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ESTIMATION OF DROTAVERINE AND OMEPRAZOLE IN COMBINED DOSAGE FORM BY SPECTROPHOTOMETRIC METHODS

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ABSTRACT
Two simple, precise, accurate and reproducible spectrophotometric methods have been developed for the simultaneous estimation of Drotaverine HCl (DRO) and Omeprazole (OME) in combined tablet dosage form. The first method is the Area under curve method, the sampling wavelength range selected for estimation of drotaverine and omeprazole are 227.5-231.5 nm and 300.0-304.0 nm respectively with linearity in the concentration ranges of 4-24 ìg /ml and 1-6 ìg/ml respectively. Second method is based on two wavelength calculations, wavelengths selected for estimation of drotaverine were 300.0 nm and 304.0 nm and for Omeprazole were 279.5 nm and 290.5 nm over the concentration ranges of 4-16 ìg/ml and 1-6 ìg/ml for drotaverine and omeprazole respectively. The results of the analysis were validated statistically and recovery studies were carried out as per ICH guidelines.

Keywords: *Drotaverine; Omeprazole; Area under curve method; Two-wavelength method; ICH guidelines.*

INTRODUCTION

Chemically drotaverine hydrochloride is 1-[(3,4-Diethoxyphenyl)-methylene]-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline and is official in Pharmacopoeia of Poland [1]. Omeprazole is 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole. It is official in IP [2], USP [3] and BP [4]. Drotaverine (DRO) is an analog of *Papaver somnifera* and is used as an anti-spasmodic drug. It causes inhibition of phospodiesterase enzyme which causes reduction in contraction of smooth muscles. It is thus used in gastric ulcer diseases and gastro-intestinal cancer [5]. Omeprazole (OME) is the proton pump inhibitor. In the acidic conditions of the stomach, it reacts with a cysteine group in H^+/K^+- ATPase, thereby destroying the ability of the parietal cells to produce gastric acid[5]. Thus together both these drugs have synergestic effect in controlling the gastric ulcer diseases.

Various methods such as, HPLC [6-12], HPTLC [6, 9, 13-14], UV spectrophotometry methods [6, 13-18] have been reported for individual drugs in formulation but no method has been reported for this combination anywhere before. Literature survey reveals that no method has been reported for simultaneous analysis of DRO and OME in its combination. Here an attempt has been made to develop simple, rapid and accurate spectroscopic methods for simultaneous estimation of DRO and OME from its formulation.

MATERIAL AND METHODS

Instrumentation

A Shimadzu UV/Visible spectrophotometer, model 1700 (Japan) was employed with spectral bandwidth of 2 nm and wavelength accuracy of ± 0.5 nm, with automatic wavelength correction employing a pair of quartz cells. A Shimadzu electronic analytical balance (AX-200) was used for weighing the sample.

Reagents and chemicals

Pure gift samples of Drotaverine and Omeprazole obtained from Sanofi-Aventis, Mumbai, India were used in the study. The pharmaceutical dosage form used in this study was Ranispas-DV (Penta Biotech, India) labeled to contain 40 mg of Drotaverine HCl and 10 mg of Omeprazole per tablet.

Standard stock solution (for both methods)

Standard stock solutions (100 µg/ml) of DRO and OME were prepared by dissolving separately 10 mg of each drug each in 100 ml methanol. The working standard solutions of these drugs were obtained by dilution of the respective stock solution with methanol.

Method A – Area under curve method

The AUC (area under curve) method involves the calculation of integrated value of absorbance with respect to the wavelength between two selected wavelengths ë1 and ë2. Area calculation processing item calculates the area bound by the curve and the horizontal axis. The horizontal axis is selected by taking the wavelength at which absorbances are approximately same. This wavelength range is selected on the basis of repeated observations so as to get the linearity between area under curve and concentration. Suitable dilutions of standard stock solution of both drugs were prepared and scanned in the spectrum

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mode from the wavelength range 400–200 nm respectively. The sampling wavelength ranges selected for estimation of DRO and OME are 227.5-231.5 nm ($ë_1$-$ë_2$) and 300.0-304.0 nm ($ë_3$-$ë_4$) respectively as shown in fig. 2 where both drugs showed linearity (table 1). The mixed standards of DRO and OME were prepared in the ratio of concentration 4:1 µg/ml and their areas under curve were measured at the selected wavelength ranges. The "X" value = Area under curve of the component/concentration of the component in g/l. were determined for the two drugs at the selected wavelength ranges. A set of two equations was formed using these "X" values as follows,

$A_1 = 157.7C_{DRO} + 161.4C_{OME}$ ——————————--- (I)

$A_2 = 45.4C_{DRO} + 203.4C_{OME}$ ——————————— (II)

Where – 157.7 and 45.4 are X value of DRO at $ë_1$-$ë_2$ and$ë_3$-$ë_4$ respectively. 161.4 and 203.4 are X value of OME at $ë_1$-$ë_2$ and $ë_3$-$ë_4$ respectively. A_1 and A_2 are areas of mixed standard at ë1-$ë_2$ and $ë_3$-$ë_4$ respectively.
C_{DRO} and C_{OME} are concentration in g/l.

The concentration of C_{DRO} and C_{OME} in mixed standard and tablet formulation can be obtained by solving equation (I) and (II)

Method B – Two wavelength method

For the two-wavelength method, appropriate dilutions of two drugs (16 µg/ml of DRO and 4µg/ml OME) were prepared separately using standard stock solutions and the same were scanned in the range of 400 nm to 200 nm to obtain overlain spectra (Fig 1). The drotaverine shows same absorbances at 279.5 nm and 290.5 nm but different at 300.0 nm and 304.0 nm while omeprazole has same absorbances at 300.0 nm and 304.0 nm but different at 279.5 nm and 290.5 nm hence the absorbances of DRO was measured at 300.0 nm and 304.0 nm and for OME at 279.5 nm and 290.5 nm where the drugs showed good linearity with regression coefficients (Table 1). Mixed standards were prepared and absorbances were measured at the selected wavelengths. The concentrations of both the drugs in

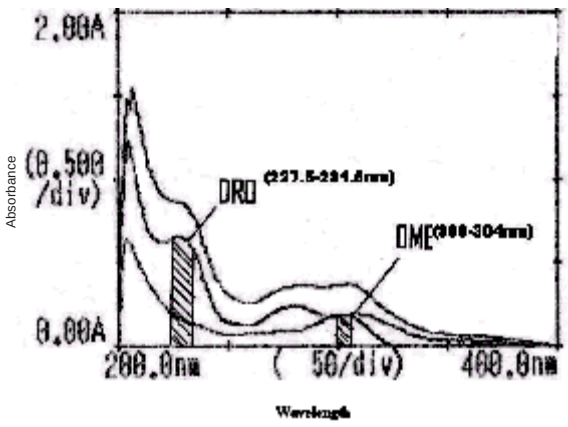

Fig. 1. *Area under curve method*

Table 1. *Optical Characteristics and Validation Data of Drotaverine and Omeprazole*

Parameters	Drotaverine		Omeprazole	
	Method-A	Method-B	Method-A	Method-B
Working wavelengths	227.5-231.5 nm	300-304 nm	300-304 nm	279.5-290.5 nm
Beer-Lamberts law ranges (µg/mL)	1-6	4-24	1-6	4-24
Precision*				
Interday (%RSD)				
Intraday (%RSD)	1.0730	1.4701	1.0110	1.5708
LOD (µg/ml)*	1.8134	1.1930	1.4035	0.2998
LOQ (µg/ml)*	0.6224	0.1949	0.1490	0.1676
Regression Values: I. Slope*	0.1270	0.9900	0.9548	0.2048
II. Intercept*	0.1405	0.0015	0.1597	0.011
III. Regression coefficient(r²)*	0.9998	-0.8013	0.0104	0.0005
	0.9995	0.9975	0.9979	0.9987

** average of six estimations, Method-A – Area under curve method, Method-B – Two-wavelength method*

mixed standards and the sample solution were calculated by using following formula:-

A=abc————————— (III)

Where a=absorbance difference, b=path length and c=concentration in gL^{-1},

The absorptivity values for DRO =22.8 …….. (Abs304.0-Abs300.0 nm)

The absorptivity values for OME =44.4…….. (Abs290.5-Abs279.5 nm)

Assay of tablet formulation by method A and method B

Twenty tablets were weighed and crushed to fine powder. An accurately weighed powder sample equivalent to 40 mg of Drotaverine was transferred to a 100 ml volumetric flask.and dissolved in 50 ml of methanol. After the dissolution, the volume was made up to the mark with the same solvent. The solution was sonicated for about 30 min and was then filtered through Whatmann filter paper No.41. The solution was suitably diluted with methanol to obtain sample solutions containing DRO and OME in the concentrations ratio of 16:4 µg/ml respectively. Area under curve of sample solutions were recorded at 227.5-231.5 nm for DRO and 300.0-304.0 nm for OME and the concentration of two drugs in the sample solution were determined by using equations (I) and (II) for Area under curve method (Method-I). The absorbances of solutions were recorded at 300.0nm and 304.0nm for DRO and 279.5 and 290.5 nm for OME. The concentrations of each drug in sample solutions were calculated using equations (III). The results of the analysis and statistical validation data of the tablet formulation are given in Table 2.

Recovery studies

The accuracy of the proposed methods were determined by performing recovery studies at 80%, 100% and 120% of the test concentration as per ICH guidelines. The sample solutions were spiked with standard solution. The statistical validation data of recovery study is given in Table 3.

Table 2. *Statistical Validation Data of Tablet Formulation*

Component	Amount present (mg)	Method	%Amount found	Standard deviation*	Relative standard Deviation*	Standard error*
DRO	40	A	101.05	0.0696	0.0549	0.0268
	40	B	101.04	0.8307	0.8221	0.3391
OME	10	A	98.72	0.5115	0.5181	0.2088
	10	B	99.32	0.6585	0.6630	0.2688

** average of six estimations, Method-A – Area under curve method and Method-B – Two-wavelength method*

Table 3. *Statistical Validation of Recovery Studies*

Level of % recovery	Methods	% Recovery*		Relative standard Deviation*		Standard error*	
		DRO	OME	DRO	OME	DRO	OME
80	A	100.52	100.60	0.157 4	0.4453	0.09135	0.2587
	B	100.52	99.39	0.3739	0.2932	0.2170	0.1683
100	A	100.80	100.29	0.5446	0.4736	0.3170	0.2742
	B	100.80	100.29	0.5446	0.4736	0.3170	0.2742
120	A	100.70	101.02	0.6996	1.2136	0.4067	0.7018
	B	100.65	100	0.397 4	0.5237	0.2309	0.3024

** average of three estimations at each level of recovery.*
Where, Method-A – Area under curve method and Method-B – Two-wavelength method

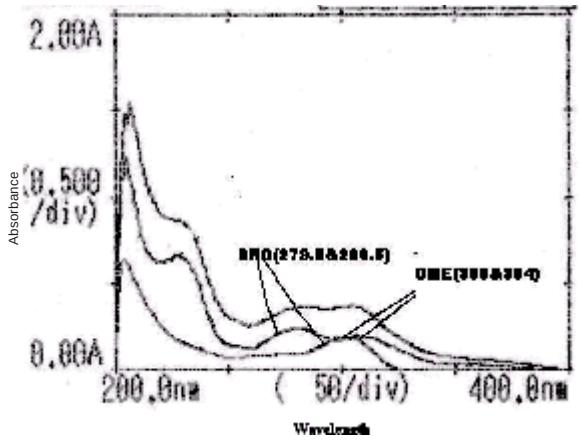

Fig. 2. *Two wavelength method*

RESULTS

An attempt has been done to develop two spectroscopic methods for determination of DRO and OME used for treatment of peptic ulcer. The developed methods were validated as per ICH as shown in Table 1. Also the proposed methods were applied for the assay of commercially available tablets containing DRO and OME (n =6) which had RSD values less than 2 as shown in Table 2.The accuracy of the proposed methods was confirmed .by performing the recovery studies (Table 3). Also the results of the proposed methods were evaluated stastistically using t test and f test to show that there is no significant difference between said methods for the analysis of DRO and OME, the results of which are given in Table 4.

Table 4. *Statistical Significance of Difference between Two Methods*

	DRO	OME
t value	0.03919	0.1340
F value	4.96	2.424

where
t =0.03919 and t=0.1340 for DRO and OME respectively, at 10 degrees of freedom, F=4.96 and F=2.424 for DRO and OME respectively, at (1, 10) degrees of freedom

CONCLUSIONS

Drotaverine and Omeprazole are available in combined tablet dosage form for the treatment of gastric ulcer. No single UV spectrophotometric method has been reported so far for the estimation of both the drugs in combined tablet dosage form. Here two simple UV spectrophotometric methods (Area under curve method and Two wavelength method) were developed for their simultaneous analysis. The RSD values for the tablet assay by both the methods is less than 2%. The % recovery was between 98-102% indicating high degree of accuracy of the proposed methods. The results of the t test and F test also indicates that there exists no significant difference between the two methods for the analysis of Drotaverine and Omeprazole in bulk and formulation. The developed methods are simple, rapid, precise, accurate and can be employed for the routine estimation of Drotaverine and Omeprazole in both bulk and tablet dosage form.

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