International Journal of Advances in Pharmaceutical Analysis
IJAPA Vol. 5 Issue 4 (2015) 85-92

Development of Stability Indicating Assay Method for Estimation of Ibuprofen and Famotidine in Combined Dosage Form in Tablet

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Abstract

A simple, precise, accurate, simultaneous stability indicating RP-HPLC method for the estimation of IBU (Ibuprofen) and FMT (Famotidine) in combined dosage form was developed using Grace RP-C18 (4.6 x 250mm, 5µm) in an gradient mode with mobile phase comprising of Methanol: Water (pH 2.5 using OPA) The flow rate was 0.7 mL/ min and effluent was monitored at 240.0 nm. The retention times were found to be 6.68 min for IBU and 1.76 min for FMT. The assay exhibited a linear dynamic range of 30- 150 µg/mL for IBU and 1- 5 µg/mL for FMT. The calibration curves were linear (r^2 = 0.994 for IBU and r^2 = 0.997 for FMT) over the entire linear range. Mean % recovery was found to be 99.82 % for IBU and 99.91 % for FMT with % RSD was NMT 2 for both estimations which fully agrees with system suitability which is in good agreement with labeled amount of formulation. The % RSD for Intra- Day & Inter-Day Precision was NMT than 2 for both the drugs. The developed method was validated as per ICH guidelines.

Keywords: IBU, FMT, RP-HPLC, Assay method, Method Validation.

1. Introduction

The technique High Performance Liquid Chromatography (HPLC) is so called because of its improved performance over the classical column chromatography. The technique basically involves the use of porous material as a stationary phase and the liquid mobile phase is pumped into the column under high pressure. The development of this technique is attributed to the small particle size of stationary phase. As the particle size is small the resistance to the flow of mobile phase is very high that is the reason why the high pressure is recommended.[1, 18] Analytical method development and validation are key elements of any pharmaceutical development program. HPLC analysis method is developed to identify, quantity or purifying compounds of interest. This technical brief will focus on development and validation activities as applied to drug products. Method validation is the process of proving that an analytical method is acceptable for its intended purpose. The parameters for method validation as defined by ICH (International Conference on Harmonization) guidelines are Accuracy, Precision, Specificity, Limit of Detection, Limit of Quantitation, Linearity, Range, Robustness and Ruggedness[2]. From the literature review [7-16] it has been found that only three analytical methods for the above combination have been reported. Therefore the attempt is made to develop simple, accurate, precise rapid and economical RP-HPLC method for determination of Ibuprofen (IBU) and Famotidine (FMT) in combine dosage form. Ibuprofen [Figure 1]. Chemically is (RS)-2-(4-(2-methylpropyl) phenyl) propanoic acid.It is white crystalline powder used as analgesic having solubility in methanol, ethanol and in water 21 mg/Lt. While famotidine [Figure 2] chemically is 3-[({2-[(diaminomethylidene)amino]-1,3-thiazol-4-yl}methyl)sulfanyl]-N'-sulfamoylpropanimid amide.[5,6,19,20] It is white to pale yellow crystalline. Used as anti-ulcer having solubility in methanol and freely soluble in glacial acetic acid, slightly soluble in water.

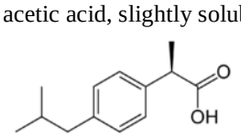

Figure 1: Chemical Structure of Ibuprofen

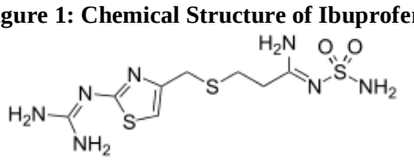

Figure 2: Chemical Structure of Famotidine

2. Experimental

2.1 Reagents & Chemicals

Standard samples of IBU & FMT were received as gift samples from The Leben Laboratories Akola (Maharashtra) and Taj Pharmaceuticals, Mumbai (Maharashtra). The marketed formulation Duexis (Horizon Pharma) was purchased from the local market containing IBU 800 mg and FMT 26.6 mg and all the chemicals used were are of analytical grade.

2.2 Instruments

HPLC System of Younglin Quaternary pump with UV- VIS detector (190-990 nm) Software – Autochro. Analytical balance of citizen model CY 104 (microanalytical balance) was used for weighing purpose also the ultrasonicator servewell instruments model RC-SYSTEM MU-1700 used for sonication purpose.

2.3 Preparation of Standard Solutions

Standard Stock Solution (A): Accurately weighed quantity of IBU (30.0 mg) was transferred to 50.0 mL volumetric flask and dissolved in methanol. The volume was made up to mark with methanol to get final concentration of 600 µg/mL. The resultant solution was then sonicated for 10.0 min in ultrasonicator.

Standard Stock Solution (B) Accurately weighed quantity of FMT (10.0 mg) was transferred to 50.0 mL volumetric flask and dissolved in methanol. The volume was made up to mark with methanol to get final concentration of 200 µg/mL. The resultant solution was then sonicated for 10.0 min in ultrasonicator.

Working Standard Solution (C) 0.5 mL of solution (A) and 0.05 mL of solution (B) was transferred to 10.0 mL volumetric flask and then the volume was made up to the mark with mobile phase to get final concentration of (30.0 µg/mL of IBU & 1.0 µg/mL of FMT) respectively. The resultant solution was then sonicated for 10.0 min in ultrasonicator.

2.4 Optimization of Mobile Phase and Chromatographic Conditions

Procedure: The chromatographic conditions were set as per the optimized parameters. The mobile phase was allowed to equilibrate with stationary phase as was indicated by a steady baseline. Solution (C) was injected in the Rheodyne injector (20.0 µl) and the respective chromatograms were recorded. Various mobile phases were tried by permutations and combinations and also by varying column, flow rate, column temperature and type of

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buffers with varying pH and solvents. The various mobile phases tried are as follows.

- **Trial 1** Methanol: Water (70: 30) pH 7
- **Trial 2** Methanol: Water (75: 25) pH 7
- **Trial 3** Methanol: Water (80:20) pH 7
- **Trial 4** Methanol: Water (85: 15) pH 2.5

Above mentioned mobile phases were tried. The mobile phase containing Methanol: water (85: 15) at pH 2.5, injection volume- 20.0 µL flow rate of 0.7 mL/min was selected, due to its high resolving power, sensitivity and suitability, for the determination of IBU and FMT. The chromatogram is shown in **Figure 3**. Hence the following optimized chromatographic parameters were selected to carry out further experimentation.

- **Column** : Grace RP-C18 (4.6 x 250mm, 5µm)
- **Flow Rate** : 0.7 mL/min
- **Wavelength** : 240.0 nm
- **Injection Volume** : 20.0 µL
- **Column Temperature** : Ambient
- **Run Time** : 10.0 min
- **Mobile Phase** : Methanol: Water (85:15)
- **pH** : 2.5 (Using OPA)

2.5 System Suitability Studies

System suitability is a pharmacopoeial requirement and is used to verify, whether the resolution and reproducibility of the chromatographic system are adequate for analysis to be carried out. It is performed to ensure that the system is operating properly and read to deliver results with acceptable accuracy and precision. The tests were performed by collecting data from five replicate injections of standard solutions.

Procedure: The chromatographic conditions were set as per the optimized parameters and mobile phase was allowed to equilibrate with stationary phase as was indicated by the steady baseline. Five replicate injections of mixed working standard solution (C) were injected in to the system, the chromatograms were recorded for both the drugs and the results are shown in **Table 1 & 2.**

2.6 Analysis of Standard Laboratory Mixtures

2.6.1 Preparation of Standard Laboratory Mixtures (Standard)

IBU Standard Stock Solution (A): Accurately weighed quantity of IBU (30.0 mg) was transferred to 50.0 mL volumetric flask and dissolved in methanol. The volume was made up to mark with methanol to get final concentration of (600 µg/mL of IBU). The resultant solution was then sonicated for 10.0 min in ultrasonicator.

FMT Standard Stock Solution (B): Accurately weighed quantity of FMT (10.0 mg) was transferred to 50.0 mL volumetric flask and dissolved in methanol. The volume was made up to mark with methanol to get final concentration of (200 µg/mL of FMT). The resultant solution was then sonicated for 10.0 min in ultrasonicator.

Mixed Standard Solutions: 0.5 mL of solution (A) and 0.05 mL of solution (B) was then transferred to 10.0 mL volumetric flask and volume was made up to the mark with mobile phase to get final concentration of (30.0 µg/mL of IBU & 1.0 µg/mL of FMT) respectively.

2.6.2 Preparation of Standard Laboratory Mixtures (Sample)

Accurately weighed 800.0 mg of IBU and 26.6 mg of FMT (as per labeled requirement of marketed formulation) was transferred to 50.0 mL volumetric flask and dissolved in sufficient quantity of methanol. Then the volume was made up to the mark with methanol. The resultant solution was then sonicated in ultrasonicator for 10.0 min. then aliquot portions of 0.0075 mL and 0.0057 mL was then transferred to two separate 10.0 mL volumetric flask and then volume was made up to the mark with mobile phase to get final concentrations of (120.0 µg/mL & 90.0 µg/mL of IBU and 4.0 µg/mL & 3.0 µg/mL of FMT) respectively. The peak area of standard laboratory mixture and sample laboratory mixture was compared to obtain the concentration. The amount of each drug estimated in laboratory mixture was calculated using following formula –

$$\% \text{ Estimation} = \frac{At}{As} \times \frac{Ds}{Dt} \times \frac{Ws}{Wt} \times 100$$

Where,

At = Area count for sample solution
As = Area count for standard solution
Ds = Dilution factor for standard
Dt = Dilution factor for sample
Ws = Weight of standard (mg)
Wt = Weight of sample (mg)

The results are shown in **Table 3.**

2.7 Analysis of Marketed Formulation

2.7.1 Preparation of Standard Solutions

Prepared as per the methodology adopted for laboratory mixtures

2.7.2 Preparation of Sample Solutions

Ten Tablets were weighed accurately and ground to fine powder. An accurately weighed quantity of Tablet powder equivalent to (800 mg of IBU & 26.6 mg of FMT) were transferred to 50.0 mL of volumetric flask and dissolved in sufficient amount of methanol. Then the volume was made up to the mark with methanol. The resultant solution was then filtered through whatman filter paper (no. 41). The filtered solution was then sonicated in ultrasonicator for 10.0 min. aliquot portions of 0.0075 mL was then transferred to the three separate 10.0 mL volumetric flask and then the volume was mad up to the mark with mobile phase to get final concentration of (120.0 µg/mL of IBU and 4.0 µg/mL of FMT) respectively.

Procedure: Equal volume (20.0 µL) of standard and sample solution was injected separately after equilibrium of stationary phase. The chromatograms were recorded and the response i.e. peak area of major peaks were measured. The amount of drug in a Tablet was calculated using following formula

$$\text{mg/Tablet} = \frac{AT1 \times WS1 \times Ds \times P1}{AS1 \times WT \times Dt} \times \text{Avg. wt}$$

Where,

AT1= Average area of IBU/FMT peaks in Test chromatogram

AS1 = Average area of IBU/FMT peaks in Standard chromatogram

Ds = Dilution factor for standard

Dt = Dilution factor for test

P1 = Potency of working standards of IBU/FMT of % w/w basis

Avg. wt = Average weight of 10 Tablets

Further calculate the amount of IBU/FMT present in % of Label claim using following formula

$$\% \text{ Label Claim} = \frac{\text{Assay (mg/Tablet)} \times 100}{\text{Label claim of IBU/FMT}}$$

The results are shown in **Table 4**, while chromatogram is shown in **Figure 4.**

2.8 Method Validation

1. Linearity

Preparation of Standard Solutions

IBU Standard Stock Solution (A): Accurately weighed quantity of IBU (30.0 mg) was transferred to 50.0 mL volumetric flask and dissolved in methanol. The volume was made up to mark with methanol to get final concentration of (600 µg/mL of IBU). The resultant solution was then sonicated for 10.0 min in ultrasonicator.

FMT Standard Stock Solution (B): Accurately weighed quantity of FMT (10.0 mg) was transferred to 50.0 mL volumetric flask and dissolved in methanol. The volume was made up to mark with methanol to get final concentration of (200 µg/mL of FMT). The resultant solution was then sonicated for 10.0 min in ultrasonicator.

Mixed Standard Solutions: aliquots portions of 0.5 to 2.5 mL from the standard stock solutions A and aliquots portions of 0.05 to 0.25 mL from the standard stock solution B were transferred to five 10.0 mL volumetric flasks and then volume was made up to the mark with mobile phase to get 5 different mixed standard solutions having concentrations of (30.0:1.0, 60.0:2.0, 90.0:3.0, 120.0:4.0, 150.0:5.0 µg/mL of IBU & FMT) respectively. The resultant solutions was then sonicated in ultrasonicator for 10.0 min

Procedure: Equal volumes (20.0 µL) of 5 mixed standard solutions were injected separately after equilibrium of stationary phase. The chromatograms were recorded and the response i.e. peak area of major peaks were measured. Then calibration curve (Peak area *vs* concentration) was plotted and it is shown in **Figure 5 & 6**. The observations are shown in **Table 5.**

2. Accuracy

Preparation of Standard Solutions: Standard solutions of (IBU & FMT) were prepared at the level of 80 %, 10.00 %, 120 %.

Preparation of Sample Solution: To the preanalysed sample solution (60 µg/mL of IBU & 2 µg/mL of FMT) a known amount of standard solutions of pure drugs (IBU & FMT) were added in different levels i.e. 80%, 10.00 %, 120%. The results of recovery studies shown in **Table 6**. The percent recovery was then calculated by using formula;

$$\% \text{ Recovery} = \frac{E_w - B}{C} \times 100$$

Where,

E_w = Total drug estimated (mg)

B= Amount of drug contributed by pre analyzed Tablet powder (mg)

C= Weight of pure drug added (mg)

3. Precision

3.1 Intra-Day Precision

It was determined by analyzing the 3 different solutions having concentration **(**90.0 µg/mL of IBU & 3.0 µg/mL of FMT) at 3 different times over a period of day.

3.2 Inter-Day Precision

It was determined by analyzing the 3 different solutions having concentration **(**90.0 µg/mL of IBU & 3.0 µg/mL of FMT) at 3 days over a period of week.

Procedure: Equal volumes (20.0 µL) of these solutions were injected separately after equilibrium of stationary phase. The chromatograms were recorded and the response i.e. peak areas, retention time of major peaks were measured. The results are shown in **Table 7.**

4. Robustness

Preparation of Sample Solution: Sample solution of marketed formulation was prepared as per the methodology adopted for marketed formulation analysis.

Procedure: Equal volume (20.0 µL) of sample solution was injected separately after equilibrium of stationary phase. Then deliberate variation in method parameters such as flow rate (<0.2mL/min), change in detection wavelength (<2 nm) was carried out. The chromatograms were recorded and the response i.e. peak area, retention time of the major peaks were measured. The results are shown in **Table 8 & 9** chromatograms are shown in **Figure 14 & 15.**

5. Ruggedness

Ruggedness of the method was studied by two different analysts using same operational and environmental conditions. A sample solutions prepared as per the methodology adopted in section 5.2 having concentration (120.0 µg/mL of IBU & 4.0 µg/mL of FMT) respectively, were analyzed and concentrations were determined. The results are shown in **Table 10 & 11.**

3. Results and Discussion

3.1 Optimization of Mobile Phase and Chromatographic Conditions

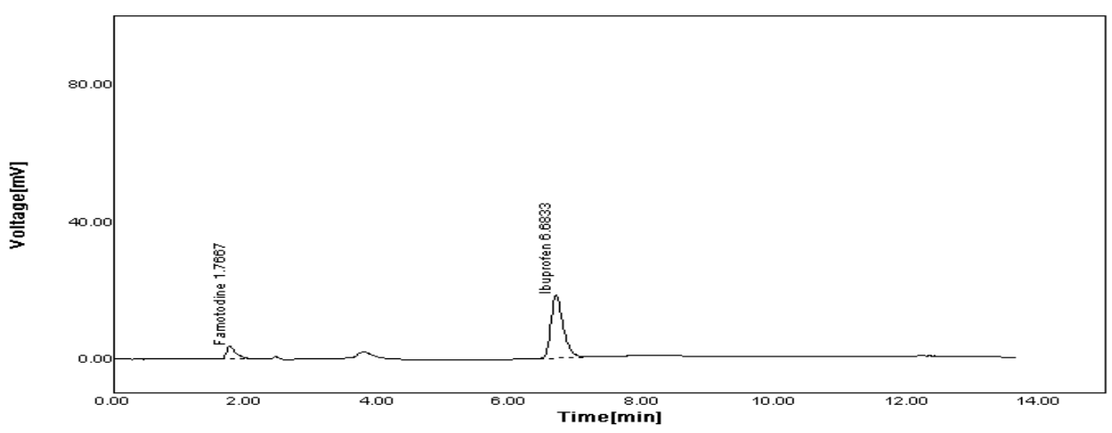

Figure 3: Optimized Chromatogram of IBU & FMT

Observation

Good resolution with minimized tailing also proper peak shape and system suitability was observed within the limits. Hence the above chromatographic parameters are finalized.

3.2 System Suitability Studies

Table 1 Result of System Suitability Studies for (IBU)

System Suitability Test (IBU)					
Sr. No	**Area Reproducibility**	**Retention Time**	**Tailing Factor**	**Resolution**	**Theoretical Plates**
1	3086.20	6.616	1.348	19.00	6851
2	3083.11	6.612	1.344	19.05	6852
3	3088.31	6.641	1.352	19.01	6822
4	3087.25	6.661	1.325	18.99	6872
5	3086.16	6.651	1.331	19.00	6378
Mean	3086.206	6.6362	1.3364	19.01	6755.2
%RSD	0.019	0.679	1.026	0.573	1.812
Limit	**NMT 2%**	**NMT 1%**	**< 2**	**> 2**	**> 2000**

Observation

All the parameters of system suitability are observed within the limits for IBU.

Table 2 Results of System Suitability Studies for (FMT)

System Suitability Test (FMT)					
Sr. No	**Area Reproducibility**	**Retention Time**	**Tailing Factor**	**Resolution**	**Theoretical plates**
1	82.4619	1.816	1.205	0	3605.9
2	83.4516	1.912	1.221	0	3604.1
3	82.4618	1.901	1.252	0	3606.1
4	83.4612	1.951	1.241	0	3605
5	82.4722	1.916	1.224	0	3609
Mean	82.4617	1.9192	1.2348	0	3606.02
%RSD	1.32	0.318	1.117	0	0.0594267
Limit	**NMT 2%**	**NMT 1%**	**< 2**	**> 2**	**> 2000**

Observation

All the parameters of system suitability are observed within the limits for FMT.

3.3 Analysis of Standard Laboratory Mixtures

Table 3 Results of Analysis of Standard Laboratory Mixtures

Average Wt.=796 mg								
Std weight(mg)		**Sample weight (mg)**	**Area of Std**		**Area of Sample**		**% Labeled Claim**	
IBU	**FMT**		**IBU**	**FMT**	**IBU**	**FMT**	**IBU**	**FMT**
120.0	4	794	5817.66	173.802	5953.49	124.33	99.83	99.92
		796			5958.68	128.36	99.87	99.64
		798			5956.82	125.16	99.85	98.94

3.4 Analysis of Marketed Formulation

Table 4 Results of Marketed Formulation Analysis

Sr. No.	**IBU**		**FMT**	
	Assay (mg)	**Assay (%)**	**Assay (mg)**	**Assay (%)**
1	120.85	99.83	4.47	99.91
2	119.24	99.83	4.49	99.92
3	119.02	99.80	4.46	99.91
Mean	119.70	99.82	4.47	99.913333
SD	0.1138	0.024119	0.3510	0.04520
% RSD	0.061	0.648763	0.35	0.417598

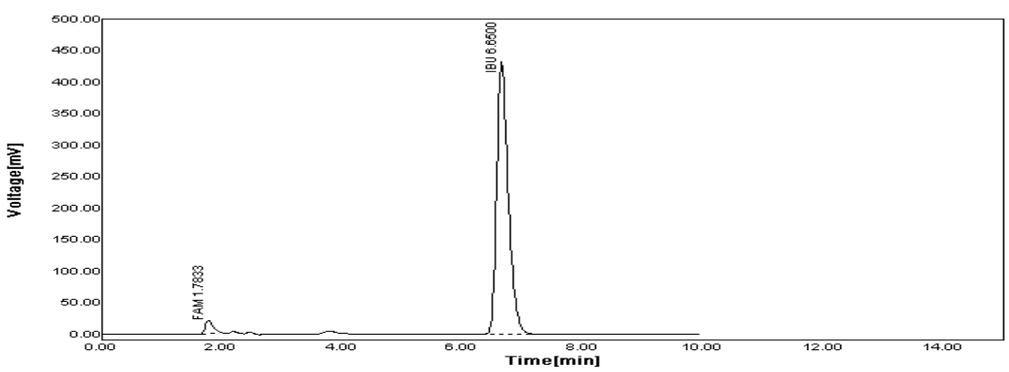

Figure 4: Chromatogram of Marketed Formulation

The proposed method was applied to the determination of IBU & FMT in marketed formulation the **mean % amount** found was **99.82 (IBU) & 99.91 (FMT)** with **% RSD** values is **NMT 2.0%** indicates the developed method was successfully applied for analysis of marketed formulation. All the results found are in good agreement with the label content of marketed formulation.

3.5 Method Validation

[1] Linearity

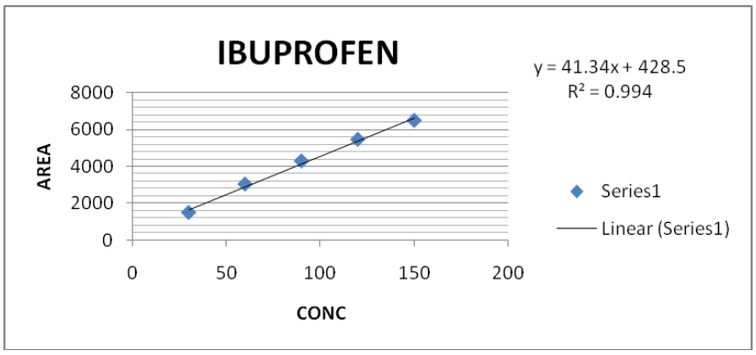

Figure 5: Calibration Curve of IBU

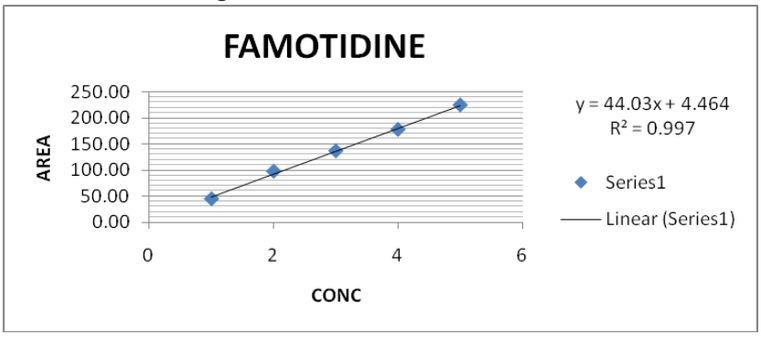

Figure 6: Calibration Curve of FMT

Table 5: Linearity Studies of IBU & FMT

Concentration (µg/mL)		Peak Area	
IBU	**FMT**	**IBU**	**FMT**
30	1	1493.371	44.87
60	2	3032.038	97.92
90	3	4285.055	137.02
120	4	5455.017	178.06
150	5	6484.243	224.97
	Mean	6149.9448	136.568
	SD	123.88	1.18
	%RSD	1.62	0.62

In both calibration curves the $\mathbf{r^2}$ value was found to be **0.997** which nearly equals to unity. The regression equation for IBU was **y = 41.34x + 428.5** while for FMT it was **y = 44.03x + 4.464**. It indicates the capability of developed method to estimate both the drugs over the desired concentration range.

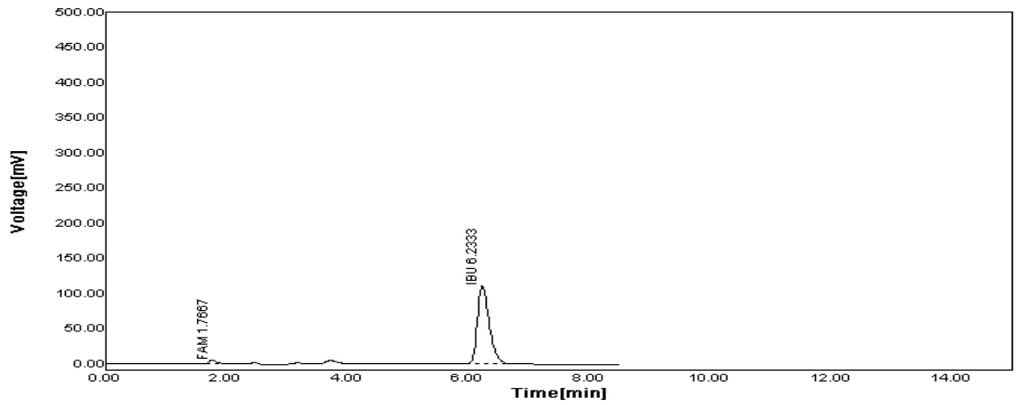

Figure 7 Linearity Chromatogram for (30 µg/mL of IBU & 1 µg/mL of FMT)

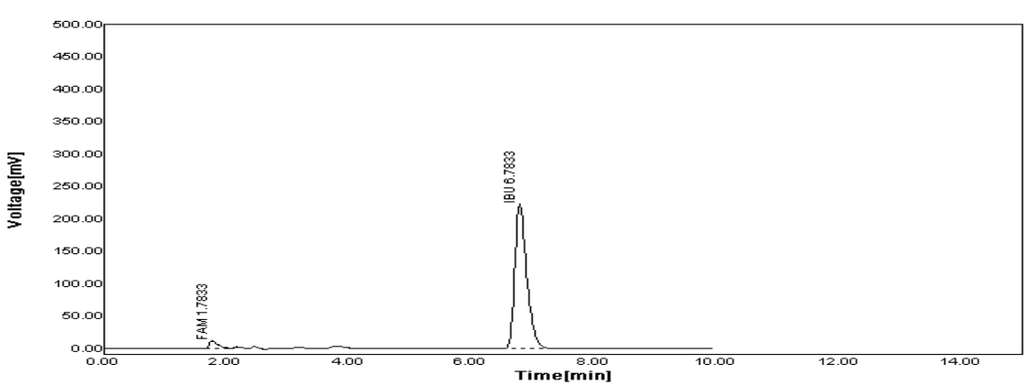

Figure 8 Linearity Chromatogram for (60 µg/mL of IBU & 2 µg/mL of FMT)

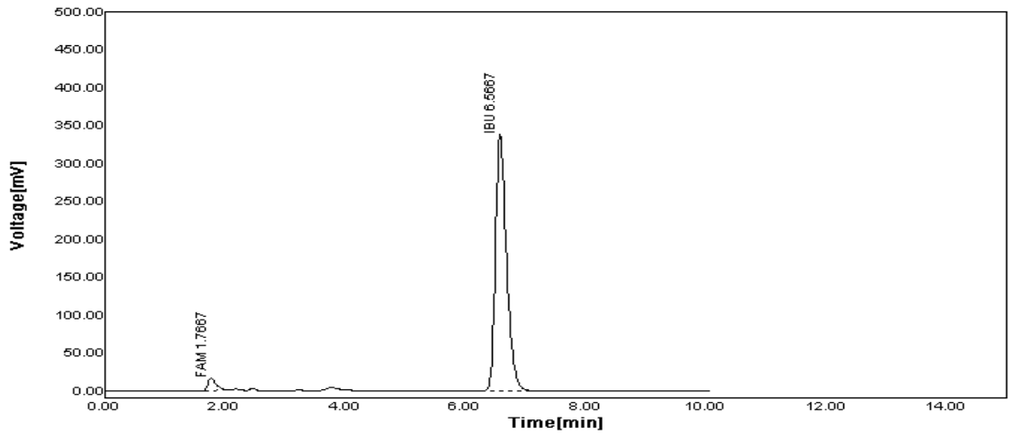

Figure 9 Linearity Chromatogram for (90 µg/mL of IBU & 3 µg/mL of FMT)

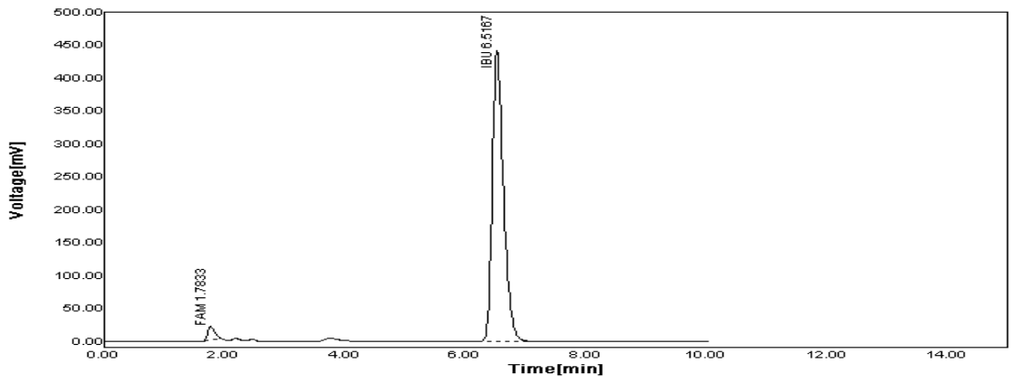

Figure 10 Linearity Chromatogram for (120 µg/mL of IBU & 4 µg/mL of FMT)

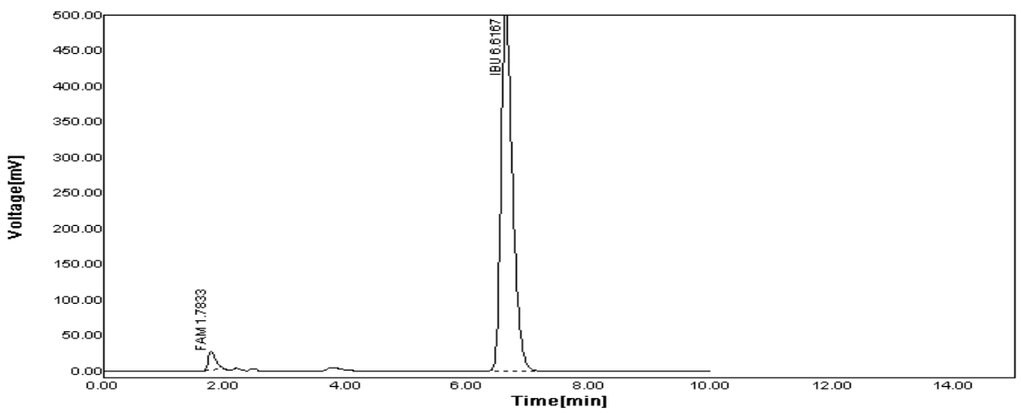

Figure 11 Linearity Chromatogram for (150 µg/mL of IBU & 5 µg/mL of FMT)

2. Accuracy

This is performed on the basis of recovery studies by standard addition method. Standard solutions of pure drugs (IBU & FMT) were added in different levels i.e. 80%, 100 %, 120%.

Table 6: Results of Recovery Studies

Level of % Recovery	Amount present (mg/tab)		Amount taken (µg/ml)		Amount of Std. Drug Added(µg/ml)		Total Amount Recovered (µg/ml)		%Recovery	
	IBU	FMT	IBU	FMT	IBU	FMT	IBU	FMT	IBU	FMT
80%	800	27	60	2	48	1.6	799.11	27.09	98.77	98.63
	800	27	60	2	48	1.6	798.23	27.16	98.77	98.82
	800	27	60	2	48	1.6	800.12	26.87	98.56	98.56
100%	800	27	60	2	60	2	799.63	26.23	99.09	98.82
	800	27	60	2	60	2	800.09	27.36	99.54	99.15
	800	27	60	2	60	2	800.87	27.89	99.63	98.37
120%	800	27	60	2	72	2.4	802.15	26.23	97.84	98.91
	800	27	60	2	72	2.4	799.87	27.32	97.74	99.03
	800	27	60	2	72	2.4	798.99	26.08	97.81	98.98

The **mean % recovery** with **% RSD** for IBU was found to be **98.63, 0.195** and for FMT it was **98.54, 0.147**. The % RSD not more than **2** which fully agrees with system suitability hence the developed RP-HPLC method was found to be sufficiently **accurate.**

3. Precision

Table 7: Results of Precision Studies

Sr. No.	IBU		FMT	
	Peak Area Sample	%Assay	Peak Area Sample	%Assay
1	4406.381	98.41	138.66	99.99
2	4404.452	98.39	133.23	99.98
3	4402.541	98.34	132.98	99.82
4	4401.214	98.33	133.45	99.97
5	4403.675	98.37	132.89	99.86
6	4405.012	98.40	133.21	99.92
	Mean	98.37333333	**Mean**	99.923333
	SD	0.32659863	**SD**	0.188984
	%RSD	0.32865822	**%RSD**	0.1859337

Precision was determined by peak area. Reproducibility in retention time and peak area is observed in precision studies with a **%RSD (NMT than 2%)** for both retention time and peak area which is in agreement with system suitability. Therefore, the proposed HPLC method for the determination of IBU and FMT was found to be sufficiently **precise.**

4. Robustness

Table 8: Robustness studies of IBU

Condition	Mean	± SD n=3	%RSD
Change in flow rate (± 0.1 ml)	7624.83	123.88	1.62
Change in detection wavelength (± 2 nm)	7268.08	80.75	1.11

Table 9: Robustness studies of FMT

Condition	Mean	± SD n=3	%RSD
Change in flow rate (± 0.1 ml)	259.79	1.18	0.62
Change in detection wavelength (± 2 nm)	263.03	1.52	0.58

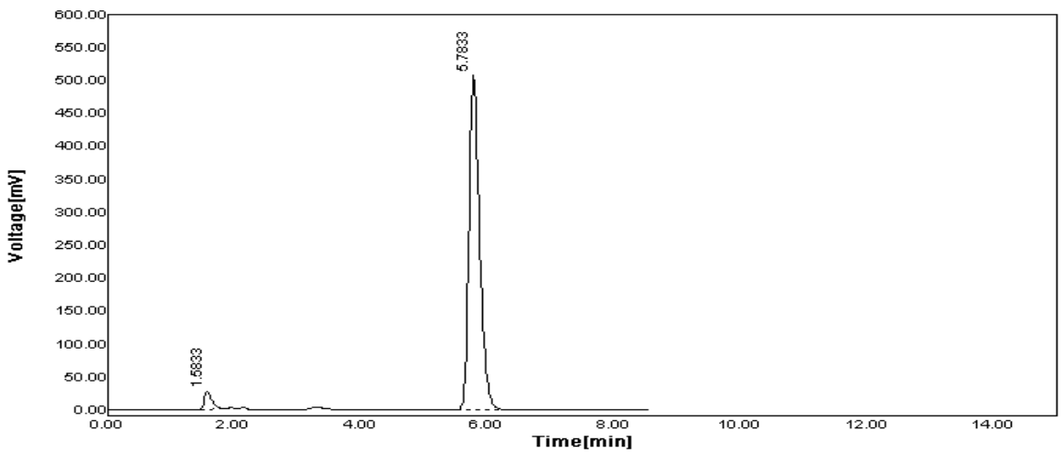

Figure 12 Chromatogram of Robustness (<0.1mL/min)

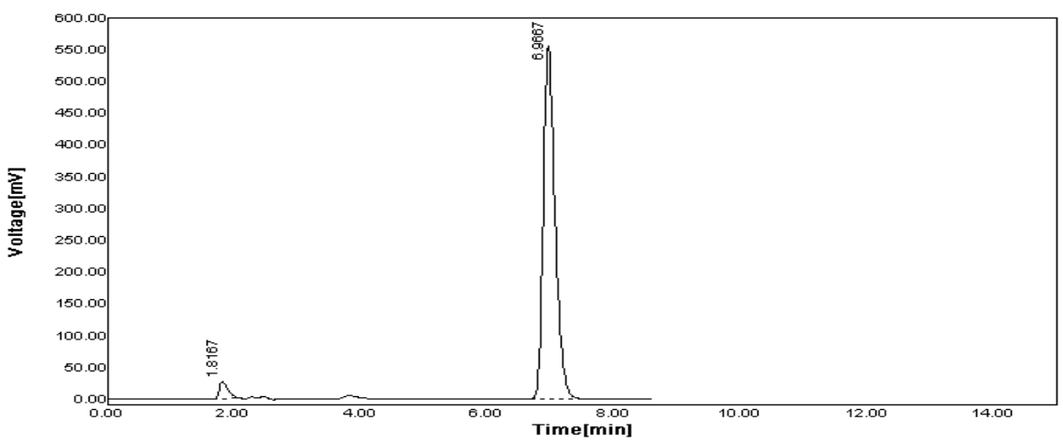

Figure 13: Chromatogram of Robustness (<2.0 nm)

The results of assay of test solution was not get affected by varying the conditions. They are fully agree with the results obtained under original conditions. The **% RSD** for **(Retention time, Peak area and % Amount Found)** was not more than **2%** for both (IBU & FMT) which was in agreement with system suitability. Hence the proposed HPLC method for the determination of IBU and FMT in a tablet was found to be **robust.**

5. Ruggedness

Table 10: Results of ruggedness study for IBU

Sr. No	Observations	% Drug estimation		
		Intra-day	Inter-day	Different Analyst
1	I	99.612	98.822	98.932
2	II	99.51	99.447	99.530
3	III	99.512	99.324	99.676
Mean		99.547	99.264	99.573
±S.D.		0.0550	0.309	0.493
%R.S.D.		0.0553	0.313	0.495

Table 11: Results of ruggedness study for FMT

Sr. No	Observations	% Drug estimation		
		Intra-day	Inter-day	Different Analyst
1	I	98.712	98.824	98.876
2	II	99.622	99.657	99.624
3	III	99.543	99.722	99.922
Mean		99.393	99.397	99.472
±S.D.		0.578	0.581	0.474
%R.S.D.		0.590	0.585	0.476

Ruggedness was determined as Intra-day, Inter-day & Different Analyst. % amount of drugs were found with **% RSD (NMT than 2%)** which was in agreement with system suitability. Therefore, the proposed HPLC method for the determination of IBU and FMT in a tablet was found to be sufficiently **rugged.**

4. Conclusion

The developed RP-HPLC method was found to be linear over wider concentration range. Therefore the developed RP-HPLC method can be applied for routine quantitative and qualitative analysis of IBU and FMT in bulk and pharmaceutical formulations like tablets. This method was also used to check quality of product after different storage condition and when stress degradation is carried out. The developed RP-HPLC method was validated as per the ICH guidelines. The developed RP-HPLC method has a stability indicating nature hence the proposed method could be employed for the stability studies on pharmaceutical preparations within pharmaceutical industry.

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