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UV-SPECTROPHOTOMETRIC SIMULTANEOUS DETERMINATION OF IBUPROFEN AND FAMOTIDINE IN COMBINED TABLET DOSAGE FORM

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ABSTRACT

A combination of the Non-Steroidal Anti Inflammatory Drug, Ibuprofen (IBU) and the Histamine H2-receptor antagonist, Famotidine (FAM) is indicated for the relief of signs and symptoms of Rheumatoid Arthritis and Osteoarthritis and to decrease the risk of upper Gastrointestinal ulcers. The aim of the present work was to develop accurate and rapid two UV-Spectrophotometric methods for the simultaneous determination of IBU and FAM in Pharmaceutical formulation. Method A- is simultaneous equation method, wavelengths were selected at 264 nm (λmax for IBU) and 287 nm (λmax for FAM). Method B- is Absorption ratio method (Q-analysis) using two wavelengths, 271 nm (iso-absorptive point at which both the drugs exhibit absorbance) and 264 nm (λmax of IBU). Both the drugs obey the Beer Lambert's law in the concentration range of 80-640 µg/ml for IBU and 2-22 µg/ml for FAM. Method A – the Correlation co-efficient (r^2 values) of IBU and FAM were found to be 0.9985 and 0.9982 respectively and for Method B the Correlation co-efficient (r^2 values) of IBU and FAM were found to be 0.998 and 0.997 respectively. Parameters such as linearity, accuracy, precision, LOD and LOQ values were used for validation of both the methods as per ICH guidelines and can be adopted for the routine analysis of IBU and FAM in pure and tablet dosage form.

KEYWORDS: Ibuprofen, Famotidine, UV-Spectrophotometry, Simultaneous equation method, Q-analysis method.

INTRODUCTION

Ibuprofen 2-[4-(2-methylpropyl) phenyl] propanoic acid is Nonsteroidal Anti-inflammatory Agents (NSAIAs). Famotidine 3-[({2-[(diaminomethylidene) a mino]-1, 3-thiazol-4-yl} methyl) sulfanyl]-N'-sulfamoylpropanimidamide is Histamine H2 Antagonists. The combination of both drugs is indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis.[1,2] Based on the literature review, it is found that number of studies involving methods development for estimation of IBU and FAM have been carried out in formulations/biological fluid with single or combination with other drugs. Thus, number of analytical methods including RP-HPLC[3], LC-MS[4], GC-MS[5], spectroflourimetry, UV-spectrometry[6], Capillary Electrophoresis[7] have been developed. The literature revealed that there was no mention of the Simultaneous equation and Q-analysis methods based on UV-Spectrophotometric for determination of IBU and FAM in combined dosage form tn solvent methanol. Method validation is an important issue in pharmaceutical analysis. So in this paper simple, rapid, precise and accurate spectrophotometric methods have been developed for the determination of IBU and FAM in combined dosage form and validated as per the ICH guideline.

MATERIALS AND METHODS

Apparatus and Software

UV-Visible double beam spectrophotometer (SHIMADZU 1800) with 10 mm matched quartz cells was used and Shimadzu UV PC Software (UV probe) version 2.31. All weighing were done on precision balance (REPTECH), and Ultrasonicateri-cleaner was used (CYBERLAB) to degas the solutions.

Reagent and Chemical

Active Pharmaceutical Ingredient (API) of IBU and FAM supplied by Zydus Cadila Health Care Ltd. Ahmedabad. The pharmaceutical dosage form used in study was DUEXIS® (label claim, IBU 800 mg and FAM 26.6mg) manufactured by (Horizon Pharma, Inc., IL). Methanol AR grade was purchased from (Finar Chemicals Pvt. Ltd, Ahmedabad, India).

Selection of common solvent

Based on drug profile, the solubility of both drugs was in Methanol. So Methanol was selected as the common solvent.

Preparation of Standard stock solution

80 mg of IBU and 26.6 mg of FAM of standard API were weighed and transferred in 100 ml volumetric flask, dissolved and diluted up to the mark with Methanol to get final concentration 800 µg/ml of IBU and 266 µg/ml of FAM. FAM solution then further diluted to get concentration was 26.6 µg/ml and both concentrations were as per label claimed (1:30.07).

Preparation of Sample solution (Tablet)

Amount of the powdered tablets equivalent to 80 mg IBU and 2.66 mg FAM was weighed and dissolved with Methanol to 100 ml volumetric flask. The mixture was mixed and sonicated for 10 min and made up to the mark, to get final concentration 800 µg/ml and 26.6 µg/ml of IBU and FAM respectively. After that filter with whatmann filter paper (No.41) to remove unwanted particle. The filtrate was used as Sample solution.

Development of the methods

Method A: Simultaneous equation method

Selection of working wavelength

The standard stock solutions were scanned in between the wavelength range 200-400 nm to observe the λ_{max}. From spectra of drugs, λ_{max} of IBU and FAM were selected at 264 nm and 287 nm respectively for the analysis (Fig. 1,2).

Method B: Q-analysis method

Selection of working wavelength

The standard stock solutions were scanned in between the wavelength range 200-400 nm. From spectra of drugs, wavelength of IBU was selected at 264 nm and Iso-absorptive point of FAM at 271 nm for the analysis. (Fig. 3).

Validation of proposed method

The proposed method was validated according to the International Conference on Harmonization(ICH) guidelines.[8,9]

Linearity

The linear response of was determined by analyzing six independent levels of the calibration curve in the range of 80 µg/ml to 640 µg/ml for IBU and 2 µg/ml to 22 µg/ml for FAM (Table 1). Result should be expressed in terms of Correlation co-efficient(r^2). (Fig. 5, 6).

Accuracy (% Recovery)

Accuracy may often be expressed as % Recovery by the assay of known, added amount of analyte. It's measure of the exactness of the analytical method. The recovery experiments were carried out in triplicate by sparking previously analyzed samples of the IBU (400 µg/ml) and FAM (13.3 µg/ml) with three different concentrations of standards at 80%, 100% and 120% respectively.

Precision

Repeatability (Intra-assay Precision)

Repeatability was performed by preparing the sample (test) solution of IBU (400 µg/ml) and FAM (13.3 µg/ml) for six times and analyzed as per the proposed method. Percentage relative standard deviation (%RSD) should be less than 2%.

Intermediate Precision (intra-day precision)

Variation of results within same day is called Intra-day precision. The Intra-day precision was determined for standard solution of IBU (400 µg/ml) and FAM (13.3 µg/ml) for the three different time points on the same day.

Reproducibility (inter-day precision)

It expresses within laboratory variations as on different days analysis or equipment within the laboratory. Variation of results amongst days called Inter-day precision. The Inter-day precision was determined for standard solution of IBU (400 µg/ml) and FAM (13.3 µg/ml) for three days.

Limit of detection and Limit of quantification

LOD and LOQ of dug calculated using the following equations:

$$\mathbf{LOD = 3.3 \times \sigma/S}$$

$$\mathbf{LOQ = 10 \times \sigma/S}$$

Where, σ = the standard deviation of the response

and S = slope of the calibration curve.

Assay of pharmaceutical formulation by Method A.

The proposed validated method was successfully applied to determine IBU and FAM in their tablet dosage form. The result obtained for IBU and FAM was comparable with the corresponding labelled amounts.

For IBU,

$$C_x = (A_2 a_{y1} - A_1 a_{y2}) / (a_{x2} a_{y1} - a_{x1} a_{y2})$$

For FAM,

$$C_y = (A_1 a_{x2} - A_2 a_{x1}) / (ax_2 a_{y1} - a_{x1} a_{y2})$$

Where,

C_x and C_y are the conc. of IBU and FAM respectively.

A_1 and A_2 are the absorbance of mixed standard at 264 nm and 287 nm

a_{x1}, a_{x2} are the absorptivity of IBU at 264 nm and 287 nm respectively

a_{y1},a_{y2} are the absorptivity of FAM at 264 nm and 287 nm respectively

Assay of pharmaceutical formulation by Method B

For IBU,

$$C_x = (Q_0 - Q_2) A / (Q_1 - Q_2) a_1$$

For FAM,

$$C_y = (Q_0 - Q_1) A / (Q_2 - Q_1) a_2$$

Where,

C_x and C_y are the conc. of IBU and FAM respectively.

A is the absorbance of sample at the iso-absorptive wavelength 271 nm.

a_1, a_2 are the absorptivity of IBU and FAM respectively at the 271 nm

Q_1 is the absorbance of IBU at 264 nm / absorbance of IBU at 271 nm

Q_2 is the absorbance of FAM at 264 nm / absorbance of FAM at 271 nm

Q_0 is the absorbance of sample solution at 264 nm / absorbance at 271 nm

Ruggedness

Ruggedness of the proposed analytical method was determined by analyzing the same sample solution by two analysts and two different instruments using similar experimental condition. %RSD should be less than 5%.

RESULTS AND DISCUSSION

Two UV spectrophotometric methods for the simultaneous determination of IBU and FAM in Pharmaceutical formulation. Method A- is simultaneous equation method, wavelengths were selected at 264 nm (λ_{max} for IBU) and 287 nm (λ_{max} for FAM). Method B- is Absorption ratio method (Q-analysis) using two wavelengths, 271 nm (iso-absorptive point at which both the drugs exhibit absorbance) and 264 nm (λmax of IBU). All the methods were found linearity

range between 80-640 µg/ml for IBU and 2-22 µg/ml for FAM. The proposed methods were found to be simple, sensitive, rapid, accurate, precise and economic for the routine analysis of IBU and FAM in combined pharmaceutical formulation. Accuracy was determined by calculating the recovery, and the mean was determined (Table 1,2). Precision was calculated as repeatability, intraday and intermediate variation in term of % RSD for IBU and FAM. LOD values for IBU and FAM were found to be 9.57 and 0.22µg/ml respectively and for LOQ values were found to be 29.00 and 0.65µg/ml respectively indicates sensitivity of the proposed methods. The method was successfully used to determine the amounts of IBU and FAM present in tablets. The results obtained are in good agreement with the corresponding labelled amount (Table 3). Characteristic parameters and summary of validation parameters for both methods are given in Table 4. By observing the validation parameters, the method was found to be sensitive, accurate and precise. Hence the methods can be employed for the routine analysis of IBU and FAM in tablet formulations. Two developed UV-Spectrometric methods for the simultaneous estimation of both the drugs were validated according to ICH guideline Q2(R1) and the results of validation parameters for two methods are reported in Table-2.

Table 1: Linearity data of IBU and FAM.

Method A: Simultaneous equation method				**Method B: Q-Ratio method**			
IBU Conc. (µg/ml)	**Abs. ***	**FAM Conc. (µg/ml)**	**Abs. ***	**IBU Conc. (µg/ml)**	**Abs. ***	**FAM Conc. (µg/ml)**	**Abs. ***
160	0.291	5.32	0.274	160	0.291	5.32	0.213
240	0.412	7.98	0.383	240	0.412	7.98	0.271
320	0.531	10.64	0.518	320	0.531	10.64	0.344
400	0.624	13.3	0.630	400	0.624	13.3	0.413
480	0.749	15.96	0.761	480	0.749	15.96	0.479
560	0.875	18.62	0.884	560	0.875	18.62	0.554

Abs.- Absorbance

* Mean value of three determinations

Table 2: Summary of validation parameter by proposed methods.

Validation Parameter	**Method A**		**Method B**	
	IBU	**FAM**	**IBU**	**FAM**
Beer's range	80-640 µg/mL	2-22 µg/mL	80-640 µg/mL	2-22 µg/mL
Linearity Equation	Y =0.001x +0.063	Y = 0.046x + 0.022	Y =0.001x +0.063	Y = 0.025x +0.070
Correlation coefficient	0.9985	0.9982	0.998	0.997

**Repeatability	0.861	0.856	0.938	0.962
*Intraday precision (%RSD)	1.195	1.301	1.218	1.080
*Inter day precision (%RSD)	1.373	1.565	1.351	1.871
LOD (µg/ml)	17.82	0.37	19.43	0.52
LOQ (µg/ml)	54.00	1.13	58.90	1.60
* % Recovery				
80%	99.40 ± 0.44	99.40 ± 0.10	99.17 ± 0.80	98.99 ± 0.74
100%	99.47 ± 0.45	100.61 ± 1.79	99.42 ± 0.71	99.35 ± 0.66
120%	99.57 ± 1.43	99.57 ± 1.43	99.36 ± 0.72	99.70 ± 0.34
*%Assay	99.32 ± 0.47	99.73 ± 0.51	99.61 ± 0.57	99.16 ± 0.49

** Mean value of six determinations; * Mean value of three determinations

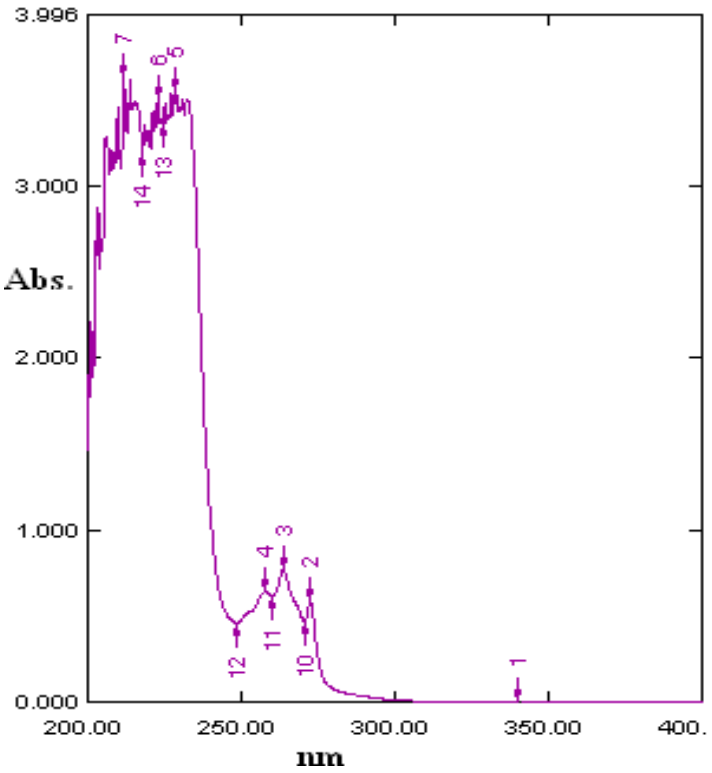

Fig. 1 λ_{max} of IBU at 264nm

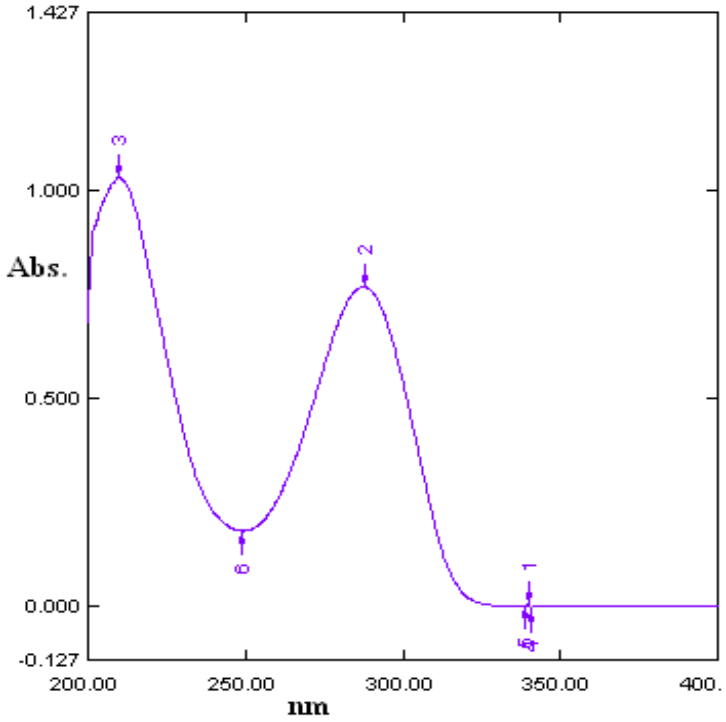

Fig. 2 λ_{max} of FAM at 287nm

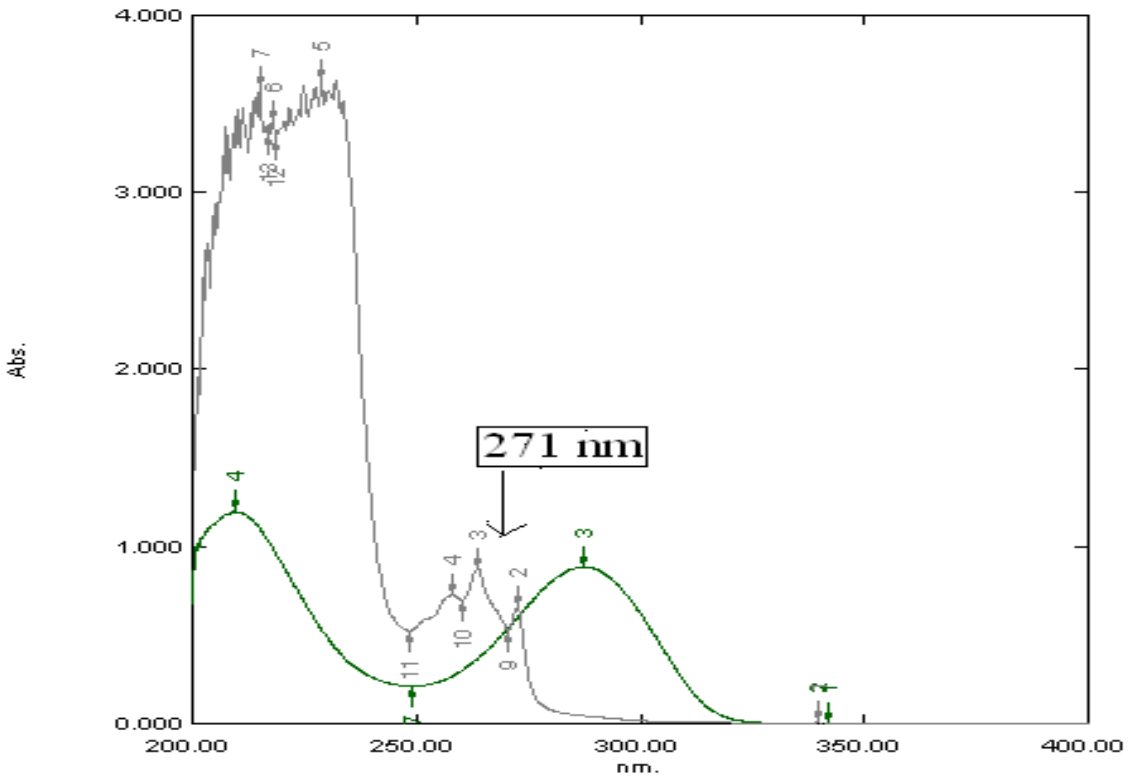

Fig. 3 Iso-absorptive point at 271 nm.

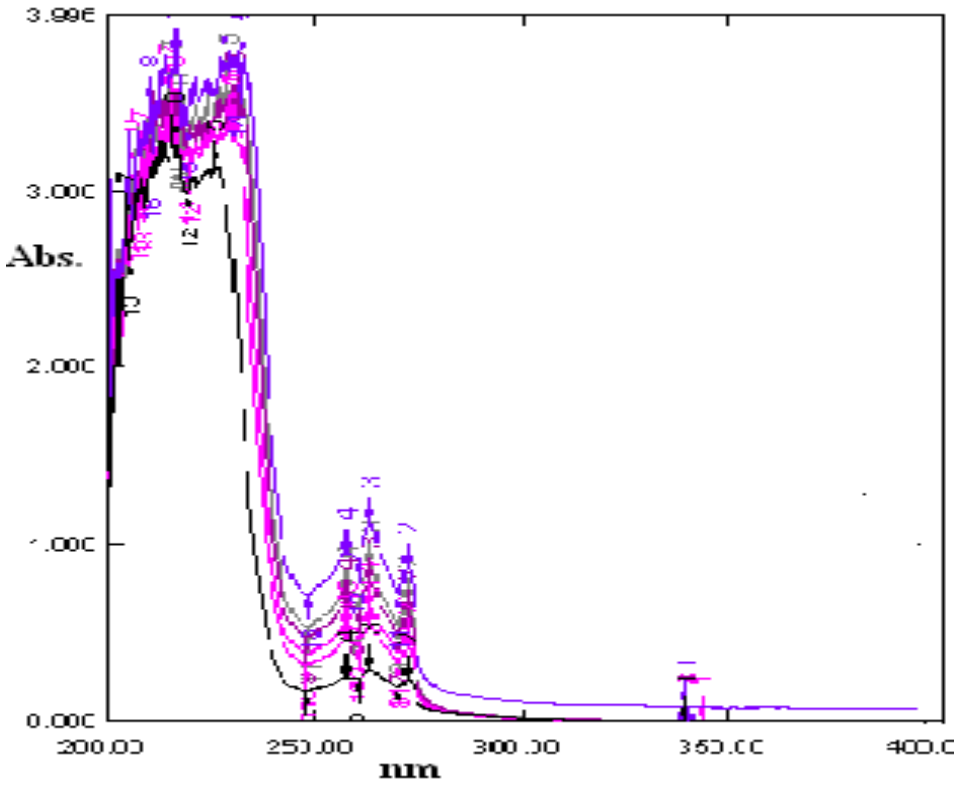

Fig. 4 Linearity of IBU at 264 nm

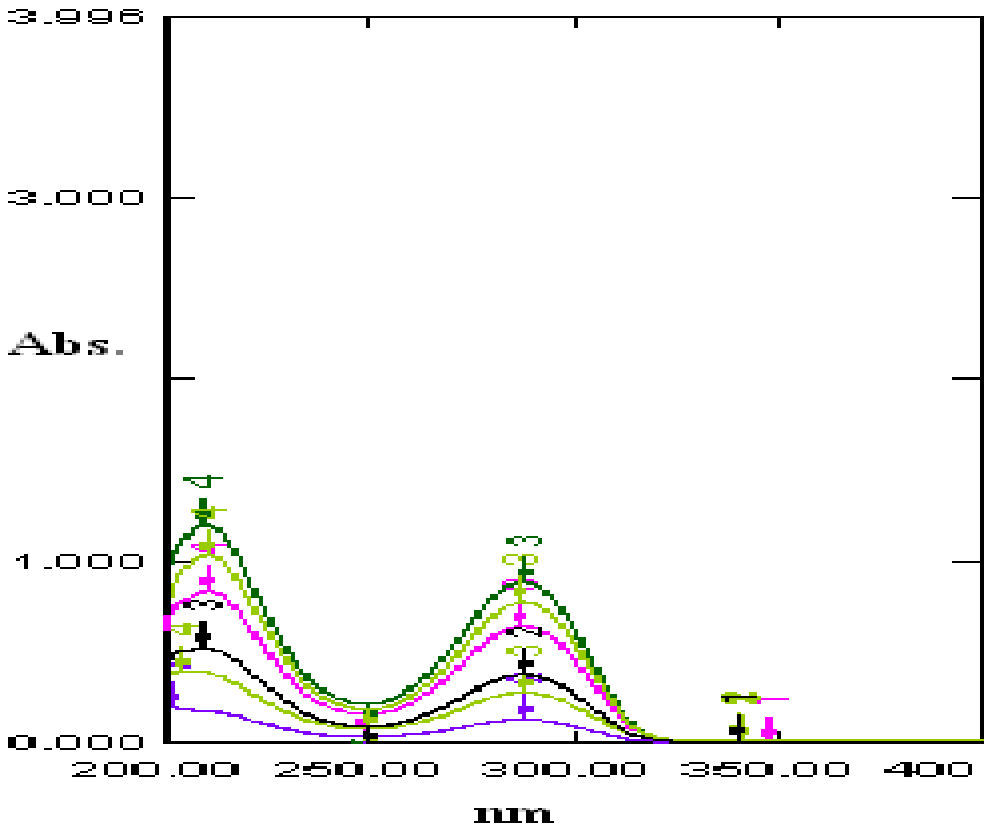

Fig. 5 Linearity of FAM at 287 nm

CONCLUSION

The proposed spectrophotometric methods provide simple, specific, precise, accurate and reproducible quantitative analysis for determination of IBU and FAM in tablet dosage form. The methods were validated as per ICH guidelines in terms of linearity, accuracy, precision, limits of detection (LOD) and quantification (LOQ) and ruggedness. The method can be used for routine analysis of IBU and FAM in combined dosage form.

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