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Visible Spectrophotometric Methods for the Determination of Drotaverine Hydrochloride in Bulk and in Pharmaceutical Formulations

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Abstract: Three simple, sensitive and accurate visible spectrophotometric methods (A, B and C) have been developed for the estimation of drotoverine hydrochloride in bulk and in pharmaceutical formulations. Method A, B are based on the Ion pair complex of the drug with two dyes namely erichrome black T and orange G in acidic buffer solution followed by their extraction into organic solvent, chloroform. The absorbance of chloroform layer was measured at the respective wavelength of maximum absorbance against the reagent blank. Method C is based on the oxidation /reduction reaction between drotaverine hydrochloride and folin-ciocalteu phenol's reagent to form a blue colored chromogen. All the variables have been optimized. The concentrations of measurements are reproducible within a relative standard deviation of less than 1%. The linearity was found to be 5 to 40, 5 to 30, and 10 to 70 µg/mL for method A, B and C respectively. The proposed methods were validated statistically. Recovery studies were carried out by standard addition method.

Keywords: Drotaverine hydrochloride, Folins-ciocalteu phenol's reagent, Erichrome black T.

Introduction

Drotaverine hydrochloride is an analogue of papaverine with smooth muscle relaxant properties. It is a non-anticholinergic antispasmodic, which selectively inhibits phos-phodiesterase IV and is accompanied by a mild calcium channel-blocking effect. Adverse effects with drotaverine hydro-chloride, such as hypotension, vertigo, nausea, and palpitation, are mostly mild. Chemically the drug is known as 1Z–1-(3, 4- diethoxy phenyl) methylene]-6, 7-diethoxy 1,2,3,4-tetra hydro isoquinoline hydrochloride (Figure1). Literature survey reveals that a few methods have been reported so far for the determination of drotaverine hydrochloride which includes spectropho- tometric and HPLC methods [1-7].

This paper describes three visible spectrophotometric methods for the determination of drotaverine hydrochloride by making use of the reported procedures. Method A and B have been developed for the estimation drotaverine hydrochloride by using erichrome black T and orange G. These methods are based on the formation of ion pair complexes of the drotaverine hydrochloride with erichrome black T and orange G in acetate buffer of pH 3.5, followed by their extraction into chloroform layer. The absorbance of the chloroform layer for each method was measured at its maximum absorbance against the reagent blank and in method C the reduction of heteropolyacid complex by organic reagents was utilized as the basis for the determination of several organic compounds particularly phenols, amines and enols. Among the various heteropoly acids, phospho poly molybdo tungstic acid, the well known folin-coicalteu phenol's reagent was preferred by a number of workers for determination of drugs containing phenolic and amino groups. The authors adopted the folin-coicalteu phenol's reagent for the first time to determine drotaverine hydrochloride in bulk and dosage formulations. This method is based on the formation of blue colored chromogen, when drug reacts with folin-coicalteu phenol's reagent under alkaline condition.

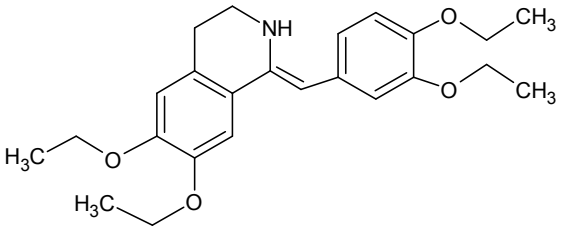

Figure 1: Structure of Drotaverine Hydrochloride

Materials and Methods

Pharmaceutical grade drotaverine hydrochloride was kindly gifted by the Blue Cross Pharmaceuticals Ltd., Nashik, and Mumbai, India and certified to contain 99.99 % of drotaverine hydrochloride. The spectral and absorbance measurements were made on Shimadzu UV-1800 double beam UV-Visible spectrophotometer with 10 mm matched quartz cells. All the chemicals used were of analytical grade and solutions were prepared with distilled water.

Preparation of standard drug solution: 100 mg of drotaverine hydrochloride was accurately weighed and dissolved in 100 mL distilled water (1mg/mL).

Method A and B: Erichrome black T (0.1 % w/v): (S.D. Fine chemicals Ltd., Mumbai, India.) 100 mg of EBT was dissolved in 100 mL of distilled water and washed with chloroform to remove chloroform soluble impurities. **Orange G (0.2 %w/v):** (NR. CHEM. Bombay, India.) 200 mg of orange G dissolved in 100 mL of distilled water and washed with chloroform to remove chloroform soluble impurities. **Acetate Buffer (pH 3.5):** 4 gm of anhydrous sodium acetate in about 840 mL of water and sufficient amount of glacial acetic acid to adjust pH to 3.5 (about 155 mL) and diluted with water to 1000 mL.**Chloroform:** (S.D.Fine chemicals Ltd., Mumbai, India.) Chloroform was purified as described by Vogel.

Method C:

Folin-coicalteu phenol's reagent: (Merck Specialties Pvt .Ltd, Mumbai, India.) 10 mL of folin-coicalteu phenol reagent was diluted to 50 mL with distilled water. **Sodium hydroxide (0.1N):** (S.D. Fine chemicals Ltd., Mumbai, India.) 4 gm of sodium hydroxide dissolved in 1000 mL of distilled water.

Experimental

Method A and B:

Into a series of 60mL separating funnels, appropriate aliquots of the standard drug solution (Table-1) were pipetted out and 1mL of distilled water was added. To each separating funnel, ace- tate buffer solution of pH 3.5 (1.5 mL for method A; 2.5 mL for method B) and dye solution (1 mL of 0.1 % w/v erichrome black T for method A; 1 mL of 0.2 % w/v orange G solution for method B) were added respectively. The solution in each separating funnel was mixed thoroughly and suc- cessively extracted with chloroform. The combined chloroform extract was transferred to 10 mL volumetric flask after passing it through a bed of anhydrous sodium sulphate and diluted to volume with chloroform. The absorbance was measured with in 1hr of complex extraction against the rea- gent blank prepared in a similar manner without drug at the absorption maxima 508 nm for method A and 486 nm for method B. The data that proves the linearity is shown in Table - 1.

Method C:

Aliquots of drotaverine hydrochloride solution (10-70 µg/mL) were transferred to a series of 10 mL volumetric flask and 0.5 mL 0.1N of sodium hydroxide solution was added. Then 1.5 mL of folin-coicalteu phenol's reagent was added and kept aside for 5 min at room temperature. The solutions were made up to the volume with distilled water and the absorbance was measured at 674 nm against the reagent blank. The blue colored species was stable for 3 hrs. The amount of the drug was computed from Beer Lambert's plot.

Procedure for the assay of drotaverine hydrochloride in tablets: Twenty tablets were weighed and ground to fine powder. An accurately weighed powder sample equivalent to 100 mg of drotaverine hydrochloride was taken and sample solution was prepared as described for the standard and filtered prior to analysis. An appropriate aliquot was withdrawn and the estimation of drug content was carried out as described under the procedure for calibration curve.

Results and Discussion

The proposed methods are simple, rapid, accurate and precise. Drotaverine hydrochloride was found to yield a clear pink colored complex with erichrome black T and orange colored complex with orange G, extractable with chloroform having the absorption maxima of 508 and 486 nm respectively. The colored products are due to the ion pair complex formation of the drug with the dye in the presence of acetate buffer of pH 3.5. The blue colored complex formed in method C is probably due to the reduction of 1, 2 and 3 oxygen atoms from tungstate and / or molybdate in folin-coicalteu phenol's reagent, there by producing one or more of the possible reduced species which has a characteristic intense blue color.

Optimization of parameters: Investigations were carried out to establish the most favorable conditions for the formation of the colored product.

Method A and B: The influence of different pH buffers [pH range 2.5 to 6.8] on the reaction has been studied. It was observed that absorbance started decreasing above pH 3.5 and no color was found with phosphate buffer of pH 6.8. Hence acetate buffer of pH 3.5 used in further studies. The influence of different amounts of pH 3.5 buffer on reaction has been studied. It was observed that the absorbance started decreasing above 1.5 ml for method A and 2.5 mL for method B. Hence 1.5 mL of acetate buffer for method A and 2.5 mL for method B were used respectively, in further studies. The effect of changing the concentrations of erichrome black T and orange G over the range of 1 to 5 mL was examined and it was observed that the absorbance started decreasing above 1.0 mL for method A and B. Hence 1.0 ml of 0.1 % w/v erichrome black T and 1.0 mL of 0.2 % w/v orange G solution was used in further studies. There was no effect of time on the stability of the color up to 1 hour after extraction. However a decrease in the absorbance was noted there after. Hence, it is recommended that the absorbance should be measured within this time.

Method C: The effects of various parameters such as nature of alkali, reaction time, volume of sodium hydroxide solution, folin-coicalteu phenol's reagent and the stability of colored species formed were studied; 0.5 mL of 0.1 N sodium hydroxide and 1.5 mL of folin-coicalteu phenol's reagent were considered optimal. Several alkalies like sodium carbonate, sodium hydroxide were tried but sodium hydroxide was preferred for the high sensitivity .The reaction time was found to be 5 min. and the color was stable for 3 hours. The results are shown in Table - 2.

Conformity to Beer's law: The optical characteristics such as Beer's law limit, molar absorptivity, Sandell´sensitivity and the regression analysis using the method of least square was made for the slope (b), intercept (a). Correlation coefficient (r), % range of error (0.05 and 0.01 confidence limits), and % RSD were also determined for the proposed methods and results are presented in Table-3. Commercial formulations containing drotaverine hydrochloride were successfully analyzed by the reference and proposed methods. The results obtained by the proposed and reference methods for dosage forms are summarized in Table-4. Recovery studies were performed by adding a fixed amount of the drug to the pre analysed formulations and the results are presented in Table - 4. Interference studies reveals that the common excipients and other additives usually present in the dosage forms did not interfere in the proposed methods.

Conclusion

All the proposed three methods are most economical, simple and accurate. So, the methods can be used for routine determination of drotaverine hydrochloride in bulk as well as in its pharmaceutical preparation.

Table 1 : Optimum conditions and results of the proposed methods for the determination of drotaverine hydrochloride

Reagent	Method A	Method B
Drug solution taken (µg/mL)	5-40	5-30
Volume of buffer (mL)	1.5	2.5
pH of buffer solution	3.5	3.5
Volume of reagent employed (mL)	1.0	1.0
λ max (nm)	508	486

Table 2: Optimum conditions and results of the proposed method for the determination of drotaverine hydrochloride

Reagent	Method C
Drug solution taken	10-70 µg/mL
Volume of 0.1 N NaoH	0.5 mL
Volume of reagent employed	1.5 mL
λ max	674 nm

Table 3: Optical characteristics and precision of the proposed methods for drotaverine hydrochloride

Parameters	**Method**		
	A	**B**	**C**
λ max (nm)	508	486	674
Beer's law limit (mcg/mL)	10-50	5-30	10-70
Sand ell's sensitivity (mcg/cm^2/0.001A.U)	0.0454	0.0230	0.5997
Molar Absorptivity (L mol^{-1}cm^{-1})	0.0954×10^6	0.1879×10^6	0.0716×10^6
Correlation coefficient(r^2)	0.999	0.999	0.998
Regression equation (y=b+ax)**			
Slope(a)	0.0212	0.0413	0.0169
Intercept(b)	0.0218	0.0180	-0.0069
Range of errors*			
Confidence limit with 0.05 level	0.6164	0.3381	0.5799
Confidence limit with 0.01 level	0.9120	0.5002	0.8748
% Relative Standard Deviation*	0.7372	0.4044	0.7072

*

Average of eight determinations

** Y=B+AX, Y IS THE ABSORBANCE AND X IS THE CONCENTERATION IN µG/ML

Table 4: Assay and recovery of drotaverine hydrochloride in pharmaceutical formulations

Pharmaceutical formulations	Labeled amount found (mg)	Amount found in [a] (mg) using proposed methods ± S.D			Found by reference method [c] ±S.D	%Recovery by proposed methods [b] ± S.D		
		A	B	C		A	B	C
Tablet-1	80	80.075 ±0.141	79.865 ±0.686	79.975 ±0.505	80.258 ±0.859	100.313 ±0.196	99.973 ±0.183	99.826 ±0.126
Tablet-2	80	80.051 ±0.526	80.187 ±0.418	80.016 ±0.615	79.866 ±0.863	100.041 ±0.164	100.161 ±0.129	100.160 ±0.144
Tablet-3	80	79.731 ±0.688	79.811 ±0.608	80.053 ±0.506	80.076 ±0.477	99.952 ±0.273	100.254 ±0.266	100.416 ±0.323

[a]Average ± standard deviation of six determinations.
[b]Recovery of 10 mg added to the pre-analyzed pharmaceutical formulations (average of three determinations).
[C] U.V method using distilled water as solvent at λ max 230 nm.

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