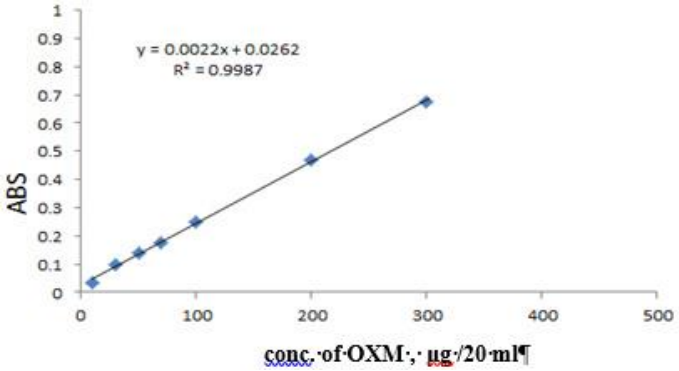

Fig.4. Calibration curve for OXM determination using (1.2 ml of 500 mg ml^{-1}$KMnO_4$

In method (B), OXM is quantitatively oxidized with $KMnO_4$ in the presence of NaOH, resulting in the formation of the bluish-green colour of manganate (MnO^2) appeared absorption peak at 610 nm (Fig. 5).

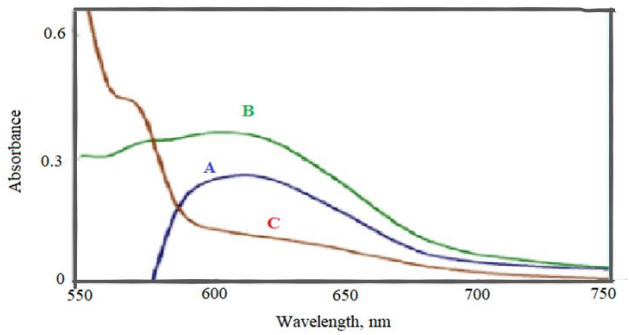

Fig. 5. The absorption spectra of sample (50 µg OXM + KMnO4 + NaOH) Vs. blank solution (KMnO4 + NaOH) (A), sample Vs. distilled water (B) and blank Vs. distilled water (C)

The chemical reaction of OXM with $KMnO_4$ can be presented as the following equation:

OXM+$KMnO_4$+OH^-→oxidation product of OMX+MnO_4^{2-}+H_2O (Bluish-green colour)

Under the optimum operating conditions, a linear calibration curve was obtained over the concentration range of 10 -70 µg of OXM (i.e. 0.5 - 3.5µg/ml) (Fig. 6). Higher concentrations show a negative deviation from Beer's law.

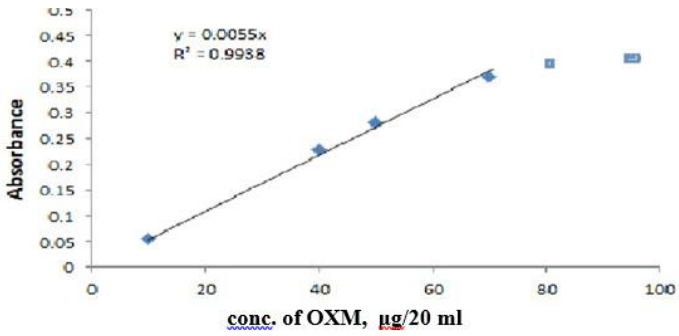

Fig. 6. Calibration curve for OXM determination using (1 ml of 1000 µg/ml KMnO4 reagent and 0.1M of NaOH)

The effect of KMnO4 concentration on the absorbance of a solution containing different amounts of OXM (20–70 µg) was studied. It was found as shown in Table 3, the absorbance is increased as the concentration of potassium permanganate increased and reached the maximum value on using 1 ml of 1000 µg/ml KMnO4 which gave the highest determination coefficient value (r^2=0.9966). Therefore, 1 ml of KMnO4 was selected as the optimum volume for the reaction.

The effect of various alkaline solutions (0.1M) such as NaOH, Na2CO3, KOH, and NaHCO3 was investigated. Maximum sensitivity and stability were obtained only in an alkaline solution of NaOH. While Na2CO3 and NaHCO3 exhibited low sensitivity, which is apparently due to pH variation. The experimental results in Table 4 show that the absorbance was not affected when 3-5 ml of 0.1M NaOH were used in a total volume of 20 ml and 3.0 ml was found optimum.

3.1. Temperature and reaction time effect

In method (A), The influence of reaction time on the absorbance was investigated by following the colour development of the product at room temperature and different temperatures up to 75°C using a water bath with thermostatic control. The experimental results in Table 5 show that the reaction of OXM with $KMnO_4$ in the presence of H_2SO_4 was found to be complete in 10 min at room temperature (25±2). Whereas in method (B) the oxidation of OXM with KMnO4 was completed in 15 min.

Table 3

Effect of $KMnO_4$ amount on absorbance.

ml of $KMnO_4$ solution (1000 µg/ml)	Absorbance/µg OXM added						r^2
	20	25	40	50	70	blank	
0.5	0.0981	0.1023	0.1168	0.1381	0.1922	0.1140	0.9532
0.8	0.1109	0.1276	0.1640	0.1989	0.3081	0.1501	0.9645
1.0	0.1645	0.1912	0.2579	0.2887	0.3862	0.1578	0.9966
1.2	0.1584	0.1892	0.2403	0.2786	0.3622	0.2252	0.9956
1.5	0.1329	0.1632	0.2316	0.2612	0.3515	0.2893	0.9956

Table 4

Effect of various alkaline solutions on the absorbance

Type of base solution (0.1N)	Absorbance/ml base added					pH range
	1.5	2.0	2.5	3.0	4.0	
NaOH	0.1649	0.1963	0.2387	0.2411	0.2512	10.8-11.2
KOH	0.1981	0.2187	0.2511	0.2831	0.2840	11.0-11.9
Na_2CO_3	0.1309	0.1653	0.1946	0.2001	0.2097	8.60-10.1
$NaHCO_3$	0.1421	0.1699	0.1987	0.2110	0.2168	8.74-9.85

Table 5

Effect of temperature and time of reaction on the absorbance

Temperature (°C)	Absorbance /standing time (min.)		
	5	10	15
5	0.0932	0.0957	0.0981
R.T *	0.0998	0.1418	0.1417
50	0.0944	0.1251	0.1262
75	0.0860	0.1270	0.1399

* R.T.=Room Temp.= (25±2 °**C**)

3.2. Time effect on colour development

In method (A), the colour development of unreacted $KMnO_4$ was studied by measuring the absorbance at 545 nm with increasing time and the coluor of remaining $KMnO_4$ was found to be stable up to 40 min. Thereafter, an appreciable decrease in the absorbance after 40 min could be due to the slow reaction between excess MnO with a relatively high concentration of Mn^{2+}. While in method (B) the stability of the coloured product was found constant for at least 25 min at room temperature. The resultsfor both methods are shown in Fig. 7

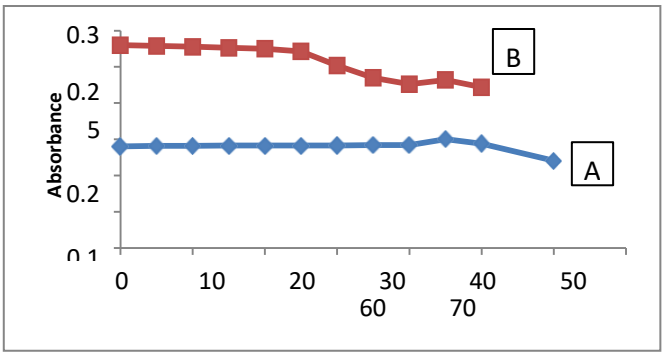

Fig. 7. Effect of time on the absorbance of the product in both methods (A) and (B).

3.4 Stoichiometry of the reaction

The molar ratio of the reaction of OXM with $KMnO_4$ was investigated by both Jop's of continuous variation and mole ratiomethods (Delevie, 1997) using equimolar concentrations 3.38×10^{-4}M of OXM and $KMnO_4$.The results in Fig. 8 indicate that the composition of the product of the reaction OXM with $KMnO_4$ in method (A) was formed in the ratio 1:2 OXM to $KMnO_4$.

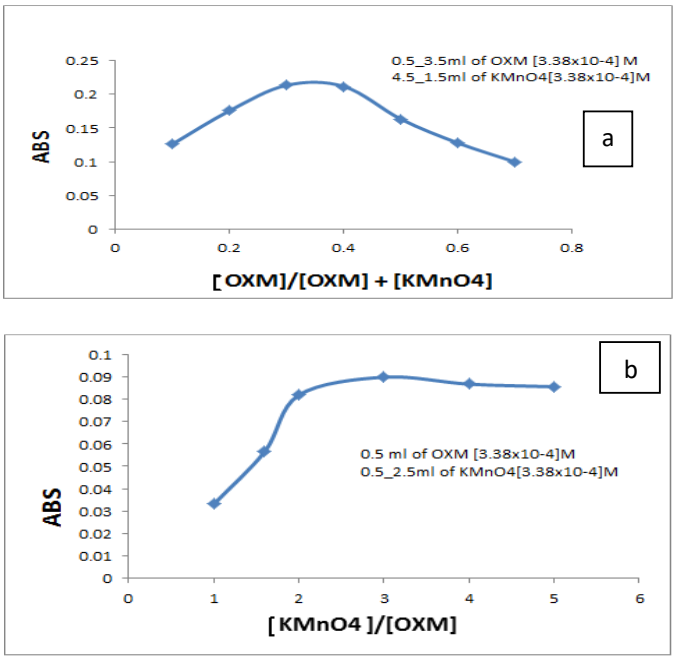

Fig. 8. Determination of the stoichiometry of the reaction by (**a**) A Continuous variation and (**b**) mole ratio plots for oxidation ofOXM with KMnO4 under the optimum conditions.

Accordingly, the proposed reaction equation between the OXM and $KMnO_4$ in the acidic solution of H_2SO_4 can be represented by the following chemical equation:

$OXM+2KMnO_4+16H^+ \rightarrow$ Oxidation product of $OXM+2Mn^{2+}+8H_2O+2K^++KMnO_4$ (Absorbance is measured at 545 nm)

3.3. Quantification

Linearity for both methods A and B were described by the equation of regression and the corresponding determination coefficient (r^2) for OXM was calculated by the recommended methods and represented excellent linearity. The detection limits (LOD) and quantitation (LOQ) were found according to ICH guidelines (International Conference on Harmonization, 2005). The limits of Beer's law, molar absorptivity (ε_{max}), Sandall's sensitivity, accuracy (relative error %), precision (RSD) for methods (A) and (B), were also evaluated and the results are shown in Table 6, which indicate that the proposed both methods are sensitive, precise and accurate.

Table 6

Data of statistical and optical characteristics for both methods (A) and (B)

Parameters	Data of method	
	(A)	**(B)**
Beer's law range (µg/ml)	1.0-30	0.5 – 3.5
Molar absorptivity (l./mol.cm)	0.64×10^4	3.26×10^4
LOD (µg/ml)	0.162	--------
LOQ (µg/ml)	0.542	--------
Relative error range (%)*	- 0.7 to 0.8	-2.68 to 0.614
Determination coefficient (r^2)	0.9987	0.9938
Slope (a)#	0.0022	0.0055
Intercept (b)#	0.0262	0.000
Sandall's sensitivity (µg/cm^2)	0.0448	0.0090
RSD (%)*	<0.176	<0.929

3.4 Interference

The influence of some foreign substances which are often present in the drug was investigated. The methods were based on the addition of different concentrations of diverse foreign substances to 50 µg/ml of OXM and the absorbance was then measured according to the proposed procedure for methods (A) and (B). The data in Table 7 indicate that there are no significant interferences produced by these foreign substances on both proposed procedures.

Table 7

Effect of foreign compounds on the assay of OXM.

Excipients	Recovery (%)* of 50 µg OXM/µg foreign compound added			
	Method A		Method B	
	100	500	100	500
NaCl#	97.7	98.8	98.3	95.5
Na_2HPO_4 #	96.3	99.5	96.7	94.1
Glucose	97.7	104	97.3	96.8
Lactose	95.6	96.5	96.3	95.2
Starch	98.8	103.9	101.8	105.2
Sorbitol	99.4	100.6	102.4	103.4

* Average of five determinations

An active materials present in nasal drops

4. Applications

Four different pharmaceutical preparations (drops and spray) contain OXM have been analysed by applying the proposed procedure of methods (A) and (B). The data are listed in Table 8. For all preparations examined, the assay results of both recommended methods are precise.

Table 8

Analysis of OXM in pharmaceutical preparations

Pharmaceutical preparation	Method (A)					Method (B)				
	OXM		Relative error (%)	Recovery (%)	RSD (%)	OXM		Relative error (%)	Recovery (%)	RSD (%)
	Present (µg)	Found (µg)				Present (µg)	Found (µg)			
Nazordin drops 0.05 g OXM /100ml (S.D.I.-Iraq)	10	10.16	1.6	101.6	0.664	10	9.87	1.25	98.7	0.818
	20	20.38	1.9	101.9	0.626	20	19.88	-0.618	99.4	0.281
Nazordin drops 0.05g OXM /100ml (N.D.I.-Iraq)	10	9.81	-2.1	98.1	0.78	10	9.73	-1.11	97.3	0.191
	20	19.78	-1.27	98.9	0.91	20	19.72	-1.09	98.6	0.731
Nasa clear spray 0.05g OXM /100ml (Syria)	20	19.6	-2.04	98.0	0.75	---	---	---	---	---
	50	50.7	1.4	101.4	0.20	50	48.55	2.9	97.1	0.855
Oximet drops (0.05%) (Pharaonia-Eygpt)	20	21.58	7.78	107.9	0.60	20	18.96	5.2	94.8	1.191
	50	53.25	6.5	106.5	0.37	---	---	----	----	----

*Average of four determinations

4.1. Evaluation of the proposed method

The standard additions method was followed to check the validity of the suggested method (A) which proves that the recommended method can be successfully applied for determining OXM without interferences. The data are shown and listed in Fig. 9 and Table 9, respectively.

5. Conclusion

The objective of this work was to develop sensitive, simple and accurate two spectrophotometric methods to assay OXM in its pharmaceutical formulations (drops and spray). Both methods have the advantages of being accurate and did not require organic solvents, any chemical sample pretreatment, expensive reagents, and solvent extraction step. The sample recoveries in all formulations were precise and in good agreement with their respective label claims and hence both methods were recommended for quality control and routine analysis of OXM.

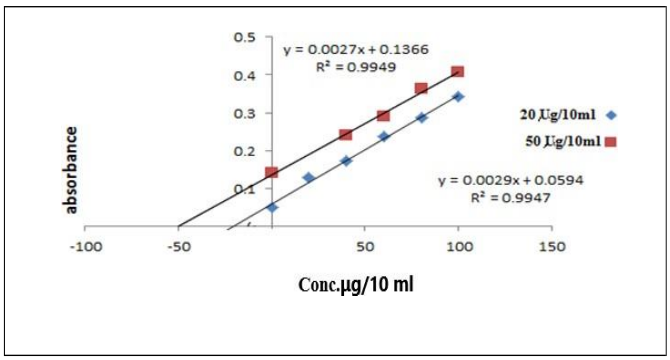

Fig. 9. Calibration graphs of standard addition methods for analysis of OXM in nasaclear spray

Table 9

Standard additions method for OXM analysis

Drug	OXM present (µg)	OXM measured (µg)	Recovery (%)
Nasa clear spray	20	20.48	102.4
0.05 g OXM/100ml (Syria)	50	50.59	101.0

Reference

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