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SIMULTANEOUS DETERMINATION OF FAMOTIDINE AND IBUPROFEN IN COMBINED PHARMACEUTICAL DOSAGE FORM BY RP-HPLC METHOD

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ABSTRACT

A simple, rapid reverse phase High-performance liquid chromatographic method was developed and validated for the simultaneous estimation of Famotidine and Ibuprofen in bulk and pharmaceutical dosage forms. Chromatography was carried out by using Chromosil C-18,column having 250 x 4.6mm internal diameter with a mixture of Water, Acetonitrile and T.E.A in the ratio of 80:10:10 (v/v/v) as mobile phase. Determination of the different analytical parameters such as linearity, precision, accuracy, and specificity, limit of detection (LOD) and limit of quantification (LOQ) was done. The calibration curve was found to be linear for each analyte in the desired concentration range.The % recovery was found to be 99.74 and 100.74 for Famotidine and Ibuprofen respectively. The proposed method is highly sensitive, precise and accurate, which was evident from the LOD value of 1.5 and 0.5 ppm for Famotidine and Ibuprofen respectively and hence the present method can be applied successfully for the quantification of active pharmaceutical ingredient (API) content in the combined formulations of Famotidine and Ibuprofen.

KEYWORDS: **Famotidine, Ibuprofen, HPLC, Method development, Validation, 278 nm**

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INTRODUCTION

Famotidine

Famotidine is a histamine H_2-receptor antagonist that inhibits stomach acid production, and it is commonly used in the treatment of peptic ulcer disease (PUD) andgastroesophageal reflux disease (GERD/GORD). Unlike cimetidine, the first H_2 antagonist, famotidine has no effect on the cytochrome P450 enzyme system, and does not appear to interact with other drugs.[1] Famotidine was developed by Yamanouchi Pharmaceutical Co.[2] It was licensed in the mid-80s by Merck & Co.[3]

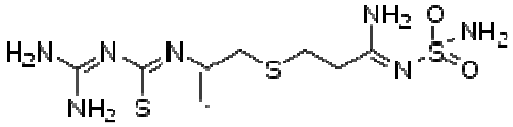


Figure 1
Structure of Famotidine

Famotidine is given to surgery patients before operations to prevent postoperative nausea and to reduce the risk of aspiration pneumonitis. Famotidine is also given to some patients who take NSAIDs, to prevent peptic ulcers.[4] It serves as an alternative to proton-pump inhibitors.[5] Famotidine has also been used in combination with an H1 antagonist to treat and prevent urticaria caused by an acute allergic reaction.[6] It has been found to decrease the debilitating effects of chronic heart failure by blocking histamine. [7] Common adverse effects with Formotidine were headache, dizziness, and constipation or diarrhea.[8]

Ibuprofen

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) used for relief of symptoms of arthritis, fever,[9] as an analgesic (pain reliever), especially where there is an inflammatory component, and dysmenorrhea. It was derived from propanoic acid by the research arm of Boots Group during the 1960s.[10] It was discovered by Andrew RM Dunlop, with colleagues Stewart Adams, John Nicholson, Vonleigh Simmons, Jeff Wilson and Colin Burrows, and was patented in 1961.

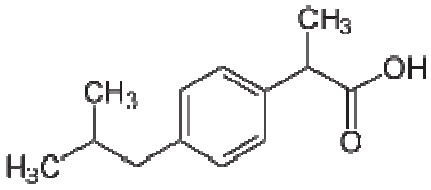


Figure 2
Structure of Ibuprofen

Ibuprofen work by inhibiting the enzyme cyclooxygenase (COX) , which converts arachidonic acid to prostaglandin H_2 (PGH_2). PGH_2, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane A_2 (which stimulates platelet aggregation, leading to the formation of blood clots). Common adverse effects include nausea, dyspepsia, gastrointestinal ulceration/bleeding, raised liver enzymes diarrhea, constipation, epistaxis, headache, dizz

iness, priapism, rash, salt and fluid retention, andhypertension.[11] Famotidine and ibuprofen is a combination drug. Ibuprofen treats the symptoms of arthritis. Famotidine helps reduce the risk of ulcers in the stomach or intestines that can be caused by long-term use of ibuprofen.

Experimental

Chemicals and Reagents

Famotidine and Ibuprofen as pure standard reference drugs were purchased from Reddy's Laboratory, Hyderabad and pharmaceutical formulation from local market were used for this present study. Water, Acetonitrile, methanol and orthophosphoric acid,Tri Ethyl Amine (all HPLC grade) were purchased from Merck Specialties Private Limited, Mumbai, India.(10)

Instrumentation

To develop a High Pressure Liquid Chromatographic method for quantitative estimation of Famotidine and Ibuprofen,(10) an isocratic PEAK HPLC instrument with Hypersil C18 column (250 mm x 4.6 mm, 5µ) was used. The instrument is equipped with a LC 20AT pump for solvent delivery and variable wavelength programmable LC – 7000 UV-detector. A 20µL Rheodyne inject port was used for injecting the samples. Data was analyzed by using PEAK software. UV-2306 Spectrophotometer was used for wavelength checking. Denver analytical Balance was used to weigh the drug.(10)

Experimental Condition

Flow rate of the mobile phase was changed from 0.5 – 1.5 ml/min for optimum separation. A minimum flow rate as well as minimum run time gives the maximum saving on the usage of solvents. It was found from the experiments that 1.0 ml/min flow rate was ideal for the successful elution of the analyte. The HPLC system was hence operated using an isocratic mode at a flow rate of 1.0 ml/min at 25 ± 2^{oc}. For analysis the most suitable mobile phase was found to be Water, Acetonitrile and TEA in the ratio of 80:10:10. Detection was carried out at wavelength of 278 nm.

Preparation of Mobile Phase

For the preparation of mobile phase suitable for the present determination Water, acetonitrile and TEA acid of HPLC grade were mixed, filtered and degassed in such a way that the final volume consisted of these in the ratio 80:10:10 respectively, whose pH was adjusted to 6.1.

Preparation of mixed standard solution

Famotidine and Ibuprofen (1mg/ml) standard stock solutions were prepared using mobile phase as a solvent. Aliquots of mixed standard solutions of Famotidine and Ibuprofen were diluted in mobile phase to get a final concentration of 50-100ppm.

Preparation of sample solution of pharmaceutical formulation

Pharmaceutical form (Duexis) containing 800 mg of Ibuprofen and 26.6 mg of Famotidine was weighed and dissolved in 25 ml of Mobile phase and sonicated for 15 min. Using mobile phase the volume was made up to 50 ml and filtered through 0.45µ membrane filter. The final mixed sample solution corresponding to 52 ppm of Famotidine was prepared. Pharmaceutical form (Duexis) containing 800 mg of Ibuprofen and 26.6 mg of Famotidine was weighed and dissolved in 25 ml of Mobile phase and sonicated for 15 min. Using mobile phase the volume was made up to 100 ml and filtered through 0.45µ membrane filter. The final mixed sample solution corresponding to 800ppm of Ibuprofen was prepared. From this sample solution 1ml was transferred into 10 ml volumetric flask and make up to 10 ml gives 80 ppm final concentration of Ibuprofen.

Recording of chromatograms

After stabilization of the base line with the optimized chromatographic conditions standard solutions containing 50-100 ppm of Famotidine and Ibuprofen were injected and the corresponding chromatograms were recorded. Retention time of Famotidine and Ibuprofen were found to be 2.59 and 6.76 mins respectively. Likewise for sample solution chromatograms were recorded. Calibration

curves were plotted using peak area retentions of standard drug peaks against concentration of corresponding standard solutions.

RESULTS AND DISCUSSION

Method validation

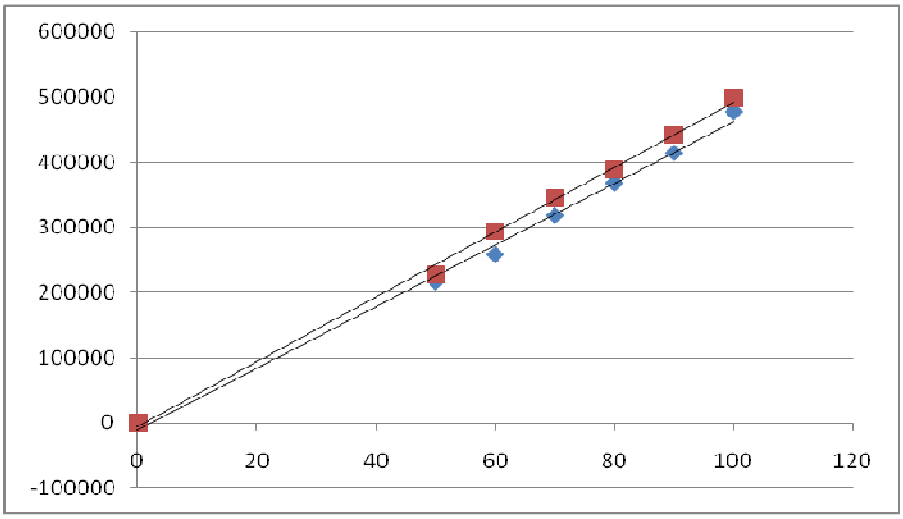
The method was validated by determining linearity, precision, accuracy, specificity, ruggedness and robustness by analyzing 40-100 ppm of both Olmesartan and Hydrochlorothiazide.

S.NO	TEST	RESULT
	H.P.L.C CONDITIONS	
1	ELUTION	ISOCRATIC
2	A.P.I CONC	70ppm
3	MOBILE PHASE	Water:ACN:TEA 80:10:10
4	PH	6.1
5	COLUMN	C18
6	WAVE LENGTH	278nm
7	FLOW	1ml\min
8	RUNTIME	10min
9	RETENSION TIME	Famotidine 2.59 Ibuprofen 6.76
10	AREA	Famotidine 318644 Ibuprofen 346055
11	TH.PLATES	Famotidine 7863 Ibuprofen 45105
12	TAILING FACTOR	Famotidine 1.79 Ibuprofen 1.55
13	PUMP PRESURE	9.4psi

Table 1
Optimized chromatographic conditions for estimation of Olmesartan and Hydrochlorothiazide

Linearity

The linearity of the response for Famotidine and Ibuprofen assay method was determined by preparing and injecting standard solutions of Famotidine and Ibuprofen. The linear regression data for the calibration curves indicate that the response is linear over the concentration range studied with correlation coefficient (r^2) value, slope and intercept as shown in table 3.[9]



Graph 1
Calibration Plot for Famotidine and Ibuprofen

LINEARITY CONC (PPM)	FAMOTIDINE AREA	IBUPROFEN AREA	FAMOTIDINE	IBUPROFEN
50	217240	228092	INTERCEPT = 1226 SLOPE = 5250 C.C = 0.999	INTERCEPT = 6341.1 SLOPE= 4987.622 C.C = 0.999
60	258879	294813		
70	318644	346055		
80	368791	389451		
90	414797	442934		
100	478024	498697		

Table 2
Linearity test result

Precision

The precision of the assay was studied with respect to both repeatability and intermediate precision. Repeatability was calculated from six replicate injections of freshly prepared Famotidine and Ibuprofen combined test solution in the same equipment at a concentration value of 70 ppm on the same day. The experiment was repeated by assaying freshly prepared solution at the same concentration additionally on two consecutive days to determine intermediate precision. Peak areas of the drugs were determined and precision as % RSD was reported.

INJECTION	FAMOTIDINE AREA	IBUPROFEN AREA	FAMOTIDINE R.S.D	IBUPROFEN R.S.D
1	318644	346055	0.36	0.98
2	317542	345223		
3	318602	345647		
4	316493	353973		
5	316493	345891		
6	316059	345547		

Table 3
Intraday precision

INJECTION	FAMOTIDINE AREA	IBUPROFEN AREA	FAMOTIDINE R.S.D	IBUPROFEN R.S.D
1	318858	345711	1.6	0.32
2	316421	346019		
3	315686	347584		
4	326115	348330		
5	326577	347938		
6	315424	346019		

Table 4
Interday precision

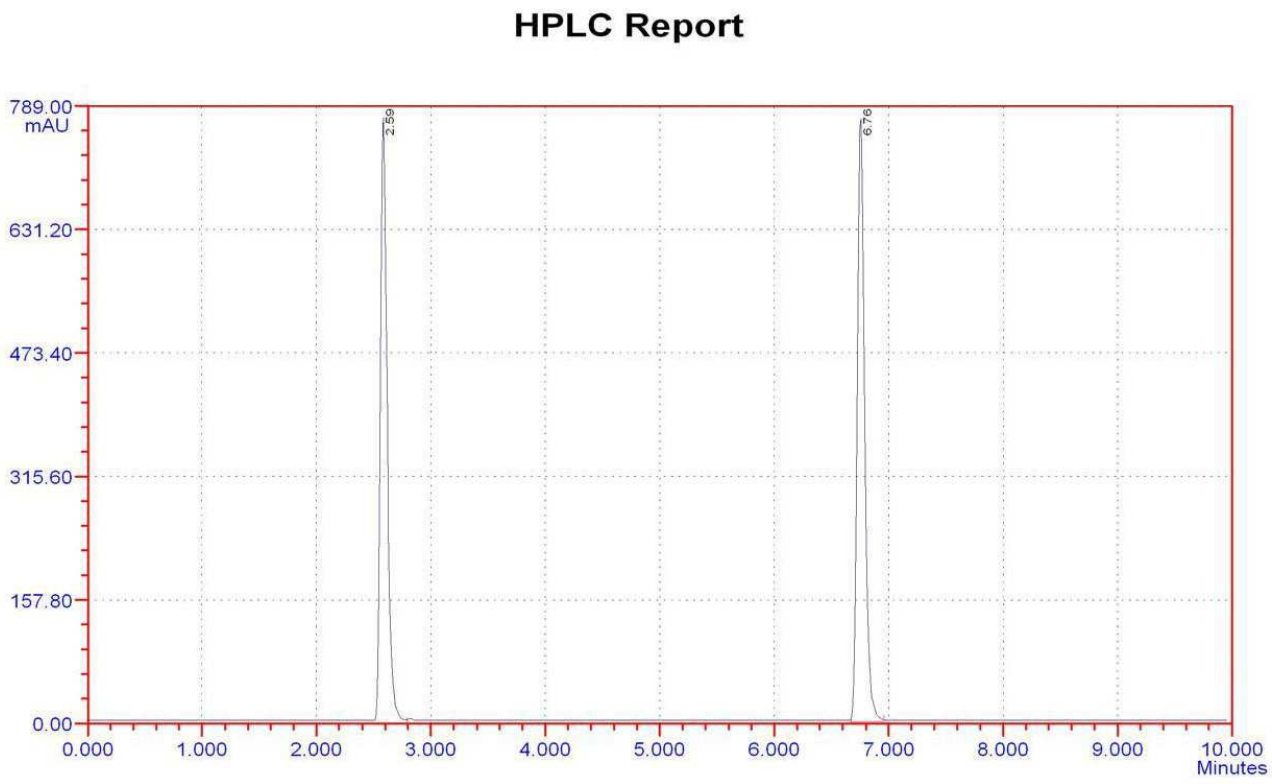


Figure 2
Typical chromatogram of standard Famotidine and Ibuprofen Recovery

The recovery of the standard solutions was done by adding them to pre-analyzed sample solution at different levels i.e. 50%, 75%, and 100% separately to study the accuracy of the above method. The corresponding results were recorded.

Recovery	Conc. of sample	Famotidine Recovery	Ibuprofen Recovery	Famotidine recovery % of	Ibuprofen recovery % of
50%	50ppm	49.91	49.86	99.82	99.74
75%	75ppm	75.09	74.95	100.12	99.933
100 %	100ppm	100.525	100.976	100.525	100.976

Table 5
Recovery of Olmesaartan, Hydrochlorothiazide

Limit of detection (LOD) and limit of quantification (LOQ)

LOD and LOQ were determined from standard deviation of y-intercept of regression line and slope method as per ICH guidelines.

	TEST	Famotidine	Ibuprofen
TEST-4	L.O.Q	1 ppm	1.5 ppm
TEST-5	L.O,D	0.3 ppm	0.5 ppm

Table 6
LOD and LOQ test results

Robustness

Typical variations in liquid chromatography conditions were used to evaluate the robustness of the assay method. In this study, the chromatographic parameters monitored were retention time, area, capacity factor, tailing factor and theoretical plates. The robustness acceptance criteria set in the validation were the same established on system suitability test describe above.

Parameter	Modification	Famotidine Area	Ibuprofen Area	Famotidine % of change	Ibuprofen % of change
Standard	……	318644	346055	……...	……
MP	Water:ACN:TEA 75:15:10	318946	347118	0.095	0.307
PH	5.7	319394	347316	0.235	0.364
Wavelength	284nm	320023	349194	0.43	0.91

Table 7
Robustness study

Analysis of marketed formulations

The validated HPLC method was adopted for the quantification of Famotidine and Ibuprofen in their combined pharmaceutical dosage form and the typical chromatograms of the formulation are shown in fig. The results of analysis are given in Table 8. The contents of the pharmaceutical dosage form were found to be in the range of 100±2% with RSD less than 2% which indicate suitability for routine analysis of Famotidine and Ibuprofen in pharmaceutical dosage form.

S.NO	FORMULATION	DOSAGE	SAMPLE CONC	DRUG ESTIMATED	% OF DRUG ESTIMATED
Famotidine	DUEXIS	26.6mg	52 ppm	51.86	99.73

S.NO	FORMULATION	DOSAGE	SAMPLE CONC	DRUG ESTIMATED	% OF DRUG ESTIMATED
Ibuprofen	DUEXIS	800mg	80 ppm	79.12	98.9

Table 8
Formulation

CONCLUSION

The proposed study describes a new RP-HPLC method using simple mobile phase for the estimation of Famotidine and Ibuprofen in combined pharmaceutical dosage formulations. The method was validated and found to be simple, sensitive, accurate and precise. It was also proved to be convenient and effective for the determination of Famotidine and Ibuprofen in the pharmaceutical dosage form. The percentage of recovery shows that the method is free from interference of the excipients used in formulation. Moreover, the lower solvent consumption along with the short analytical run time leads to cost effective chromatographic method[9].

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