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Simultaneous determination of Rabeprazole sodium and Domperidone

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ABSTRACT

Three simple and sensitive methods were developed for the determination of a mixture of Rabeprazole sodium RB and Domperidone DP without prior separation. The first method A, isoabsorptive point comprised of measurement the total content of the mixture at their isoabsorptive point, while the content of RB was determined by measuring the first order derivative of its spectra at 231 nm, and the content of DP could be calculated by subtraction. The second method, B was based on the mean centering of ratio spectra, the concentration of RB was determined by measuring the amplitude at 256.4 nm and the concentration of DP was determined by measuring the amplitude at 311.8 nm. The third method C, dual wavelength method, the wavelengths selected for determination of Rabeprazole were 270 nm & 301 nm, whereas, the wavelengths selected for determination of Domperidone were 260 and 297.2 nm. The percentages mean accuracy for RB were 99.74 ± 0.498 % for method (A), 100.52 ± 0.478 % for (B) and 100.43 ± 0.502 % for (C) respectively. And that of DP were 100.28 ± 0.488 % for method (A), 99.24 ± 0.551 % for (B) and 99.95 ± 0.516 % for (C) respectively. The obtained results were statistically compared with those obtained by the official methods, showing no significant difference with respect to accuracy and precision.

Keywords: Rabeprazole, Domperidone, Isoabsorptive point, Mean centering, Dual wavelength.

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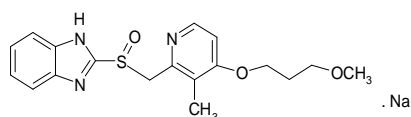
1. INTRODUCTION

Rabeprazole sodium (RB) (Fig. 1) is a proton pump inhibitor. It is used in the treatment of sever gastro-oesophageal reflux disease, also used for the treatment of active peptic ulcer disease (Sweerman & Martindale, 2004). It is a prodrug that requires activation in the acid environment (Gilman et al., 2001). As a Proton pump inhibitor it is used in the treatment of Zollinger-Ellison syndrome, (Sweerman & Martindale, 2004; Gilman et al., 2001). While Domperidone (DP) (Fig. 1) is a dopamine antagonist, used as an antiemetic for the short-term treatment of nausea and vomiting of various etiologies. It is also used for its prokinetic actions in dyspepsia. RB and DP are co-formulated together in commercial tablets for abdominal disturbance. Determination of RB was determined by several methods including spectrophotometric methods (El-Gindy et al., 2003; Garcia et al., 2006; Sabnis et al., 2008; Syed & Syeda, 2008), spectrofluorimetric methods (Khan et al., 2009; Osman, 2009), TLC-densitometric methods (Raval et al., 2008), HPLC methods (Garcia et al., 2004; Asfak et al., 2007; Rao et al., 2008). It was also determined by electrochemical methods (Radi et al., 2004; Moneeb, 2008). While DP was determined by several methods involving spectrophotometric methods (Mohamed et al., 1989; Al-khamis et al., 1990; Salem et al., 2002; Sherje et al., 2008), TLC-densitometric methods (Gosavi et al., 2006; Patel et al., 2007), HPLC methods (Yamamoto et al.,

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1998; Ali et al., 2006; Michaud et al., 2007; Thanikachalam & Kannappan, 2008), electrochemical methods (Wahdan & El-Ghany, 2005; El-Shahawi et al., 2006). Also determination of the mixture of the two drugs by spectrophotometric method (Patel et al., 2010), TLC-densitometric method (Chitlange et al., 2010; Patel et al., 2007) and HPLC methods (Kalirajan et al., 2008; Sabnis et al., 2008) were reported.

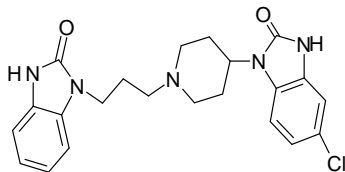
The aim of this work is to develop easy, sensitive and fast methods that can be applied for the routine analysis of the drugs simultaneously in laboratory mixtures and in their pharmaceutical formulations without previous separation.



Molecular formula : $C_{18}H_{20}N_3NaO_3S$

Molecular weight : 381.4

Rabeprazole sodium



Molecular formula : $C_{22}H_{24}ClN_5O_2$

Molecular weight : 425.99

Domperidone

2. EXPERIMENTAL

2.1. Apparatus

SHIMADZU UV-Visible spectrophotometer-model 1601 PC, with two matched 1-cm quartz cells, connected to an IBM compatible personal computer (PC) and HP-600 inject printer. Bundled UV-PC personal spectroscopy soft ware version (3.7). The spectral band width was 0.2 nm with wavelength scanning speed of 2800 nm/min., (Shimadzu, Kyoto, Japan).all computations were performed using Matlab ® version 6.5

2.2. Reference Samples

2.2.1. Rabeprazole sodium (RB)

Pure sample was kindly supplied by Global Nabi Co., batch number 90330; (Giza - Egypt). Its percentages purity was 100.26 ± 0.461 % according to the reported method (El-Gindy et al., 2003).

2.2.2. Domperidone (DP)

Pure sample was kindly supplied by Minapharm Co., batch number ZR03361PU1971; (10th of Ramadan - Egypt). Its percentage purity was 99.75 ± 0.462 % according to the reported method (Thanikachalam et al., 2008).

2.3. Pharmaceutical formulations

Rabesym-D 20/10 tablets-Batch number C6960016. Each tablet is claimed to contain 20 mg of RB and 10 mg of DP. Manufactured by: Symbiosis pharmaceuticals, Pvt. Ltd, (India).

2.4. Standard solutions

2.4.1. *RB stock standard solution:* (0.2 mg mL⁻¹) in methanol for the three methods.

2.4.2. *DP stock standard solution:* (0.2 mg mL⁻¹) in methanol for the three methods.

2.5. Laboratory prepared mixtures containing different ratios of RB and DP.

Into a series of 25-ml volumetric flasks, aliquots of RB and DP were transferred from their corresponding stock solutions (0.2 mg mL⁻¹) each, and then the volume was completed with methanol. That prepares mixtures containing different ratios of the two drugs.

2.6. Procedures

2.6.1. Spectral characteristics of RB and DP

The zero order absorption spectra of 24 µg mL⁻¹RB , 24 µg mL⁻¹DP and a (1:1) mixture containing 12 µg mL⁻¹of each RB and DP in methanol were recorded and presented .

2.6.2. Linearity

2.6.2.1. *For method (A):* For the determination of RB, aliquots (0.5, 1,.....4.5 mL) from RB stock solution (0.2 mg mL⁻¹) in methanol were accurately transferred into a series of 25-ml volumetric flasks and the volume was completed to the mark with methanol and the spectra were recorded from 200 – 350 nm and were stored in computer and the first derivative spectra ¹D, were gotten. The peak amplitudes of the ¹D spectra, with $\Delta \lambda = 4$, scaling factor 10 at 231 nm was measured then a calibration curve relating the peak amplitude of the first derivative at 231 nm to the corresponding concentration of RB was constructed and the corresponding regression equation (1) was computed.

For DP determination, aliquots (0.5, 1.5.....5.5 mL) from DP stock solution (0.2 mg mL⁻¹) in methanol were accurately transferred into a series of 25-ml volumetric flasks and the volume was completed to the mark with methanol and the spectra were recorded from 200 – 350 nm and were stored in computer and their zero-order absorption spectra were measured at 299.5 nm (isabsorptive point), the calibration graph relating the absorbance to the corresponding concentration of DP in µg/ml was constructed and the regression equation (2) was computed.

2.6.2.2. *For method (B):* Aliquots (1, 2,....6 mL) of RB and DP stock standard solutions (0.2 mg mL⁻¹) in methanol) were transferred each separately into a series of 25-ml measuring flasks, the volumes were completed to the mark with methanol. The absorption spectra of the resulting solutions were measured in the range of 200-350 nm. The scanned spectra of RB were divided by the normalized absorption spectrum of DP and the obtained ratio spectra were then mean centered. The same was applied to DP spectra as they were divided by the normalized RB spectrum and were then mean centered. The calibration curves for both RB and DP were constructed by plotting the mean centered values at 256.4

nm and 311.8 nm for RB and DP, respectively, versus the corresponding concentration.

2.6.2.3. For method (C): Aliquots (0.5, 1.5,....., 5.5 ml) of RB and DP stock standard solutions (0.2 mg mL^{-1} in methanol) were transferred each separately into two series of 25-ml measuring flasks, the volumes were completed to the mark with methanol. The absorption spectra of the resulting solutions were measured in the range of 200-350 nm.

For the determination of RB, the two wavelengths 270 and 301 nm were selected and the absorbance difference of RB and these wavelengths was recorded. While for the determination of DP, 260 and 297.2 nm were selected and the absorbance difference of DP and these wavelengths was recorded. Calibration curves relating the absorbance difference at the selected wavelengths to the corresponding concentrations of RB and DP were constructed and the corresponding regression equations were computed.

2.6.3. Analysis of laboratory prepared mixtures

2.6.3.1. For method (A): The absorption spectra of laboratory prepared mixtures [2.5.] were recorded. For the determination of RB the first order absorption of the obtained spectra of the mixtures were recorded, then the concentration was calculated using regression equation (1). For the determination of the mixture, the stored spectra of the prepared mixtures were recorded by measuring the zero order absorption spectra at 299.5 nm (isoabsorptive point). The concentration of the mixtures was calculated using regression equation (2), DP concentration could be obtained after subtraction using the following equation: DP concentration = (total concentration of the mixtures – RB concentration).

2.6.3.2. For method (B): The absorption spectra of laboratory prepared mixtures [2.5.] were recorded. Then procedure was performed as described in subsection [2.6.2.2.] of Linearity

2.6.3.3. For method (C): The absorption spectra of laboratory prepared mixtures [2.5.] were recorded. The procedure was performed as described in subsection [2.6.2.3.] of Linearity

2.6.4. Application of the proposed methods for the determination of RB and DP in pharmaceutical formulations.

Analysis of Rabesym-D Tablets

Ten tablets were weighted accurately and powdered. An amount of the powder equivalent to 20 mg of RB was accurately weighted into a beaker and 80 ml of methanol was added with continuous stirring for 10 minutes using a magnetic stirrer. The solution was transferred into a 100- ml measuring flask, the volume was completed with methanol and finally was filtered, then 2.5 mL (A,C) or 3 mL (B) were accurately transferred to a 25-ml volumetric flask and volume was completed with methanol.

2.6.4.1. For method (A): The procedure was completed as described in subsection [2.6.3.1.] of Analysis of laboratory

prepared mixtures. The concentrations of RB and DP were calculated by substituting in the corresponding regression equations.

2.6.4.2. For method (B): The procedure was completed as described in subsection [2.6.2.2.] of Linearity. The concentrations of RB and DP were calculated by substituting in the corresponding regression equations.

2.6.4.3. For method (C): The procedure was completed as described in subsection [2.6.2.3.] of Linearity. The concentrations of RB and DP were calculated by substituting in the corresponding regression equations.

3- RESULTS AND DISCUSSION

3.1. For method (A)

In the isoabsorptive method, total concentration of both drugs in the mixture (T) was determined at the previously chosen isoabsorptive point. This point is determined experimentally by recording the absorbance spectra of $24 \mu\text{g mL}^{-1}$ of RB and DP separately, and that a mixture containing same total concentration ($12 \mu\text{g mL}^{-1}$ of each) as shown in Fig. (2).

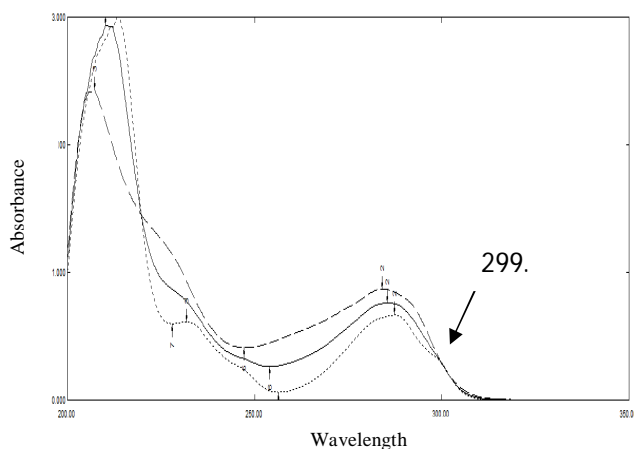


Fig. (2): Zero-order absorption spectra of $24 \mu\text{g/ml}$ of RB (---), $24 \mu\text{g/ml}$ of DP (.....) and a (1: 1) mixture containing $12 \mu\text{g/ml}$ of each (—) in methanol.

As mentioned before, RB can be determined by measuring the first order derivative of its spectra at 231 nm with no interference from DP (Fig 3), and the concentration of DP could be calculated by subtraction (Total – RB).

The linearity of the first-order absorption spectra of RB at 231 nm and the corresponding concentrations was studied, (Fig.3). Also the linearity of the zero-order absorption spectra of DP at 299.5 nm (isoabsorptive point) and the corresponding concentrations was studied, (Fig. 4). Linear relationships were obtained in the range of $4 - 36 \text{ mg mL}^{-1}$ for RB and $4 - 44 \text{ mg mL}^{-1}$ for DP and expressed by the following regression equations for RB and DP respectively;

$${}^1D_{231} = 0.0229C_{\text{RB}} - 0.0091 \quad r_1 = 0.9996 \quad \text{equation (1)}$$

$$A_{\text{iso}} = 0.0132C_{\text{T}} - 0.0227 \quad r_2 = 0.9997 \quad \text{equation (2)}$$

Where ${}^1D_{231}$ is the peak amplitude of the first derivative absorption spectra of RB at 231 nm, C_{RB} is the concentration of RB and r_1 is the correlation coefficient of equation (1). A_{iso} is the absorbance of DP at 299.5 nm, CT is the total concentration of the mixture and r_2 is the correlation coefficient of equation (2).

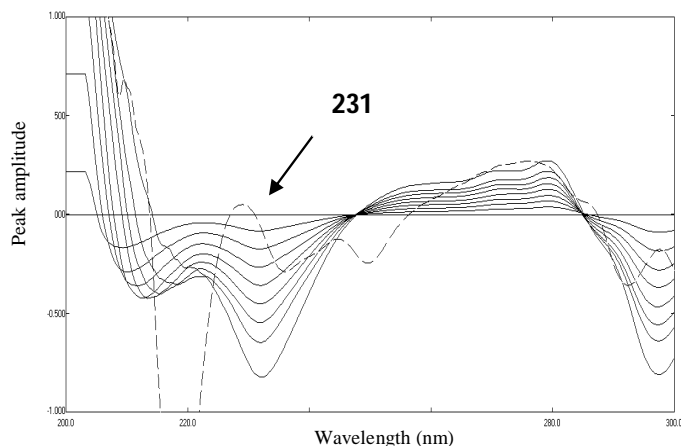


Fig. 3: First derivative absorption spectra of (4 – 36 µg/ml) RB and 20 µg/ml of DP in methanol.

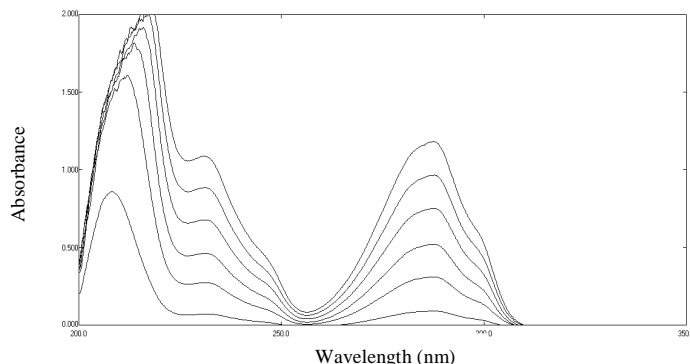


Fig. 4: Zero-order absorption spectra at 299.5 nm of DP (4 – 44 µg/ml) in methanol.

3.2. For method (B)

MCR method was applied and was able to quantitatively determine both RB and DP in their laboratory prepared mixtures and in their pharmaceutical preparation. For the determination of RB, the absorption spectra of the standard RB solutions with different concentrations were recorded in the range of 200 – 350 nm, divided by the normalized DP spectrum and then the ratio spectra were obtained. Fig. 5. The obtained ratio spectra were mean centered and the concentration of RB was determined by measuring the amplitude at 256.4 nm (corresponding to a maximum wavelength), Fig. 6.

The calibration curve relating the mean centered (MCN) values at 256.4 nm to the corresponding concentrations of RB was constructed and regression equation was computed and found to be:

$$MCN_{256.4} = 11.961C - 54.733 \quad r = 0.9995$$

Where, MCN is the amplitude at 256.4 nm, C is the concentration of RB in µg/ml and r is the correlation coefficient.

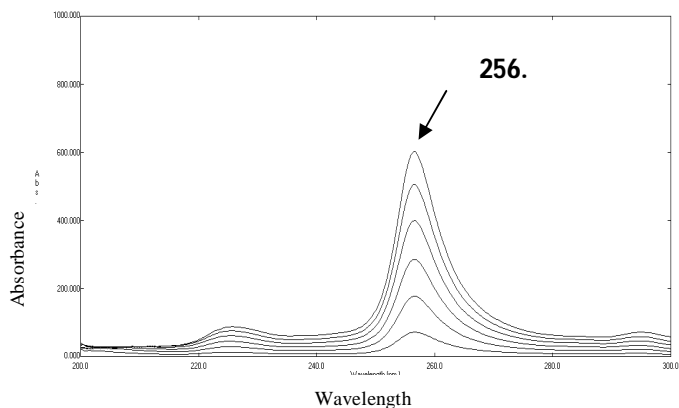


Fig. 5: Ratio spectra of RB (8-48 µg/ml), using DP normalized curve as a divisor.

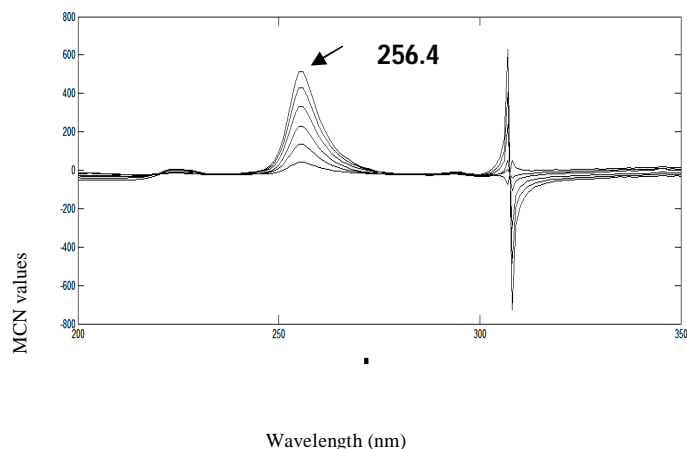


Fig 6: Mean centered ratio spectra of RB.

For the determination of DP, the absorption spectra of the standard solutions of the DP with different concentrations were recorded in the wavelength range of 200 – 350 nm, divided by the normalized RB spectrum and the ratio spectra were then obtained. The obtained ratio spectra were mean centered and the concentration of DP was determined by measuring the amplitude at 311.8 nm (corresponding to a maximum amplitude), Fig. 7.

The calibration curve relating the mean centered (MCN) values at 311.8 nm to the corresponding concentrations of DP was constructed, (Fig. 8), and the regression equation was found to be:

$$MCN_{311.8} = 1.919C + 99.16 \quad r = 0.9998$$

Where, MCN is the mean centered values at 311.8 nm, C is the concentration of DP in µg/ml and r is the correlation coefficient.

The effect of divisor concentration on the analytical parameters such as slope, intercept and correlation coefficient of the calibration graphs was also tested. Different concentrations of divisor were used but it was observed that changing the concentration had no significant effect on their linear calibration range and the calculated analytical parameters. Therefore, a normalized spectrum of each of the RB and DP was used as a divisor spectrum in the proposed method.

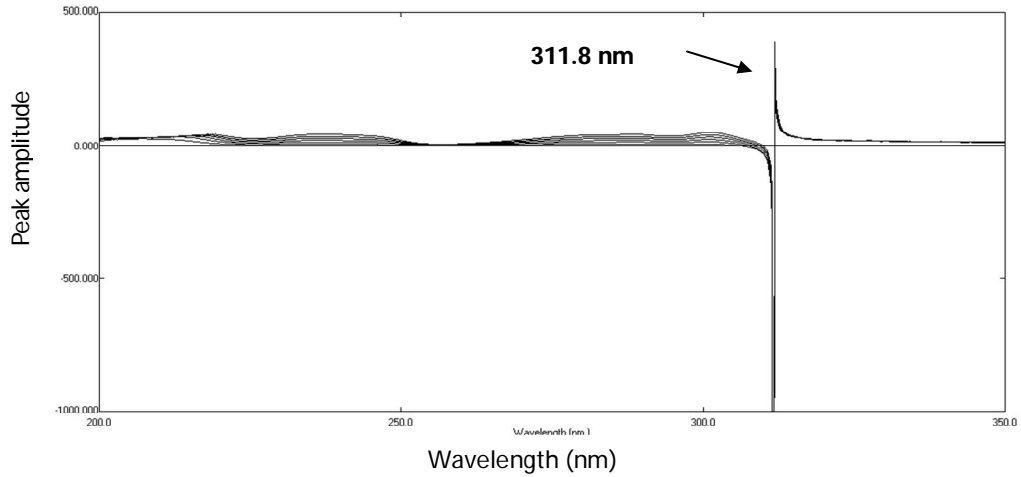


Fig 7: Ratio spectra of DP (8- 48 µg /ml), using RB normalized curve as a divisor.

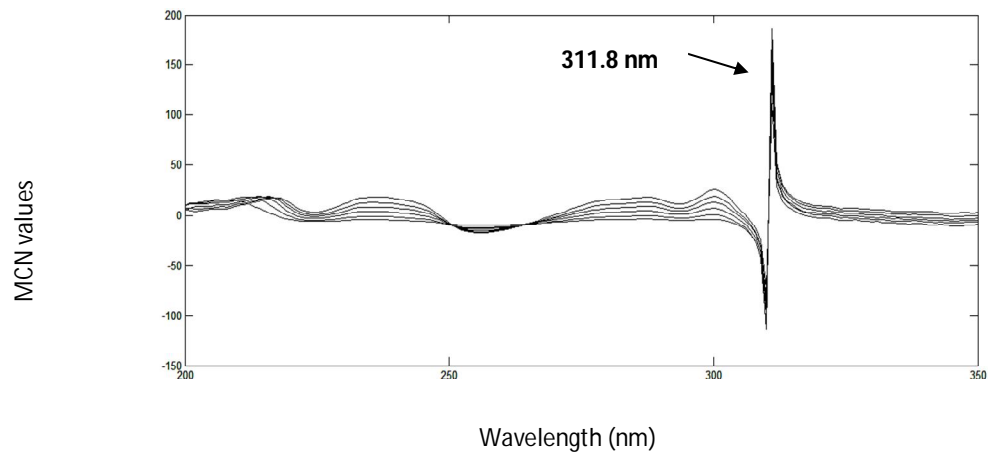


Fig 8: Mean centered ratio spectra of DP.

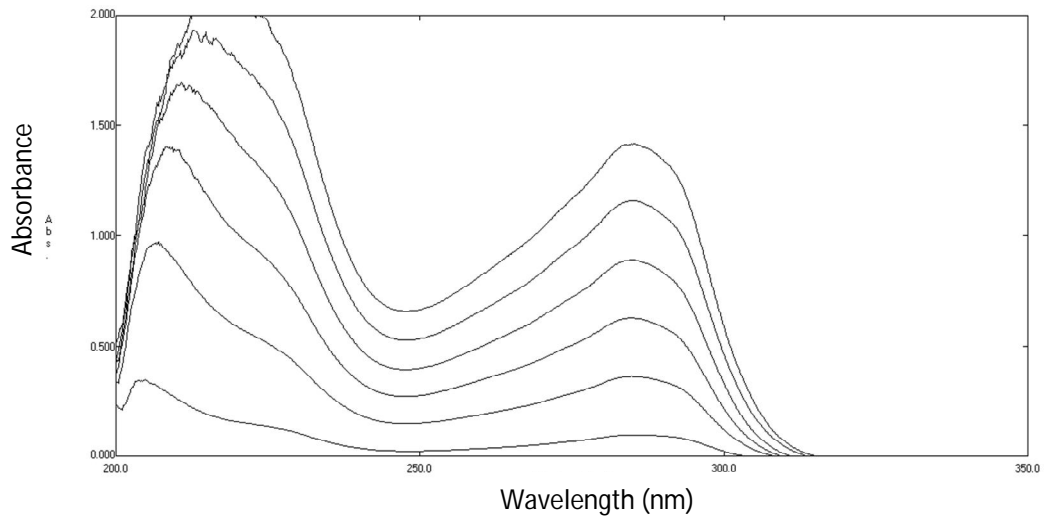


Fig 9: Zero-order absorption spectra of RB (4-44 µg/ml) in methanol.

Table 1: Results of validation parameters of the responses and the regression equations obtained by the proposed methods.

Parameter	Method (A)		Method (B)		Method (C)	
	RB	DP	RB	DP	RB	DP
Slope ^a	0.0229	0.0132	11.961	1.919	0.0124	0.0122
SE of slope	1.6 x 10 ⁻⁴	1.1 x 10 ⁻⁴	0.1370	0.0147	1.2 x 10 ⁻⁴	1.3 x 10 ⁻⁴
Intercept ^a	0.0091	0.0227	54.733	99.16	0.0019	0.0021
SE of intercept	0.0036	0.0030	4.294	0.459	0.0035	0.0038
Correlation coefficient	0.9996	0.9997	0.9995	0.9998	0.9996	0.9995
Concentration range (µg mL ⁻¹)	4 - 36	4 - 44	8 - 48	8 - 48	4 - 44	4 - 44
Average accuracy (%)	99.74	100.28	100.52	99.24	100.43	99.95
S.D.(Precision)	0.497	0.490	0.481	0.547	0.504	0.516
R.S.D. (Precision %)	0.498	0.488	0.478	0.551	0.502	0.516
Repeatability ^{a,b} (%)	0.774	0.951	0.553	0.812	0.699	0.358
Intermediate precision ^c (%)	0.638	1.250	0.491	0.730	0.821	0.372

^a Results of five determinations. ^b = 3x3 ^c = 3x3

Table 2: Determination of RB and DP in laboratory prepared mixtures by the proposed spectrophotometric methods.

Concentration (µg mL ⁻¹) RB : DP	Recovery %					
	Method (A)		Method (B)		Method (C)	
	RB	DP	RB	DP	RB	DP
24: 12	99.05	98.00	100.72	99.18	101.84	100.47
16 :16	101.90	98.51	101.34	98.24	98.84	100.97
8 :12	101.20	98.90	100.97	99.90	98.89	101.84
12 :36	101.61	98.26	100.86	98.07	101.54	101.79
36 :24	101.30	98.40	101.55	98.62	98.58	101.81
Mean	101.01	98.41	101.08	98.80	99.94	101.38
R.S.D.	1.118 %	0.337	0.342	0.756 %	1.608 %	0.616 %

Table 3: Statistical comparison of the results obtained by the proposed spectrophotometric methods and the reported methods [3,24] for RB and DP.

Item	Proposed spectrophotometric methods						Reported Method ^a [3]	Reported Method ^b [24]
	Method (A)		Method (B)		Method (C)			
	RB	DP	RB	DP	RB	DP	RB	DP
Mean	99.74	100.28	100.52	99.24	100.43	99.95	100.26	99.75
S.D.	0.497	0.490	0.481	0.547	0.504	0.516	0.463	0.461
R.S.D. %	0.498	0.488	0.478	0.551	0.502	0.516	0.461	0.462
Variance	0.247	0.240	0.231	0.299	0.254	0.266	0.214	0.212
n	9	6	6	6	6	7	6	6
Student's t- test	2.038 (2.160) ^c	1.932 (2.228) ^c	0.956 (2.228) ^c	1.753 (2.228) ^c	0.609 (2.228) ^c	0.709 (2.228) ^c		
F value	1.154 (4.82) ^c	1.132 (5.05) ^c	1.079 (5.05) ^c	1.410 (5.05) ^c	1.187 (5.05) ^c	1.254 (5.05) ^c		

^a HPLC method using methanol and water in a ratio of 70:30 v/v as a mobile phase. ^b HPLC method using methanol-acetonitrile-20 mM di-potassium hydrogen phosphate and phosphoric acid buffer pH 7.0 (20:33:47, v/v/v). ^c Figures in parentheses are the corresponding tabulated values at p = 0.05

3.3. For method (C)

The principle for dual wavelength method is “the absorbance difference between two points on the mixture spectra is directly proportional to the concentration of the component of interest”.

For the determination of RB two wavelengths (270 and 301 nm) were selected where the absorbance difference between the two wavelengths is directly proportional to the concentration of RB and the absorbance of DP at these wavelengths is constant, (Fig. 2).

Calibration curve relating the absorbance difference between 270 and 301 nm to the corresponding concentrations of RB was constructed, (Fig. 9) and regression equation was computed and found to be;

$$\Delta A = 0.0124C + 0.0019 \quad r = 0.9996$$

Where ΔA is the absorbance difference at 2710 and 301 nm, C is the concentration of RB in µg/ml and r is the correlation coefficient. For the determination of DP, two wavelengths (260 and 297.2 nm) were selected where the absorbance difference between the two wavelengths is directly proportional to the concentration of DP and the absorbance of RB at these wavelengths is constant, (Fig. 2) Calibration curve relating the absorbance difference between 260 and 297.2 nm to the corresponding concentrations of DP was constructed, (Fig. 4) and regression equation was computed and found to be;

$$\Delta A = 0.0122 C - 0.0021 \quad r = 0.9995$$

Table 4: Quantitative determination of RB and DP in pharmaceutical formulations by the proposed spectrophotometric methods and results of application of standard addition technique.

Rabesym-D Tablets	Method (A)				Method (B)				Method (C)			
	Found ^a %	Claimed amount taken (µg/ml)	Standard added (µg/ml)	Recovery % of standard added	Found ^a %	Claimed amount Taken (µg/ml)	Standard added (µg/ml)	Recovery % of standard added	Found ^a %	Claimed amount taken (µg/ml)	Standard added (µg/ml)	Recovery % of standard added
RB	98.72	20	4	99.15	101.83	24	8	101.87	98.27	20	4	100.62
	±		8	98.06	±		12	102.00	±		8	100.19
	0.429%		12	98.48	0.663%		16	100.46	0.229%		12	99.48
			16	99.29			20	101.22			20	99.00
		Mean		98.75		Mean		101.38		Mean		99.82
	R.S.D.		0.723 %		R.S.D.		0.696 %		R.S.D.		0.723 %	
DP	101.36	10	4	99.78	100.42	12	8	99.73	99.32	10	4	98.77
	±		8	100.25	±		12	100.19	±		8	101.06
	0.995 %		12	100.68	1.003 %		16	99.52	0.306%		12	101.52
			20	99.61			20	98.40			20	99.83
		Mean		100.08		Mean		99.46		Mean		100.29
	R.S.D.		0.482 %		R.S.D.		0.764 %		R.S.D.		1.238 %	

Where ΔA is the absorbance difference at 260 and 297.2 nm, C is the concentration of DP in µg/ml and r is the correlation coefficient.

The proposed methods were successfully applied for the determination of the two drugs in pure powder forms with mean recovery of 99.74± 0.498 %, (A), 100.52 ± 0.478 %, (B) and 100.43 ± 0.502 (C) for RB, and 100.28± 0.488 %, (A), 99.24 ± 0.551 % (B) and 99.95± 0.516 (C) for DP, (Table 1).

The specificity of the proposed methods was proved by the analysis of laboratory prepared mixtures containing different ratios of the two drugs. Satisfactory results were obtained for the three methods, (Table 2).

The results obtained for the analysis of RB and DP in pure powder forms by the suggested spectrophotometric methods were statistically compared with those obtained by applying the reported methods. The values of the calculated t and F are less than the tabulated ones, which reveals that there is no significant difference with respect to accuracy and precision, (Table 3).

The proposed methods have been successfully applied to assay RB and DP in Rabesym-D tablets. The validity of the proposed methods was further assessed by applying standard addition technique, (Table 4).

Validation of the proposed spectrophotometric methods was made by measuring range, accuracy, precision, repeatabilities, intermediate precision, linearity and specificity. Results obtained are depicted in (Tables 1,2).

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