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Spectrophotometric Simultaneous Determination of Famotidine and Domperidone in Combined Tablet Dosage Form by Ratio Derivative and Area under Curve Method

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ABSTRACT

Simple, precise, rapid and accurate methods for simultaneous determination of Famotidine (FAM) and Domperidone (DOM) in combined tablet dosage form have been developed. First method is based on Ratio spectra derivative and second method uses Area under curve (AUC) and methanol is used as solvent. The amplitudes at 249.78 nm and 301.07 nm of the first derivative of ratio spectra were selected to determine FAM and DOM, respectively by ratio derivative method and wavelength ranges of 282.70 - 285.23 nm and 225.87 – 228.97 nm were selected to determine FAM and DOM by AUC method in combined formulation. Beer's law is obeyed in the concentration range of 10-50 µg/mL and 5-25 µg/mL for Famotidine and Domperidone, respectively by both the methods. The % assay in commercial formulation was found to be in the range 99.01 – 100.90 % for FAM and 98.91 – 101.72 % for DOM by the proposed methods. The methods were validated with respect to linearity, precision and accuracy. Recovery was found in the range of 98.60 – 101.80 % for FAM and 98.75 – 100.2% for DOM by ratio derivative method and 98.16 – 100.4% for FAM and 98.89-100.21% for DOM by AUC method. The methods developed are simple, economical, precise and accurate and can be used for routine quality control of combined tablets.

Key words: Famotidine, Domperidone, Ratio Spectra Derivative Spectrophotometry, Area Under Curve.

INTRODUCTION

Famotidine (FAM) belongs to a class of drugs known as histamine H2 receptor antagonist used in the treatment of gastric and duodenal ulcers. It inhibits gastric acid secretion by blocking the

H2 receptors located on parietal cells [1].Chemically Famotidine (FAM) is N2- (aminosulfonyl)-3-[[{2[(diaminomethylene) amino] thiazol-4 yl}methyl] thio] propanamidine [1].

Chemically Domperidone (DOM) is 5-chloro-1-{1-[3-(2,3-dihydro-2-oxo-1H-benzimidazole-1-yl) - propyl] - 4-piperidinyl} – 1 - 3 - dihydro- benzimidazole-2-one. It is a peripheral dopamine–2-receptor antagonist. It is an unique gastro kinetic and antiemetic drug [2,3]. Few analytical techniques such as spectrophotometry [4–8], HPLC [9-11] have been reported for the individual and simultaneous determination of FAM and other antihistaminic analogues. As far as domperidone is concerned, few reports are available for its estimation in bulk and formulation such as spectrophotometry [12 - 14], HPLC [15 - 18], HPTLC [19] and bioanalytical methods [20, 21]. The method was validated for linearity, accuracy, precision, sensitivity, robustness, etc. in accordance with International Conference on Harmonization (ICH) guidelines [22].

MATERIALS AND METHODS

Instrumentation

An UV-Visible double beam spectrophotometer (Varian Cary 100) with 10 mm matched quartz cells was used. Electronic balance (Model Shimadzu AUW-220D) was used for weighing.

Reagents and chemicals

Pure drug sample of FAM, % purity 99.86 and DOM, % purity 99.92 was kindly supplied as a gift sample by Nicholas Piramal India Ltd., Mumbai and Aurobindo Pharma Ltd., Hyderabad respectively. These samples were used without further purification. Spectroscopy grade methanol was used throughout the study. Tablets each containing 20 mg of FAM and 10 mg of DOM used for analysis were Famodon manufactured by Ozone Pharmaceutical Ltd. Indore and Dompon-F procured from Aristo Pharmaceuticals Pvt. Ltd., Vapi, India.

Preparation of Standard Stock Solutions and calibration Curve

Standard stock solutions of pure drug containing 1000 µg/mL of FAM and DOM were prepared separately in methanol. Standard stock solutions were further diluted with methanol to get working standard solutions of analytes in the concentration range of 10-50 µg/mL and 5-25 µg/mL of famotidine and domperidone, respectively and scanned in the range of 200-400nm. For method A first derivative amplitudes (at interval 1.2 and filter size 9) of ratio spectra were measured at 249.78 nm and 301.07 nm for FAM and DOM, respectively. First derivative amplitudes of ratio spectra and concentrations were used to construct calibration. For method B integrated area under curve was obtained between wavelength ranges of 282.70 – 285.23 nm and 225.87 – 228.97 nm for FAM and DOM by AUC method. Integrated area under curve was used to construct two simultaneous equations and these equations were solved and used (3 and 4) to calculate amount of analytes in sample solutions.

Preparation of Sample Solution and Formulation analysis

Twenty tablets were weighed accurately and a quantity of tablet powder equivalent to 20 mg of FAM (10 mg of DOM) was weighed and dissolved in the 80 mL of methanol with the aid of ultrasonication for 15 min and solution was filtered through Whatman paper No. 41 into a 100 mL volumetric flask. Filter paper was washed with same solvent, adding washings to the volumetric flask and volume was made up to the mark with methanol. The solution was suitably

diluted further with methanol to get required final concentration of FAM (20µg/mL) and DOM (10 µg/ mL).

Theoretical aspects

Method A: Ratio Derivative

The method involves dividing the spectrum of mixture by the standardized spectra of each of the analyte to get ratio spectra and first derivative of ratio spectrum was obtained which was independent of concentration of divisor (Fig. 1). Using appropriate dilutions of standard stock solution, the two solutions were scanned separately. The ratio spectra of different FAM standards at increasing concentrations were obtained by dividing each with the stored spectrum of the standard solution of DOM (15 µg/mL) as shown in (Fig 1A).Wavelength 249.78 nm was selected for the quantification of FAM in FAM + DOM mixture. The ratio and ratio derivative spectra of the solutions of DOM at different concentrations were obtained by dividing each with the stored standard spectrum of the FAM (30µg/mL) as shown in (Fig 1B). Wavelength 301.07 nm was selected for the quantification of DOM in FAM + DOM mixture. Measured analytical signals at these wavelengths were proportional to the concentrations of the drugs over the selected concentration range. Calibration curves were prepared from the measured signals at the selected wavelength and concentration of the standard solutions. The concentrations of FAM (C_{FAM}) and DOM(C_{DOM}) in solution of tablets was calculated by using equations(1) and (2), respectively.

At 249.78 nm: C_{FAM} = (FAM Ratio derivative amplitude – 0.0008)/0.0712.... (1)
At 301.07 nm: C_{DOM} = (DOM Ratio derivative amplitude – 0.0478)/1.234.… (2)

Method B: Area Under Curve

For the simultaneous determination using the AUC method, suitable dilutions of the standard stock solutions (1000 µg/mL) of FAM and DOM were prepared separately in methanol and further diluted with methanol to make appropriate conc. range. The solutions of drugs were scanned in the range of 200-400 nm, the zero order overlain spectra shown in Fig 2. For the method, sampling wavelength ranges selected for estimation of analytes were 282.70 – 285.23 nm (λ1-λ2) and 225.87 – 228.97 nm (λ3-λ4). Mixed standards were prepared and their integrated area under the curve was measured at the selected wavelength ranges. Concentration of FAM and DOM in mixed standard and the sample solution were calculated using equation 3 and 4, respectively.

$C_{FAM} = A_2 \times a_{y1} - A_1 \times a_{y2} / a_{X2} \times a_{Y1} - a_{X1} \times a_{Y2}$ …… (3)
$C_{DOM} = A_2 - a_{X2} \times C_{FAM} / a_{Y2}$ …… (4)
Where,
a_{X1} (112.1) and a_{X2} (95.9) are the absorptivities of FAM at (λ1-λ2) and (λ3-λ4), respectively.
a_{Y1} (87.0) and a_{Y2} (72.5) are the absorptivities of DOM at (λ1-λ2) and (λ3-λ4), respectively.
A_1 and A_2 are absorbances of mixed standard at (λ1-λ2) and (λ3-λ4) respectively. C_{FAM} and C_{DOM} are the concentrations in g/100 mL.

Recovery studies

The accuracy of the proposed methods was checked by recovery study, by addition of standard drug solution to preanalysed sample solution at three different concentration levels (50 %, 100 %

and 150 %) within the range of linearity for both the drugs. The basic concentration level of sample solution selected for spiking of the drugs standard solution was 15 and 7.5 µg/mL, of FAM and DOM respectively.

Solution Stability

Method stability was checked by analyzing solution kept in fridge and at room temperature by both methods. Solution at room temperature was stable for 12 hours and solution in fridge was stable for 30 days (% RSD < 2).

Precision of the Method

Method repeatability was determined by six times repetitions of assay procedure. For intra-day precision method was repeated 5 times in a day and the average % RSD was determined. Similarly the method was repeated on five different days for inter-day precision and average % RSD was determined (Table 1). Precision of analyst was determined by repeating study by another analyst working in the laboratory.

Table 1: Optical characteristics of the proposed methods and result of precision and formulation analysis

Parameter			Famotidine		Domperidone	
			Method A	Method B	Method A	Method B
wavelength (nm)			249.78	282.70-285.23	301.07	225.87-228.97
Beer's law limit (µg/mL)			10-50	10-50	5-25	5-25
Regression Equation*		Slope (m)	0.0258	-	0.2165	-
		Intercept (c)	0.0306	-	0.1523	-
Correlation coefficient (r)			0.9998	-	0.9994	-
Precision (%RSD)	Repeatability (n=5)		0.65	0.73	0.54	0.79
	Intra-day (3x5 times)		1.11	0.72	0.52	1.37
	Inter-day(3x5 days)		1.04	0.91	1.18	0.79
	Analyst		0.72	0.91	0.62	0.83
Formulation Analysis (%Assay, %RSD), n=6		TI	98.81% ± 0.32	100.8% ± 0.45	98.91% ± 0.29	101.2% ± 0.4
		TII	99.01% ± 0.46	100.9% ± 0.38	98.91% ± 0.51	101.72% ± 0.3

RSD = Relative Standard Deviation, Y = mX + c, where Y is the absorbance and X the concentration in micrograms per milliliter*

RESULT AND DISCUSSION

Under experimental conditions described, calibration curve, assay of tablets and recovery studies were performed. Using appropriate dilutions of standard stock solution the two solutions were scanned separately. A critical evaluation of proposed method was performed by statistical analysis of data where slope, intercept, correlation coefficient are shown in Table 1. As per the ICH guidelines, the method validation parameters checked were linearity, accuracy and precision. Beer's law is obeyed in the concentration range of 10-50µg/mL and 5-25µg/mL for FAM and DOM, respectively. Correlation coefficient was greater than 0.999 for both the drugs.

The proposed methods were also evaluated by the assay of commercially available tablets containing FAM and DOM. The results of formulation analysis are presented in Table 1. Recovery was found in the range of 98.60 – 101.80 % for FAM and 98.75 – 100.2% for DOM by ratio derivative method and 98.16 – 100.4% for FAM and 98.89-100.21% for DOM by AUC method (Table 2). The accuracy is evident from the data as results are close to 100 % and standard deviation is low.

Table 2: Result of recovery studies of FAM and DOM by the proposed methods

Formulation studied	Recovery Level	Recovery of	Amount Spiked (µg/mL)	% Mean Recovery, % RSD by n=6	
				Method A	Method B
Formulation I	50%	FAM	7.5	99.60, 0.38	100.39 0.79
		DOM	3.75	98.75, 1.05	99.45, 0.97
	100%	FAM	15	98.63, 0.92	99.90, 1.03
		DOM	7.5	99.13, 1.72	98.89, 1.57
	150%	FAM	22.5	101.75, 0.74	100.05, 0.19
		DOM	11.25	99.66, 0.93	98.93, 1.34

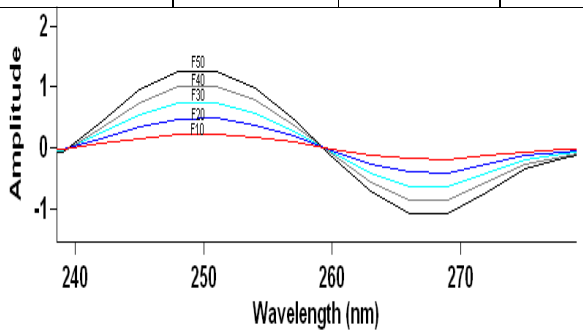

Fig.1A: First Derivative of ratio spectra of 40, 50 µg/ml of FAM When 15µg/ml of DOM is used as divisor

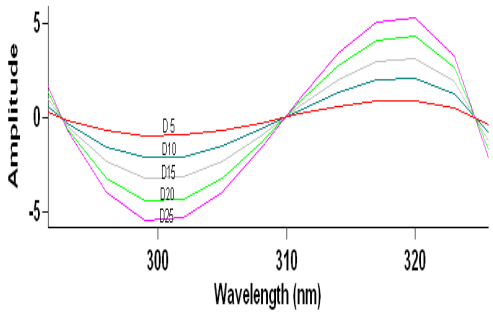

Fig.1B: First Derivative of ratio spectra of 10, 20, 30, 5,10,15,20, 25µg/ml of DOM When 30µg/ml of FAM is used as divisor

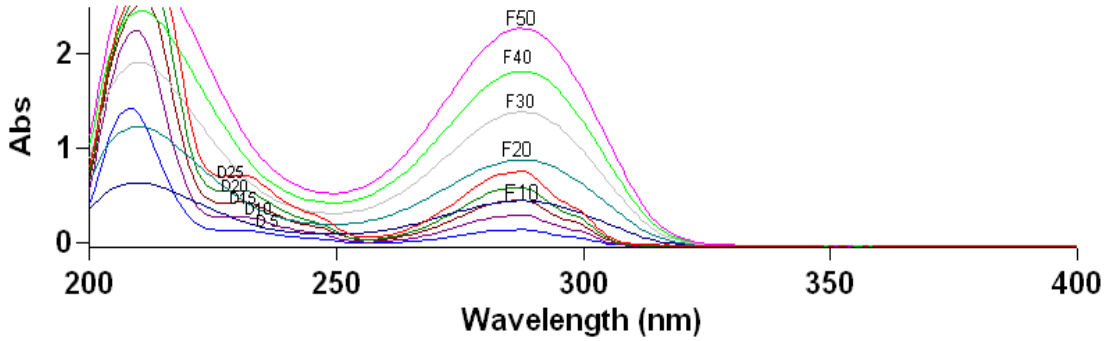

Fig. 2: Overlain spectra of FAM: 10 - 50 µg/mL; and DOM: 5 - 25µg/mL in methanol.

CONCLUSION

The validated spectrophotometric method employed here proved to be simple, economical, precise and accurate. Thus it can be used as IPQC test and for routine simultaneous determination of FAM and DOM in tablet dosage form.

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