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A Stability Indicating RP-HPLC Method for Simultaneous Determination of Ibuprofen and Famotidine

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Abstract

A stability indicating gradient RP-HPLC method is developed for simultaneous determination of ibuprofen and famotidine. Separation of degradants, ibuprofen and famotidine was carried out on Qualisil BDS C8 column (250 × 4.6 mm, 5 µm) using a mobile phase gradient consisting of methanol and water pH 3.0 at a flow rate of 1 mL/min. The detection and reference wavelengths were set at 263 nm (4 nm bandwidth) and 360 nm (80 nm bandwidth), respectively. Intentional degradation of ibuprofen and famotidine was attempted at stress condition of hydrolytic (refluxed at 80ºC for 1 h), acid (5M HCl, refluxed at 80ºC for 1 h), base (5M NaOH, refluxed at 80ºC for 1 h), oxidation (15% H2O2, for 6 h at 30 °C) and sunlight (exposed for 4 h). Degradants were eluted up to ~ 26 min whereas famotidine and ibuprofen shows retention at 6.34 ± 1.53 and 21.76 ± 0.38 min respectively. Drug-drug interaction study was also performed. The proposed method was able to separate the formed sulfamide impurity which is a major degradation product of famotidine - ibuprofen combination mixture when kept at accelerated condition (40ºC ± 75% RH for 30 days). The method obeys Beer's law in the concentration range of 3-21 µg/mL for ibuprofen (r2=0.9998) and 0.1-0.7 µg/mL for famotidine (r2=0.9999). The assay result of synthetic mixture was found to be 99.13 ± 0.14 and 100.73 ± 0.57 for ibuprofen and famotidine, respectively. The proposed method was validated as per ICH Q2 (R1) analytical method validation guidelines. The percentage recovery was found to be 96.55 ± 1.83 and 102.83 ± 0.85 for ibuprofen and famotidine, respectively. The results of present study clearly shown that the proposed method was specific as ibuprofen and famotidine were estimated in presence of their acidic, alkaline, oxidative, hydrolytic and photolytic degradation products and it may be effectively applied for estimating the content of ibuprofen and famotidine in pharmaceutical formulation.

Keywords: *Cromolyn sodium; HPLC; Cromolyn sodium alkaline degradate*

Introduction

Ibuprofen (IBU) and famotidine (FAM) are co-formulated in oral tablet dosage form indicated for the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis and to decrease the risk of developing upper gastro-intestinal ulcer [1,2] IBU and FAM are chemically incompatible. Therefore, the tablet in tablet dosage form of IBU and FAM was formulated by Horizon Pharma, USA which improves the stability of IBU and FAM under forced degradation condition [1].

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IBU (Figure 1) chemically known as (RS)-2-(4-(2-methylpropyl) phenyl) propionic acid is phenyl propionic acid derivative/ cyclooxygenase inhibitor from the class of non-steroidal anti-inflammatory drugs used in the treatment of fever, arthritis as an analgesic [2].

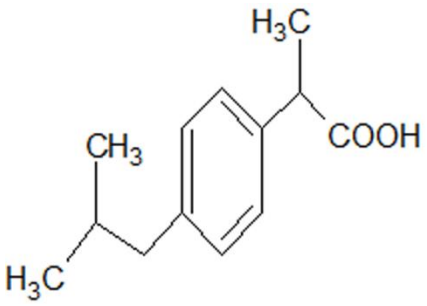

Figure 1: Structure of Cromolyn Sodium.

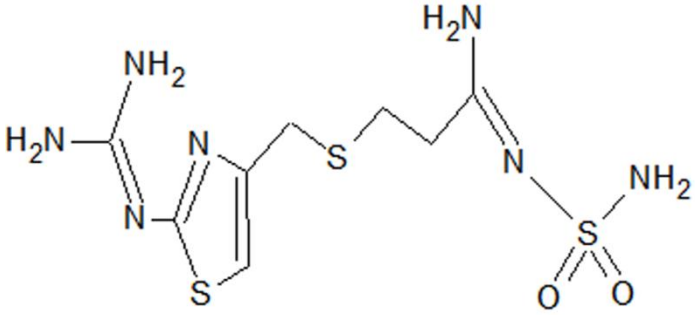

Figure 2: Structure of FAM.

Numerous studies have been carried out on FAM. Indian Pharmacopoeia [3], British Pharmacopoeia [4], European Pharmacopoeia [5] and United States Pharmacopoeia [6] described a titrimetric method for estimating the content of FAM in bulk form and liquid chromatographic method for the assays of tablet, injection and oral suspension formulations of FAM. Use of spectrophotometric [24-27] spectrofluorimetric [28], HPLC [29-32], flow injection analysis [33], HPTLC methods [34,35] for estimating the content of FAM in single component formulation has been reported in the literature. Estimation of FAM in multicomponent formulation using spectrophotometric [36,37], HPLC [38,39], flow injection analysis [39] and HPTLC methods [21,40] has been reported in the literature.

To the best of our knowledge, a number of liquid chromatographic methods have been reported for the assay of IBU and FAM. Shah et al. [41], Karthik Kumar et al. [42], Krishnaveni and Sathyanarayana [43] and Patel et al. [44] described HPLC method for estimating the IBU and FAM but they didn't perform the stability and/or drug-drug interaction study [41-44]. Sekhar et al. [45] described HPLC method using ion pairing reagent in mobile phase preparation but they didn't perform the stability and drug-drug interaction study [45]. Ahirrao and Pawar, [46] and Reddy et al. [47] described stability indicating HPLC method using buffered mobile phase but they didn't perform drug-drug interaction study [46,47]. In all the above methods authors did not performed the drug-drug interaction study. In few research papers author has performed stability study but they used a buffered or ion pairing reagent consisting mobile phase. So, the above methods are not economic and time consuming because columns required more time for cleaning.

Therefore, there is a need to develop buffer free, ion-pairing reagent free, cost effective and less time consuming method for estimating the content of IBU and FAM. Advantages of our proposed method are as follows.

1. Buffer free mobile phase
2. Economic
3. Quick column washing
4. Stability study and

5. Drug –drug interaction study was carried out between IBU and FAM

6. All the degradants, sulfamide an interaction product, IBU and FAM were separated using single proposed gradient mobile phase.

Present work demonstrates the development, validation and application of a simple, economical, accurate, precise and selective gradient RP-HPLC method for estimating the content of IBU and FAM in combination.

Experimental

Instrument

Agilent technologies 1200 series HPLC instrument equipped with photo diode array detector, G 1311 A solvent delivery system (Quaternary pump), Rheodyne injector (20.0 µL), Qualisil BDS C8 column (250 × 4.6mm, 5 µm) and Ez-Chrom Elite software 3.3.2 was used.

Reagents and chemicals

IBU and FAM were obtained as a gift samples from Centurion Laboratories, Vadodara (Gujarat). Analytical grade chemicals and double distilled water were used in the experiments.

Chromatographic conditions

The separation and simultaneous determination of IBU, FAM with their degradation products was performed on Qualisil BDS C8 column (250 × 4.6 mm, 5 µm) using the gradient elution mode. A gradient programme consist of methanol (Solvent A) and water pH 3.0 adjusted with ortho-phosphoric acid (Solvent B) is given in Table 1. A mixture of methanol and water pH 3.0 (15:85 v/v) was used as diluent. The mobile phase was pumped at flow rate of 1mL/min. The detection and reference wavelengths were set at 263 nm (4 nm bandwidth) and 360 nm (80 nm bandwidth) respectively.

Solvent A	Solvent B	Time (min)
15	85	0
80	20	20
80	20	26
15	85	26.01
15	85	36 (Re-equilibration)

Preparation of standard solutions

Stock solution of IBU (300 µg/mL) and FAM (10 µg/mL) was prepared in HPLC- grade methanol. The working standard solution was prepared by dilution of the above stock solution with diluent to achieve the concentration of solution in the concentration range of 3-21 µg/mL and 0.1-0.7 µg/mL for IBU and FAM respectively. Mixed working standard solution of 9 µg/mL of IBU + 0.3 µg/mL of FAM was prepared.

Preparation of synthetic mixture solution

Excipients used in the tablet formulation were added in IBU + FAM mixture (30:1, w/w) [1] (Table 2) and sonicated for 20 minute after the addition of methanol. The final volume was made with methanol. The solution was filtered through 0.45 µm filter paper. The working solution was prepared by dilution of the above stock solution with diluent to obtain the concentration of 9 µg/mL of IBU and 0.3 µg/mL of FAM.

Material	%w/w	mg/tab
Famotidine	2.54	26.6
Lactose monohydrate	0.95	10.0
Microcrystalline cellulose	3.3	34.6
Croscarmellose sodium	0.38	4.0
Colloidal silicon dioxide	0.04	0.4
Magnesium stearate	0.11	1.2
Ibuprofen	89.75	800
Purified water	-	q. s.

Table 2: Tablet formulation components.

Obs.	Mobile Phase	Famotidine (FAM)	Ibuprofen (IBU)	Comment

Results and Discussion

Structural, physical and chemical properties of active pharmaceutical ingradients are very important factors in optimizing appropriate chromatographic conditions [48]. According to that, RP-HPLC column was chosen for the analysis.

Significant condition in the present study was separation of IBU and its degradation products, as well as FAM and its degradation products. IBU contains benzene ring and carboxylic acid group, whereas, FAM contains sulfamide and primary amino group. The key difference in the structure is polarity and acidity/alkalinity. For the analysis of such a mixture (compounds with high and low lipophilicity), it required a gradient mobile phase programme (Table 1) starting with low percent of organic solvent and gradual increasing of organic solvent content so as to achieve an optimal separation and retention of all the components of the mixture.

Retention behavior of IBU, FAM and their degradation products was studied using Qualisil BDS C8 column (250 × 4.6mm, 5µm) as a stationary phase. It was noticed that the optimal retention of FAM (log P value=-0.64) requires a mobile phase with low percent of organic solvent, i.e., less than 20%, v/v and its degradation products requires mobile phase with low to high percent of organic solvent. However, on the other hand, IBU (log P value=3.621) and its degradation products are more lipophilic substances and they were retained for almost 70 min under the same experimental condition. Because of this, isocratic elution was found to be time consuming and uneconomical to analyze the IBU and FAM mixture. Hence, efforts were utillized for optimizing gradient mobile phase elution programme. A number of trials were performed to establish an optimized gradient elution programme and they are presented in Table 3.

		Rt (min.)	Theoretical plate	Assemetry	Rt (min.)	Theoretical plate	Assemetry	
01.	Methanol : Water(80:20v/v)	2.24	1705	1.03	6.94	6810	0.90	FAM elutes at void volume
02.	Methanol :Water(75:25v/v)	2.20	1335	1.06	9.26	6225	0.86	FAM elutes at void volume
03.	Methanol : Water(55:45v/v) After 8 min Methanol : Water(90:10v/v)	2.23	6836	0.86	8.20	97330	1.05	FAM elutes at void volume
From above 3 runs it was concluded that FAM elutes at void volume, so we use the buffered mobile phase								
04.	Methanol : KH2PO4 10mM pH 3.08 (80:20v/v)	2.66	6327	1.26	6.66	6836	0.90	FAM elutes at void volume
05.	Methanol : KH2PO4 10mM pH 3.00(78:22v/v)	2.68	5148	1.21	7.52	6508	0.88	FAM elutes at void volume
06.	Methanol : KH2PO4 pH 3.08 10mM 70:30 v/v	2.76	8537	1.10	13.10	16484	1.06	FAM elutes at void volume
07.	Methanol : KH2PO4 pH 3.08 10mM 65:35 v/v	2.74	8537	1.21	20.54	14699	1.03	FAM elutes at void volume
From the above 4 runs using Methanol and KH_2PO_4 pH 3.08 10mM, it was concluded that FAM elutes at void volume and as the buffer concentration increases retention time of IBU also increases. So we use next buffer KH_2PO_4 10mM pH 6.80								
08.	Methanol : KH2PO4 10mM pH 6.80 (80:20v/v)	2.98	0	0.94	4.3	2554	0.65	FAM elutes at void volume
09.	Methanol : KH2PO4 10mM pH 6.80 (75:25v/v)	3.05	11887	1.13	5.02	13573	1.07	FAM elutes at void volume
10.	Methanol : KH2PO4 pH 6.8 10mM 70:30 (v/v)	3.06	0	1.07	5.65	11291	1.19	FAM elutes at void volume
From the above 3 runs using Methanol and KH_2PO_4 pH 6.80 10mM, it was concluded that FAM elutes at void volume. So we use next buffer Ammonium Acetate Buffer pH 5.5, 10mM								
11.	Methanol : Ammonium Acetate Buffer pH 5.5 10mM 80:20 v/v	2.96	7084	1.28	4.88	11858	1.01	FAM elutes at void volume

12.	Methanol : Ammonium Acetate Buffer pH 5.5 10mM 70:30 v/v	2.98	7483	1.11	7.88	13363	1.11	FAM elutes at void volume
13.	Methanol : Ammonium Acetate Buffer pH 5.5 10mM 55:45 v/v Up to 17 min & then Methanol : Ammonium Acetate Buffer pH 5.5 10mM 90:10 v/v	3.06	11282	1.20	20.14	423031	1.19	FAM elutes at void volume and IBU did not elute up to 17 min so the composition was changed & then IBU eluted at 20.14 min.
From the above 3 runs using Methanol and Ammonium Acetate Buffer pH 5.5 10mM, it was concluded that FAM elutes at void volume and IBU takes longer time to elute when higher buffer concentration used. So we use next buffer mixed phosphate buffer 10mM pH 6.80								
14.	Methanol : Mixed Phosphate Buffer pH 6.8 10mM 80:20 v/v	2.92	2038	1.00	3.65	1604	0.75	FAM elutes at void volume and peak asymmetry
15.	Methanol : Mixed Phosphate Buffer pH 6.8 10mM 70:30 v/v	2.94	793	1.11	5.83	804	0.58	FAM elutes at void volume and peak asymmetry
16.	Methanol : Mixed Phosphate Buffer pH 6.8 10mM 60:40 v/v	3.18	7254	1.47	11.22	15946	1.12	FAM elutes at void volume
17.	Methanol : Mixed Phosphate Buffer pH 6.8 10mM 50:50 v/v	3.42	10651	1.11	26.58	9074	1.57	Longer retention time of IBU and tailing
	From the above 14,15 and 16 runs using Methanol and mixed phosphate buffer pH 6.80 10mM, it was concluded that FAM elutes at void volume and in run 17 FAM elutes after the void volume but Rt of IBU is very longer 26.58 min. Finally, from run no.14 we concluded that FAM required aqueous mobile phase conc. To elute after the void volume whereas IBU required organic solvent for earlier retention time (Run 14-16). This retention behavior of IBU and FAM might be due to large difference in log *P* value -0.64 and 3.621 for FAM and IBU respectively.								
	From above conclusion we go for optimization of gradient programme using Methanol and KH_2PO_4 pH 6.80 10mM							
18.	Gradient programme	5.64	10630	1.09	14.17	91950	1.10	Run time of IBU & FAM OK but slope of the gradient is more and stable baseline was not obtained.
19.	Gradient programme	5.64	10523	1.13	16.34	120316	1.10	Run time of IBU & FAM OK but slope of the gradient is more and stable baseline was not obtained.
20.	Gradient programme	5.44	14021	1.11	22.00	15528	1.14	OK

						4		No problem at all
Gradient programme given in run 20 is OK, also it obeys all the system suitability parameters. But we thought to develop a buffer free mobile phase. So we use methanol and water pH 3 adjusted with orthophosphoric acid								
21.	Gradient programme (Optimized mobile phase and gradient programme)	6.527	43539	0.98469	22.047	446327	1.06765	Optimum mobile phase because capacity factor for IBU (7.71) and FAM (1.52) is more than 1 and less than 20 (Snyder et al.), peak symmetry for IBU (1.06) and FAM (0.98), resolution (15.42), gradient slope is also less, stable baseline, degradation products were well resolved, and IBU-FAM interaction product was also separated by using this mobile phase.
Finally, by considering the 1. system suitability parameters i. e. capacity factor (1<k'<20), resolution (>2), tailing factor (0.9-1.2) and theoretical plates (>2000) 2. separation of degradation products at acidic, alkaline, oxidative, neutral and thermal degradation from peak of IBU and FAM 3. and separation of drug-drug interaction product of IBU and FAM i.e. sulphamide the proposed method was found to be optimum.								
Column: Qualisil BDS C8 (250 x 4.6 mm, 5um) Void volume: ~3 mL and dead time ~3 min at 1mL/min flow rate								

Table 3: Mobile phase optimization trials.

For estimating IBU and FAM numerous liquid chromatographic methods were reported. But author has used buffered, ion-pairing reagent containing mobile phases for the optimization [42, 43, 45-47]. After performing the analysis it required an extensive column washing. With the continuous use of buffered mobile phases for separation column life is getting reduced [49]. Therefore, the mobile phase composition was decided to be used without buffer and ion-pairing reagent.

Selection of detection wavelength and band width

From the overlain UV spectra of IBU and FAM of mixed working standard solution, the detection wavelength 263 nm was selected. The use of narrow band width has the advantage of increasing the signal selectivity of the detector [50]. Therefore, 4 nm band width was selected for analysis.

Selection of reference wavelength and bandwidth

In the gradient analysis, absorbance value of sample was changed as the mobile phase composition varies as well as refractive index also changes during the gradient. This change in sample absorbance is not because of the sample itself but because of change in composition of mobile phase. The use of a reference wavelength is highly recommended to reduce baseline drift induced by refractive index changes during a gradient [51]. A reference wavelength of 360 nm with an 80 nm bandwidth is fine for a sample that didn't have a visible absorption band.

The representative chromatogram of IBU and FAM was shown in Figure 3.

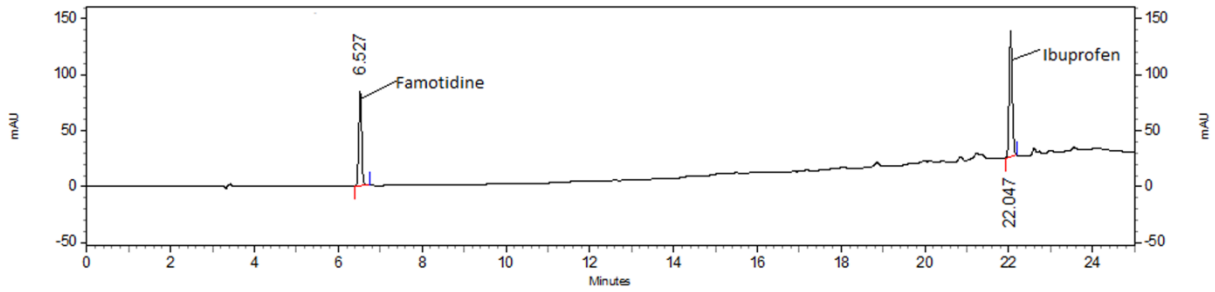

Figure 3: Chromatogram of IBU and FAM.

System suitability test

Parameters considered in system suitability study were retention time, theoretical plates, asymmetry, capacity factor and resolution. System suitability test was carried out using mixed working standard solution. Six replicate analyses were performed using same sample. Results of system suitability parameters are presented in 4 and it was found to be within the acceptance limit.

Parameters	Results (n=6) ± % RSD	
	IBU	FAM
Retention Time	21.79 ± 0.15	6.32 ± 0.49
Asymmetry	1.09 ± 1.61	1.09 ± 1.30
Theoretical Plates	425583 ± 0.27	47179 ± 0.24
Capacity Factor	7.71 ± 0.19	1.52 ± 0.79
Resolution	15.42	

Table 4: System suitability parameters

Specificity study

Stress study was performed at initial concentration of 100 µg/mL of IBU and FAM. Intentional degradation was carried out at stress conditions of hydrolytic (refluxed at 80ºC for 1 h), acid (5M HCl, refluxed at 80ºC for 1 h), base (5M NaOH, refluxed at 80ºC for 1 h), oxidation (15% H2O2, for 6 h at 30 ºC) and sunlight (exposed for 4 h). Samples were prepared in methanol.

From all forced degradation samples, about 1.0 mL solution was transferred to 10.0 mL volumetric flask and dilution was made with diluent. These samples were analyzed by HPLC as per the optimized chromatographic conditions. The results of specificity study are presented in Table 5. The result of specificity study indicated that the proposed HPLC method is able to separate IBU and FAM in presence of their degradation products obtained in different stress conditions (Figure 4). In case of IBU, oxidative and photolytic degradation was not observed.

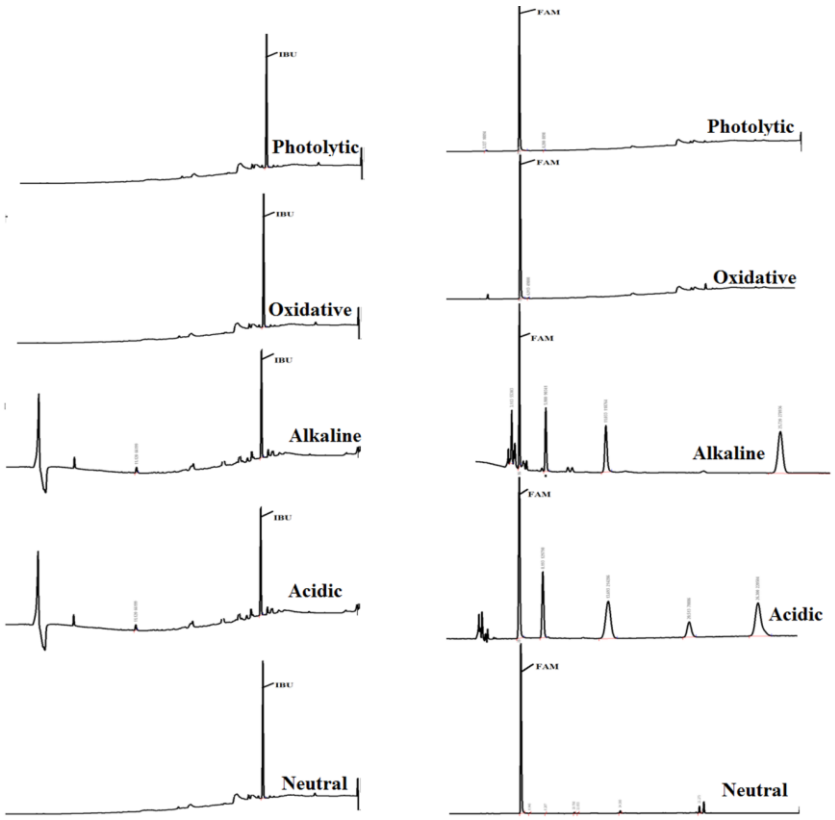

Figure 4: Overlain chromatograms of IBU and FAM in different stress conditions.

Condition	% Drug remaining (n=3)	
	IBU	FAM
5M HCl	42.08	31.12
5N NaOH	90.55	10.85
15% H_2O_2	98.04	75.41
Sunlight	92.91	76.71
Water	56.51	71.76

Table 5: Results of specificity study.

Linearity study for IBU and FAM

Different concentrations of working standard solution in the concentration range of 3-21 µg/mL for IBU and 0.1-0.7 µg/mL for FAM were prepared. Samples were injected for HPLC analysis and analyzed as per the optimized chromatographic conditions. All the measurements were repeated three times for each concentration. A calibration graph of the drug concentration versus peak area was constructed. A linear relationship was found in the concentration range of 3 - 21 µg/mL for IBU (r2=0.9998) and 0.1-0.7 µg/mL for FAM (r2=0.9999).

Analysis of synthetic mixture

The working sample solution of synthetic mixture was used for the HPLC analysis. Sample was analyzed as per optimized chromatographic conditions. Concentration and percentage drug content was determined using the following formulae.

$$Cu=(Au\times Cs)/As$$

Where,

Cu: Concentration of sample solution (µg/mL)

Cs: Concentration of standard solution (µg/mL)

Au: Peak area of sample solution

As: Peak area of standard solution (24000 for FAM of concentration 0.3 µg/mL) and (38701 for IBU of concentration 9 µg/mL)

$$\text{Percentage Drug Content} = C_{Est}/ C_{Act} \times 100$$

×

Where,

CEst: Estimated concentration (µg/mL)

CAct: Actual concentration (µg/mL)

The assay results of IBU and FAM in synthetic mixture was found to be 99.13 ± 0.14 and 100.73 ± 0.57, respectively.

Accuracy

The accuracy of the proposed method was determined by recovery study [52]. The known amount of pure IBU and FAM were spiked to pre-analyzed synthetic mixture of IBU and FAM (9 µg/mL IBU + 0.3 µg/mL FAM). Analysis of IBU and FAM was carried out at three concentration levels such as 80%, 100% and 120% within the specified linearity and range. The contents of IBU and FAM were determined by using the formulae mentioned in "Analysis of synthetic mixture".

The percentage recovery was calculated using the formula as below.

$$\text{Percentage recovery}=E/ (T+P)\times 100$$

Where,

E: Total amount of drug estimated (µg/mL)

T: Amount of drug taken from pre-analyzed synthetic mixture (µg/mL)

P: Amount of pure drug added (µg/mL)

The percentage recovery was found to be 96.55 ± 1.83 and 102.83 ± 0.85 for IBU and FAM respectively (Table 6).

Drugs	Initial amount (µg/mL)	Pure drug added (%)	Amount recovered ± SD (n=3)	Recovery (%)	%RSD
IBU	9	80	15.69 ± 0.39	96.85	2.46
	9	100	17.13 ± 0.22	95.18	1.26
	9	120	19.24 ± 0.26	97.16	1.35
FAM	0.3	80	0.55 ± 0.005	102.25	1.04
	0.3	100	0.61 ± 0.005	102.47	0.94
	0.3	120	0.69 ± 0.005	103.78	0.84

Table 6: Results of accuracy study.

Precision

The precision of the method was determined as inter-day and intra-day precision. The repeatability study (intra-day precision) was performed by analyzing the samples of IBU and FAM repeatedly within the day. The inter-day precision study was performed by analyzing the samples of IBU and FAM repeatedly at different days. Six determinations of mixed working standard solution of IBU and FAM were performed.

The result of inter-day precision was expressed as % RSD and it was found to be less than 2 (Table 7). The obtained %RSD value indicates the good precision of the method.

Drug	Concentration µg/mL	Inter-day (n=6)		Intra-day (n=6)	
		Peak area ± SD	%RSD	Peak area ± SD	%RSD
IBU	9	33739.33 ± 57.64	0.17	33731.83 ± 47.37	0.14
FAM	0.3	22164 ± 162.74	0.73	22230.5 ± 127.67	0.57

Table 7: Results of precision study**.**

Limit of detection and limit of quantitation

Limit of detection (LOD) and limit of quantitation (LOQ) of the analytical method developed for estimating the IBU and FAM content was calculated using the formulae mentioned below.

$LOD=(3.3\times\sigma)/S$

$LOD=(10\times\sigma)/S$

Where,

σ: Standard deviation of the response

S: Slope of calibration curve

The LOD was found to be 0.0453 µg/mL and 0.0068 µg/mL for IBU and FAM, respectively. The LOQ was found to be 0.1373 µg/mL and 0.0206 µg/mL for IBU and FAM, respectively.

Robustness

In a robustness study number of experimental conditions was deliberately changed. The flow rate and detection wavelength was changed by ± 0.1 and 1 unit respectively. Results of robustness study are presented in Table 8. From the results of robustness study the method was found to be robust, as no significant change was observed on the peak area and chromatographic resolution after small but deliberate variation in chromatographic conditions.

Method parameter varied	Retention Time		Resolution	Theoretical Plate		Tailing factor		Capacity Factor	
	IBU	FAM		IBU	FAM	IBU	FAM	IBU	FAM
Flow rate									
0.9 mL/min	22.45	7.11	15.86	423498	47305	1.25	1.28	7.98	1.84
1.1 mL/min	19.95	5.79	15.28	425865	47582	1.41	1.31	6.98	1.32
Detection wavelength									
262 nm	21.79	6.32	15.42	425582	47179	1.09	1.09	7.71	1.52
264 nm	21.79	6.32	15.42	425578	47205	1.09	1.09	7.71	1.52

Table 8: Results of robustness study.

Drug-drug interaction study

The physical mixture of IBU and FAM in the proportion of 30:1 as in marketed formulation was kept in stability chamber at 40 ºC ± 75% RH for 30 days. The sample solution was prepared in methanol and dilution was made with diluent. The sample was analyzed by HPLC as per optimized chromatographic conditions.

In the chromatogram of sample, one extra peak was obtained at 3.23 min which might be of sulfamide. Because, the UV spectrum of peak at 3.23 min and UV spectrum of sulfamide is to be identical one. Also both the compound shows maximum absorption at 266 nm [31] (Figure 5).

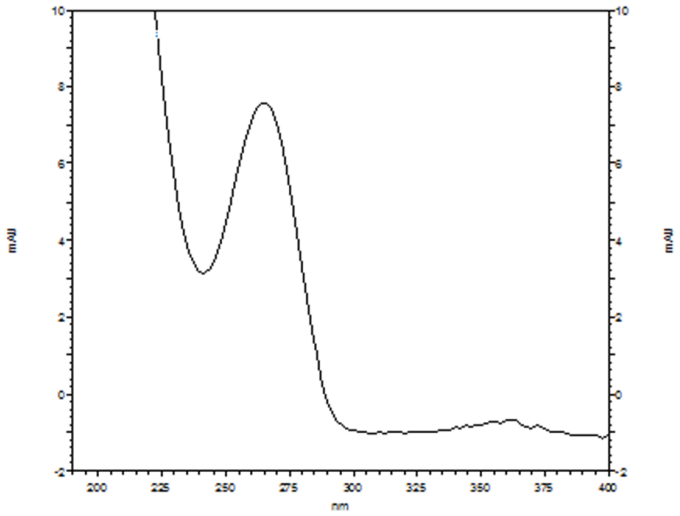

Figure 5: UV spectrum of degradation product of IBU and FAM in combination.

From the above data, the proposed HPLC method was able to resolve the sulfamide impurity which is the major degradation product of famotidine - ibuprofen combination mixture when kept for accelerated study [1,53].

Conclusion

All the degradants, sulfamide an interaction product, IBU and FAM were separated using single proposed gradient mobile phase.

Acknowledgment

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