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SIMULTANEOUS SPECTROPHOTOMETRIC ESTIMATIONS OF DROTAVERINE HYDROCHLORIDE AND OMEPRAZOLE

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ABSTRACT: Three simple spectrophotometric methods have been developed for simultaneous estimation of Drotaverine HCl and Omeprazole from tablet dosage form. Method-I involves, formation of Q-absorbance equation at 306.0 nm (isoabsorptive point) and 229.5 nm (λmax of drotaverine); simultaneous equation method (Method-II) and Method-III is the multicomponent mode of analysis in which the inbuilt software calculates the concentration of the sample solution, The absorbances of the standard solutions were taken at two wavelengths 229.5 nm (λmax of drotaverine) and 302 nm (λmax of omeprazole) in methanol and the linearity lies between 1-24 μg/ml for drotaverine and 1-6 μg/ml for omeprazole for all the three methods. The accuracy and precision of the methods were determined and validated stastically. All the methods showed good reproducibility and recovery with % RSD less than 2. All methods were found to be rapid, specific, precise and accurate and can be successfully applied for the routine analysis of drotaverine and omeprazole in bulk and combined dosage form.

Key Words: Drotaverine HCl, Omeprazole, Q-Absorbance ratio method, Simultaneous equation method, Multicomponent mode of analysis.

INTRODUCTION AND EXPERIMENTAL

Chemically drotaverine hydrochloride is 1-[(3,4-di ethoxyphenyl)methylene]-6,7-diethoxy-1, 2, 3, 4-tetrahydro isoquinoline and is official in Pharmacopoeia of Poland [1]. Omeprazole is 5-methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridinylmethylsulfinyl)-1H-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 phospo diesterase enzyme which leads to 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, omeprazole react 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 synergistic 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.

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 HCl 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 ALL THREE METHODS)

Standard stock solutions (100 µg/mL) of DRO and OME were prepared by dissolving accurately about 10 mg of each drug separately in methanol in 100 ml volumetric flask. The working standard solutions of these drugs were further diluted to get different concentration ranges for calibration curves.

METHOD I Q-ABSORBANCE RATIO METHOD:

Q-absorbance ratio method uses the ratio of absorbances measured at two selected wavelengths, one at isoabsorptive point and other being the λmax of one of the two compounds. From the stock solutions (100 µg/mL), working standard solutions of drotaverine (16 µg/mL) and omeprazole (4 µg/mL) were prepared by appropriate dilution and were scanned in the entire UV range to determine the maximum absorbance (λmax) and iso-absorptive point. Drotaverine has λmax at 229.5 nm and omeprazole has λmax at 302.0nm. Both the drugs were found to have same absorbance at 306.0 nm (iso-absorptive point). The wavelengths selected for analysis were 229.5 nm and 306.0 nm respectively (Fig.1). A series of standard solutions ranging from 4-24 µg/mL for drotaverine and 1-6 µg/mL for omeprazole both were prepared and the absorbance of solutions was recorded at 229.5 and 302.0 nm respectively to plot a calibration curve of absorbance versus concentration. The calibration curves were found to be linear in the concentration range under study (Table-1). Absorptivity values of drotaverine and omeprazole were determined at selected wavelengths. The concentration of two drugs in mixture was calculated by using following equations:

C_{DRO} = Qm – Qy/ Qx – Qy X A1/ ax1…… (1)
C_{OME} = Qm – Qx/ Qy – Qx X A1/ ay1……(2)
Qm = A2/A1, Qx = ax2/ax1 and Qy = ay2/ay1
Where A1 and A2 are the absorbances of mixture at 306.0 nm and 229.5 nm and ax1 (12.4), ax2 (40.3) and ay1 (50.0), ay2 (41.2) are absorptivities A (1%, 1 cm) of drotaverine and omeprazole at 306.0 nm and 229.5 nm.

METHOD – II: SIMULTANEOUS EQUATION METHOD: For the simultaneous equations, the standard solutions prepared were scanned in the UV range from 400nm-200 nm and the absorbance maxima (λmax) for DRO is 229.5 nm and 302.0 nm for OME and were selected as the sampling wavelengths. DRO and OME exhibited linearity with absorbances in the range of 1-24 µg/ mL and 1-6 µg/ mL, at their respective selected wavelengths.(Table-1.). For simultaneous estimation of DRO and OME, mixed standard solutions containing 16 µg/ mL DRO and 4 µg/ mL of OME were prepared by appropriate dilution of the standard stock solutions. The absorbances of the mixed standard solutions were measured at the selected wavelengths.(Fig.2) A set of two simultaneous equations were established using the mean of absorptivity coefficients of DRO and OME at the selected sampling wavelengths.

$A1 = 40.3 \times C_{DRO} + 11.2 \times C_{OME}$ ..... (3)
$A_2 = 41.2 \times C_{DRO} + 51.8 \times C_{OME}$ ..... (4)
Where, C_1 and C_2 are concentrations of DRO and OME respectively in g/ L.
A_1 and A_2 are absorbances of sample solution measured at 229.5 nm and at 302.0 nm of DRO and OME, respectively while 40.3 and 41.2 are the absorptivity values of DRO and OME at 229.5 nm and 11.2 and 51.8 are the absorptivity values at 302.0 nm of DRO and OME respectively.
The concentration of C_{DRO} and C_{OME} in mixed standard and tablet formulation can be obtained by solving equation (3) and (4). The results of the analysis and statistical validation data of the tablet formulation are given in Table – 2

METHOD – III MULTICOMPONENT MODE OF ANALYSIS:

In the third method, multicomponent mode of the instrument was used which has inbuilt software to calculate the concentration of the individual component in a mixture. The sampling wavelengths selected for the estimation of DRO and OME were 229.5 nm and 302.0 nm respectively. The concentrations of mixed solution were entered in multicomponent mode. The absorbance spectra of mix standard and sample solutions were measured at selected wavelength. The instrument processes the data and gives individual concentration of the two drugs present in sample solution directly (Fig. 2).

ASSAY OF TABLET FORMULATION BY METHOD I, II & III:

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. Absorbances of sample solutions were recorded at 306.0 nm and 229.5 nm and the concentration of two drugs in the sample solution were determined by using equations (1) and (2) for Q-absorbance ratio method (Method-I). The absorbances of solutions were recorded at 229.5 nm (λmax of drotaverine) and 302.0 nm (λmax of omeprazole). The concentrations of each drug in sample solutions were calculated using equations (3) and (4). The same tablet sample solutions were subjected to analysis in the multicomponent mode of instrument. The concentration of each drug was determined by analysis of spectral data of the sample solution with reference to the mixed standards. The analysis procedure was repeated six times for all the methods with tablet formulations. The result of analysis of tablet formulation is reported in Table- 2.

RECOVERY STUDIES:

To study the accuracy of the proposed methods, recovery studies were carried out by standard addition method at three different levels (80%, 100% and 120% of the test concentration as per ICH guidelines) [20-21]. A known amount of drug was added to pre analyzed tablet powder and percentage recoveries were calculated. The results of recovery studies were satisfactory and are presented in table 3.

Table 1: Optical Characteristics and Validation Data of Drotaverine HCl and Omeprazole

Parameters	Drotaverine HCl			Omeprazole		
	Method-I	Method-II	Method-III	Method-I	Method-II	Method-III
Working wavelengths	229.5.0 nm	229.5 nm	229.5 nm	306.0 nm	302.0 nm	302.0 nm
Beer-Lamberts Law range (µg/mL^{-1})	4-24	4-24	4-24	1-6	1-6	1-6
Precision*						
Interday (%RSD)	1.9722	1.8154	0.5869	1.9401	1.2972	0.5142
Intraday (%RSD)	1.7320	1.6244	0.4022	1.2067	0.7181	0.4189
LOD (µg/ml)*	0.2650	0.2054	0.1234	0.1230	0.1161	0.1765
LOQ (µg/ml)*	0.8401	0.6224	0.4234	0.6181	0.4011	0.2980
Regression Values:						
I. Slope*	0.0131	0.0391	-	0.0126	0.0489	-
II. Intercept*	-0.0078	0.0115	-	0.0037	0.0068	-
III. Regression coefficient(r^2)*	0.9980	0.9980	-	0.9997	0.9985	-

*Denotes average of six estimations, Where, Method-I – Q-Absorbance method,
Method-II- Simultaneous equation method , Method-III – Multi-component mode method

Table-2: Results of simultaneous estimation of marketed formulation (Ranispas Dv, Penta Biotech) for Method I, II & III

Methods	Tablet content	Label claim (mg/tab)	Label claim* (%)	RSD (%)*	SE*
I	DRO	40	99.46	1.3451	0.5491
	OME	10	100.25	1.5210	0.6209
II	DRO	40	99.87	0.8243	0.3361
	OME	10	101.08	0.8520	0.3516
III	DRO	40	100.78	1.1192	0.4606
	OME	10	100.65	1.0859	0.4463

*Denotes average of six estimations, Where, Method-I – Q-Absorbance method
Method-II- Simultaneous equation method, Method-III – Multi-component mode method

Table-3: Statistical Validation of Recovery Studies

Level of % recovery	Methods	*% Recovery		*%RSD		*SE	
		DRO	OME	DRO	OME	DRO	OME
80	I	100.43	100.27	0.3982	0.7668	0.2299	0.4427
	II	100.61	101.57	0.4993	0.8917	0.2900	0.5230
	III	100.09	100.83	0.4396	1.2625	0.2541	0.7351
100	I	99.81	99.63	0.5214	0.4362	0.3010	0.2518
	II	99.74	99.83	0.3074	0.1445	0.1770	0.0833
	III	99.32	101.17	0.6091	1.4481	0.3493	0.8457
120	I	100.14	99.83	0.5644	1.0245	0.3259	0.5915
	II	100.26	99.70	0.3697	1.1073	0.2140	0.6376
	III	100.56	99.92	0.6146	1.4842	0.3568	0.8561

*Denotes average of three estimations,Where, Method-I – Q-Absorbance method
Method-II- Simultaneous equation method , Method-III – Multi-component mode method

Fig.1. Q-Absorbance method

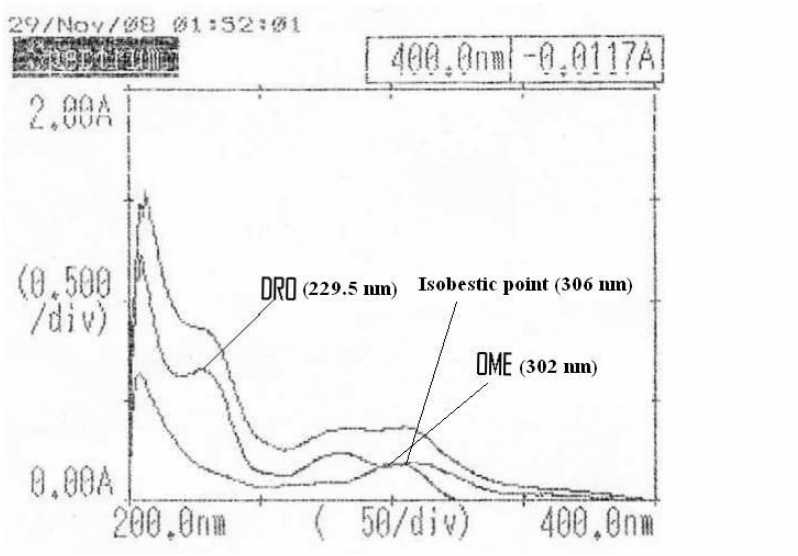

Fig. 2. Simultaneous equation method and Multicomponent mode method

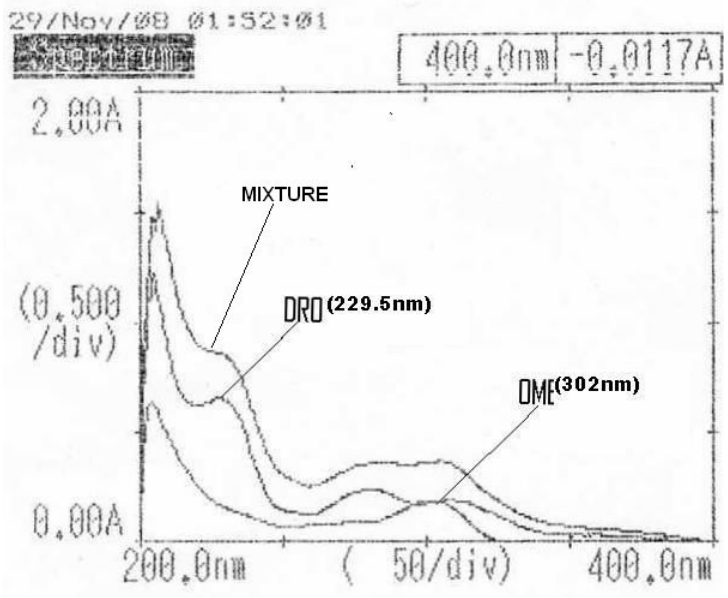

Table-4: Turkey-Kramer method of ANOVA

For Drotaverine HCl

One way Analysis of variance (ANOVA)

The P value is **0.2199** considered not significant.

Variation among column means is not significantly greater than expected by chance.

Source of Variation	Degree of freedom	Sum of square	Mean square
Treatments (between columns)	2	3.271	1.635
Residual (within columns)	15	14.616	0.9744
Total	17	17.887	-

F = 1.678 = (MStreatment/MSresidual)

Methods	Mean difference	P value
Q-Abs Vs SE method	0.01500	ns P>0.05
Q-Abs Vs Multicomponent	-0.8967	ns P>0.05
SEmethod Vs Multicomponent	-0.9117	ns P>0.05

For Omeprazole

One way Analysis of variance (ANOVA)

The P value is **0.5259** considered not significant.

Variation among column means is not significantly greater than expected by chance.

Source of Variation	Degree of freedom	Sum of square	Mean square
Treatments (between columns)	2	1.924	0.9622
Residual (within columns)	15	21.512	1.434
Total	17	23.436	-

F = 0.6710 = (MStreatment/MSresidual)

Methods	Mean difference	P value
Q-Abs Vs SE method	-0.8000	ns P>0.05
Q-Abs Vs Multicomponent	-0.3667	ns P>0.05
SEmethod Vs Multicomponent	0.4333	ns P>0.05

RESULTS AND DISCUSSION

Drotaverine and Omeprazole are available in combined tablet dosage form for the treatment of gastric ulcer. UV spectrophotometric method has not been reported so far for the estimation of both the drugs in combination tablet dosage form. Here three simple UV spectrophotometric methods (Q-absorbance ratio, Simultaneous equation method and Multi component mode method) were developed for their simultaneous analysis. The standard deviation, RSD and standard error calculated for both the methods are low, indicating high degree of precision of the methods. The RSD is also less than 2% as required by ICH guidelines. The % recovery was between 98-102% indicating high degree of accuracy of the proposed methods. The developed methods were compared statistically using Turkey-Kramer one way ANOVA which showed P>0.05 and the LSD value was 1.2144 thus considered insignificant. The calculated F value was1.678 and 0.6710 for DRO and OME respectively which is less than standard F value (table 4). 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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