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Spectrophotometric and Fluorimetric Methods for the Determination of Methoxamine Hc1 in Bulk Drugs and in Ampoules

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**SPECTROPHOTOMETRIC AND FLUORIMETRIC METHODS
FOR THE DETERMINATION OF METHOXAMINE HCl IN BULK
DRUGS AND IN AMPOULES**

Keywords : Methoxamine HCl ; spectrophotometry ; fluorimetry ; periodate ;
permanganate;cerium (IV); ampoules.

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Abstract

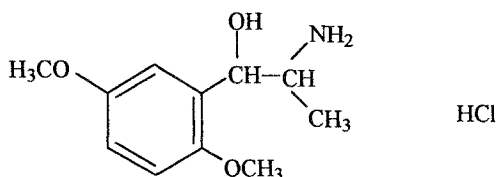
Three simple and sensitive methods for the determination of methoxamine HCl in bulk drugs and in ampoules were proposed . The methods are based on the oxidation of methoxamine HCl by sodium periodate , potassium permanganate and cerium(IV)sulphate .The first two reactions are followed spectrophotometrically by measuring the absorbance at 352 & 608 nm for the periodate and permanganate methods, respectively .The third method is based on measuring the relative

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fluorescence intensity of Ce(III) arising from Ce(IV) at 348 nm with excitation wavelength at 257 nm. The different experimental parameters were carefully studied.

Under the described conditions the proposed methods were applicable over the concentration ranges 10.0 – 40.0, 2.0-10.0 and 0.05-0.30 $\mu\text{g ml}^{-1}$ for the three methods, respectively.

Introduction:



The results obtained by the proposed methods were evaluated against the B.P. method. Methoxamine HCl, 2-amino-1-(2,5-dimethoxyphenyl) propanol hydrochloride, belongs to the therapeutic category of the adrenergic vasopressor agents. It is used primarily to raise the blood pressure of a patient whose blood pressure has dropped because of the induction of anesthesia. The drug has also been useful in terminating episodes of paroxysmal supraventricular tachycardia^{1,2}.

Screening of the literature revealed that only few chromatographic methods have been developed for the determination of Methoxamine HCl in pharmaceutical preparations. These include TLC³⁻⁷, paper chromatography^{4,8,9}, GLC^{5,10,11}, GC-Mass³ and HPLC¹². Methoxamine HCl has been determined in rabbit plasma and in pharmaceutical preparations using an HPLC method¹³.

In the B.P. methoxamine HCl was assayed by measuring the absorbance at maximum at 290 nm¹⁴. Recently, a spectrophotometric method for the determination of

methoxamine HCl in bulk powder and in pharmaceutical preparation has been reported, based on the acidic oxidation with cerium (IV) in micellar medium¹⁵. The limited spectrophotometric methods and the absence of fluorimetric methods for the determination of methoxamine HCl in pharmaceutical preparations created a great interest in developing spectrophotometric and fluorimetric methods for the determination of such a drug.

The aim of the present work was to develop simple and sensitive spectrophotometric methods for the determination of methoxamine HCl in bulk drugs and in pharmaceutical preparations, through oxidation by alkaline periodate reagent, and potassium permanganate in alkaline medium. A fluorimetric method was developed, based on oxidation of methoxamine HCl with cerium(IV) sulphate in acidic medium. The fluorescence due to the Ce (III) ions produced from Ce(IV) in the oxidation process of methoxamine HCl has been measured and used for the quantification of methoxamine HCl. The proposed methods have been successfully applied for the determination of methoxamine HCl in pharmaceutical preparation. Analytical criteria including linearity, sensitivity, precision, accuracy and recovery are discussed.

Experimental

Apparatus

The spectrophotometric measurements were made on a UNICAM UV-VIS spectrophotometer He λ 10 S α using 1.0 cm quartz cells.

The fluorimetric measurements were performed on a Perkin Elmer Model 650-10S fluorescence spectrophotometer equipped with 1.0 cm quartz cells, a 150-W Xenon, excitation and emission grating monochromators, a Hitachi 057 X-Y recorder and 650-10 X-Y recorder interface.

Materials and Reagents

All experiments were performed with analytical grade chemicals and solvents .

cerium (IV) sulphate solution 0.02 M was freshly prepared from commercial products of Merck by dissolving 200 mg $\text{Ce}(\text{SO}_4)_2 \cdot 4 \text{H}_2\text{O}$ in 25 ml 0.1 M sulphuric acid .

Potassium permanganate , 1.6% w/v was prepared by dissolving 1.6 gram potassium permanganate (Riedel-De Haenag) in 100 ml distilled water .

Sodium metaperiodate, 2% w/v was prepared by dissolving 2 gram of sodium metaperiodate (BDH Chemicals Ltd.) in 100 ml distilled water .

Authentic sample of methoxamine HCl (Lot No. 19445) and Vasoxine[®] ampoules (Lot No. H 2959A) containing 20 mg ml^{-1} methoxamine HCl were obtained from Wellcome foundation (London, England) .

Standard methoxamine HCl solution 0.5 mg ml^{-1} was prepared by dissolving 25 mg of the drug in 50 ml distilled water.

Diluted methoxamine HCl solution 0.25 mg ml^{-1} was prepared by diluting 5 ml of the standard methoxamine HCl solution to 10 ml with distilled water .

Procedures

I-Spectrophotometric methods

a- Alkaline Periodate method

Aliquots from standard methoxamine HCl solution (0.5 mg ml^{-1}) ranging from 0.2-0.8 ml (in 0.1 ml steps) were transferred into 10 ml volumetric flasks . To each flask , 1 ml of saturated sodium bicarbonate solution and 1 ml of 2% w/v of sodium metaperiodate solution were added . The flasks were swirled and completed to volume

with water . The absorbance was measured at 352 nm against reagent blank simultaneously prepared .

b-Alkaline permanganate method

Aliquots from standard methoxamine HCl solution (0.5 mg ml^{-1}) ranging from 0.1 – 0.5 ml (in 0.05 ml steps) were transferred into 10 ml volumetric flasks . To each flask 5 ml of 0.5 M sodium hydroxide solution and 0.3 ml potassium permanganate solution were added. The flasks were heated in a water bath at 60°C for 15 min. The flasks were cooled to room temperature and diluted to volume with distilled water . The absorbance was measured at 608 nm against reagent blank simultaneously prepared .

II-Fluorimetric method

Aliquots from diluted methoxamine hydrochloride solution (0.25 mg ml^{-1}) ranging from 0.1 – 0.3 ml (in 0.05 ml steps) were transferred into 10 ml volumetric flasks. To each flask , 2ml of 4M sulphuric acid and 1 ml 0.02 M cerium(IV) sulphate were added . The flasks were heated in a water bath at 110°C for ten minutes . Flasks were cooled to room temperature and diluted to volume with distilled water . One milliliter of each of the resulting solutions was transferred into 25 ml volumetric flask and diluted to volume with distilled water . The fluorescence intensities were measured at 348 nm with excitation at 257 nm. The observed fluorescence was corrected by subtracting the fluorescence intensity measured using reagent blank .

Assay of methoxamine HCl in ampoules

I- Spectrophotometric methods

One milliliter aliquot was pipetted , from the mixed contents of three Vasoxine® ampoules (each containing 20 mg ml^{-1} methoxamine hydrochloride), transferred into

50 ml calibrated flask and diluted to volume with distilled water , (40mg ml⁻¹) solution .

a- Periodate method

0.5 ml of the ampoule solution (40 mg ml⁻¹) was transferred into 10 ml volumetric flask . The procedure was completed as under alkaline periodate method starting from "1ml of saturated sodium bicarbonate -----" .

b- Alkaline permanganate method

0.3 ml of the ampoule solution (40 mg ml⁻¹) was transferred into 10 ml volumetric flask . The procedure was completed as under alkaline permanganate method ,starting from "5 ml of 0.5 M sodium hydroxide -----" .

II- Fluorimetric method

0.1 ml of the ampoule solution (40 mg ml⁻¹) was transferred into 10 ml volumetric flask . The procedure was completed as under fluorimetric method starting from " To each flask , 2ml 4 M sulphuric acid ----- "

Results and Discussion

I-Spectrophotometric methods

a- Alkaline periodate method

Alkaline periodate has been used for oxidation of several phenalkanolamines to give the corresponding aldehyde¹⁶⁻¹⁸. Methoxamine HCl being a phenalkanolamine derivative , could be oxidized with periodate. The reaction proceeded quantitatively within a few minutes at room temperature in neutral or alkaline solution. The absorbance of the produced aldehyde was measured spectrophotometrically at 352 nm (Fig. 1). The absorbance was stable for at least one hour.

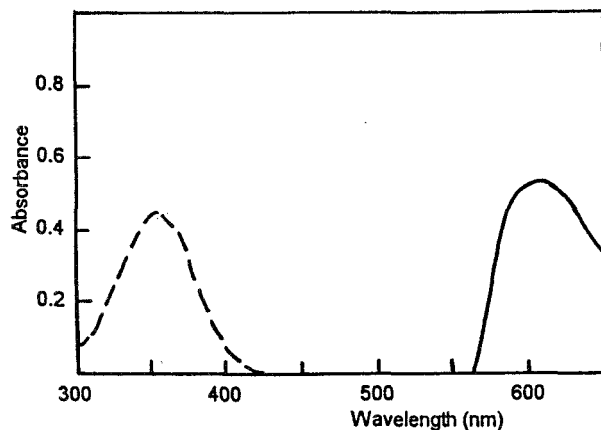


Fig. 1: Absorption spectra of the reaction products of $25 \mu\text{g ml}^{-1}$ methoxamine HCl with periodate (-----), $8 \mu\text{g ml}^{-1}$ methoxamine HCl with permanganate (—).

b- Alkaline permanganate method

Methoxamine HCl was oxidized by potassium permanganate in alkaline medium. The resulting green manganate ion was measured spectrophotometrically at λ_{max} 608 nm (Fig 1). A study for the experimental parameters necessary for the reaction revealed that maximum absorbance was obtained upon heating the drug with 0.25 mg ml^{-1} potassium permanganate in presence of 0.1 M sodium hydroxide in the final concentration, for 15 minutes at 60°C . The absorbance of the resulting solution was stable for about one hour.

II- Fluorimetric method

Methoxamine HCl was reported to be oxidized with cerium(IV)¹⁵. The cerium (IV) oxidation procedure was applied to the fluorimetric determination of methoxamine HCl. This was performed through measuring the fluorescence due to cerium (III) ions at λ excitation 257 nm with λ emission at 348 nm (Fig.2). The Ce(IV) concentration,

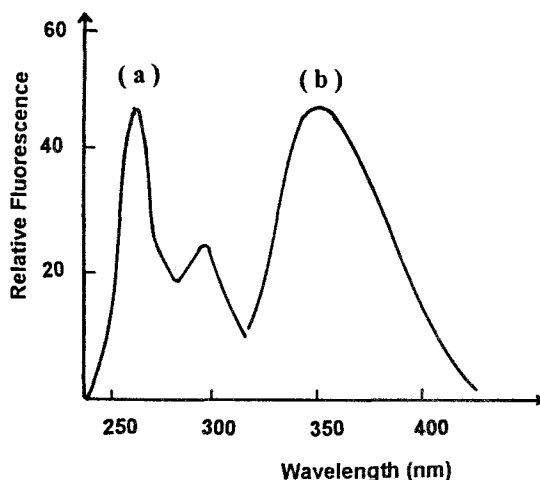


Fig. 2: Excitation (a) and emission (b) spectra for the fluorescent Ce(III) produced by oxidation of $0.15 \mu\text{g ml}^{-1}$ methoxamine HCl with Ce(IV) sulphate.

strength of the acid ,heating temperature and reaction time have been optimized to achieve maximum sensitivity. The optimum conditions were found to be 0.032 mg ml^{-1} Ce(IV), 0.032 M sulphuric acid in the final concentration and heating the reaction mixture at 110°C for 10 min. The fluorescence intensity was found to be stable for at least one hour.

Analytical Data

The calibration curves were constructed for the proposed spectrophotometric and fluorimetric methods over the concentration ranges cited in Table 1. Regression analysis indicates linear relationships with negligible intercepts . Table 1 presents the results of the statistical analysis of the experimental data : regression equations calculated from calibration graphs along with the standard deviation of the slope (S_b)

Table 1

Analytical Data of the Calibration Graphs for the Determination of Methoxamine HCl by the Proposed Methods.

Method	Selected λ nm	Conc. Range $\mu\text{g ml}^{-1}$	Intercept (a)	Slope (b)	Regression Coefficient (r)	$S_{y/x}$	S_a	S_b	RSD %	Er %	Apparent Molar Absorptivity ($\text{L mol}^{-1}\text{cm}^{-1}$)
NaIO₄	352	10.0 – 40.0	1.45×10^{-3}	0.0176	0.9999	3.92×10^{-3}	2.04×10^{-3}	1.57×10^{-4}	0.96	0.39	4.0×10^3
KMnO₄	608	2.0–10.0	-3.8×10^{-3}	0.0696	0.9999	5.03×10^{-3}	1.31×10^{-3}	2.16×10^{-4}	0.47	0.21	1.71×10^4
Fluorimetry	Ex 257 Em 348	0.05–0.30	-1.0	337.14	0.9999	0.534	2.93	2.55	0.87	0.36	—

 $S_{y/x}$ = Standard deviation of residuals. S_a = Standard deviation of intercept of regression line. S_b = Standard deviation of slope of regression line.RSD % = Relative standard deviation ($n = 6$).

Er % = Percentage standard error.

Table 2

**Determination of Methoxamine HCl In Vasoxine[®] Ampoules Using The
Proposed Spectrophotometric and Fluorimetric Methods.**

Method	Recovery \pm RSD%	Er %	t-	F-
NaIO ₄	99.95 \pm 0.89	0.38	0.375	1.62
KMnO ₄	100.24 \pm 0.76	0.21	0.13	1.18
Fluorimetric	99.7 \pm 1.01	0.45	0.564	2.08
B.P	99.2 \pm 1.1	0.29		

and intercept (S_a) on the ordinate and the standard deviation of residuals ($S_{y/x}$). The high values of the correlation coefficients of regression equations indicate good linearity and conformity to Beer's law.

Replicate determinations at different concentration levels were carried out to test the precision and accuracy of the proposed methods. The relative standard deviations (RSD%) were found to be less than 2% indicating reasonable repeatability of the proposed methods (Table 1) and the relative standard errors (Er %) were found to be less than 0.39 % indicating the high accuracy of the proposed methods. The detection

limits for methoxamine HCl ; using spectrophotometric methods were found to be $0.35 \mu\text{g ml}^{-1}$ & $0.06\mu\text{g ml}^{-1}$ for periodate and permanganate methods ,respectively and was $0.027 \mu\text{g ml}^{-1}$ for the fluorimetric method.

Ampoules assay

The proposed methods were applied to the determination of methoxamine HCl in Vasoxine[®] ampoules. The results are accurate and precise as indicated by the% recovery and RSD% less than 1.01% and Er % less than 0.45 (Table 2) . Application of the t- and F- tests showed that there was no significant difference in accuracy and precision between the proposed methods and the B.P (1993) method (Table 2) .

Conclusion

The proposed methods are simple and accurate for the determination of methoxamine HCl in bulk drugs and in pharmaceutical preparations . The fluorimetric method is the most sensitive . The periodate method , although less sensitive , is clearly superior regarding rapidity and simplicity . All methods are comparable to the B.P method .

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