DEVELOPMENT OF TRI-LAYERED TABLET OF INCOMPATIBLE DRUGS USING PLATFORM TECHNOLOGY

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ABSTRACT

The aim of present investigation is to design an immediate release dosage form of Ibuprofen and Famotidine in a single tablet formulation indicated for the relief of signs and symptoms of rheumatoid arthritis (RA) and osteoarthritis (OA) and to decrease the risk of developing upper gastrointestinal (UGI) Ulcers. An attempt was made to prepare a tri-layered tablet as Ibuprofen and Famotidine are incompatible with each other. Famotidine is a highly unstable molecule which in combination with Ibuprofen shows degradation in single unit dosage form. The in vitro release layer of Famotidine was prepared using lactose anhydrous as a diluent, pregelatinized starch and starch paste as a binder cum disintegrant in the formulation. The disintegration time of the single unit was found to be around 6 Mins with time to disintegrate the single dosage unit to disintegrate in two halves was around 75 Secs. The In-vitro release of Ibuprofen & Famotidine is rapid from tablet and showed highest drug release 99% within 30 Minutes & 98% in 30 Minutes respectively. Final formulation is shown with accelerated stability study. Intermediate barrier layer as platform technology to separate incompatible drugs was optimised using lactose monohydrate as a diluent and croscarmellose sodium as a disintegrant. The time to disintegrate tablet into two halves for final formulation was found 148 Sec.

Key words: Incompatible drugs, tri-layered tablet, platform technology, single unit dosage.

INTRODUCTION

Today, the use of multi-layered tablets has been increased as it provides various salient features overcoming problems associated with conventional dosage form. Multi-layered tablet is more suitable for gradual release of two active ingredients in combination. Multi-layered tablet technology helps in separating the two incompatible substances using a separating layer or an inert layer between layers of two different drugs.[1,2]

In the current research Famotidine is a highly unstable molecule which in combination with Ibuprofen shows degradation. Ibuprofen is acidic in nature while Famotidine is basic in nature. Hence, combination of Ibuprofen and Famotidine tends to acid base reaction resulting in degradation of Famotidine.[3,4] For such combination therapy with chemical incompatibility, multilayered dosage form is advantageous in preparing a stable formulation.[5,6]

Introduction of an intermediate layer between drug layers will result into zero direct contact of the drugs and will help us to achieve a stable formulation. Moreover, Ibuprofen and Famotidine is orally administered separately, three times a day. Patient compliance is more problematic with a regimen that requires administration of two separate dosage form. A once a day formulation is required to meet patient compliance. Hence, the single unit formulation is required for combination therapy of Ibuprofen and Famotidine.[7-9]

Ibuprofen is widely and most commonly prescribed NSAIDs all over the world. It is prescribed for mild to moderate pain management and inflammation. It is comparatively safe than other NSAIDs. While generally regarded as safe, Ibuprofen and other NSAIDs can cause gastritis, dyspepsia, and gastric and duodenal ulceration. The risk of developing gastric or duodenal ulceration can be reduced by co-therapy with the drug Famotidine. Famotidine blocks the action of the histamine type-II (H_2) receptor, leading to a reduction of acid secretion in the stomach. Although NSAID plus Famotidine co-therapy reduces risk of developing gastric or duodenal ulceration, such therapies are not widely used. One explanation for this observation is that patient compliance is more problematic with a regimen that requires administration of two separate dosage forms.[10-14]

The current research is an attempt to design immediate release layer of Famotidine and Ibuprofen in a single tablet formulation. Bilayer tablets have only one inter phase between two drug layers so incompatibility between two drugs may occur at this point. A feasibility trail of Bilayered tablet has been prepared and stability study has been evaluated. [15] Trilayer tablets can solve this kind of interphase incompatibility problem between two drugs. Introduction of an intermediate or immediate release layer between drug layers will result into no direct contact of the drugs and will help us to achieve a stable formulation. Moreover, Famotidine and Ibuprofen is orally administered separately, two times a day. Patient compliance is more problematic with a regimen that requires administration of two separate dosage form. A need of once a day formulation is required to meet patient compliance.[16] Hence, the single unit dosage formulation is required for combination therapy of Famotidine and Ibuprofen. Intermediate layer will act as a barrier layer which will separate both the drugs to come in direct contact and hence will help us to overcome the chemical incompatibility.

MATERIALS AND METHOD:

MATERIALS

Famotidine was received as a gift sample from Granules India Ltd., India. Ibuprofen was received as a gift sample from Lee Pharma Ltd., India. Microcrystalline Cellulose (Avicel PH 102), FMC Biopolymer, India. Lactose Monohydrate (Pharmatose 200M), DFE Pharma, India. Croscarmellose Sodium (Ac-Di-Sol), FMC Biopolymer, India, Colloidal Silicon Dioxide (Aerosil 200), Evonik, India. Magnesium Stearate (Ligamed MF-2-V), Peter Greven, India.FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, Roha, India. All other excipients and chemicals used were of pharmaceuticals grade and analytical grade respectively.

METHODS

Preformulation study of Drugs:

Preformulation studies were carried out to investigate physicochemical properties of drug substance alone and in combination with other drug as well as excipients.

Identification of drugs by Melting Point:

Melting point was determined by taking small amount of pure drug in a different capillary tube closed at one end. The capillary tube was placed in an electrically operated digital melting point apparatus and the temperature at which the drug melts was recorded.

Identification of Drugs and Compatibility Study by HPLC method

Identification of pure drugs, their mixture with excipients as well as mixture of both drugs was taken and spectrum was recorded. The retention time of the principal peak obtained in sample solution is concordant with that of the standard solution, as obtained in the assay. Samples were prepared by mixing individual drugs, both drugs together and drugs along with excipients uniformly. Scanned graph of pure drug was compared with standard range.

Identification of Drugs and Compatibility Study by DSC Analysis

DSC of pure drugs, their mixture with excipients as well as mixture of both drugs was taken and spectrum was recorded. Samples were prepared by mixing individual drugs, both drugs together and drugs along with excipients uniformly. Sample was scanned in the region of 30°C to 200°C. Heat from 30°C to 200°C at 20°C/min. Scanned graph of pure drug was compared with standard range.

TRI-LAYERED FORMULATION OF IBUPROFEN AND FAMOTIDINE

Immediate release part of Famotidine and Ibuprofen were prepared by wet granulation method. Trials were executed to optimize the formula for intermediate layer to effectively separate the Ibuprofen part and Famotidine part in vivo. Direct compression excipients were selected to get desire flow property of lubricated blend for intermediate layer. Different concentration of Povidone K30 as a binder and Croscarmellose Sodium as a disintegrant is

used to optimize the formula. The objective was to prepare a robust formulation to separate both layer without hampering the in-vitro dissolution and flow properties of both the layer.

A prototype formulation is prepared using prior experience of formulation of immediate release formulation. Intermediate layer was prepared using Lactose monohydrate as Diluent, Povidone as a binder, Croscarmellose sodium as a Disintegrant and Magnesium Stearate as a Lubricant. Lubricated blend of Ibuprofen Part, Intermediate layer and Famotidine part were filled in the die cavity and compressed into Tablet. (Table-1)

RESULTS AND DISCUSSION

Preformulation study of Drugs:

Melting point of Famotidine and Ibuprofen was found to be 223 – 226°C and 148 - 150°C respectively. Both values were same as reported in literature.

The HPLC chromatogram of both drugs showed peaks corresponding with standard solution as the compatibility study data of the powdered drugs and their mixture with excipients showed no interaction between drugs-excipients as well as mixture of both drugs showed clear interaction between both drugs as shown in Figure1-5. Hence, it was concluded that, the studied excipients and drugs were compatible whereas drugs combination is not compatible.

Drug compatibility study was performed by assay & RS method using probable excipients of the formulation. Ratio of drug to excipients was maintained as per their functional role during the study. Related substance data as shown in

Table-2 indicates that Famotidine is incompatible with Ibuprofen but is compatible with all the selected excipients in the study.

Compatibility study was also performed by DSC analysis method. Ibuprofen thermal peak was observed in range of 79 ℃ - 81 ℃ and for Famotidine it was observed at 168.41 ℃ (Peak I) and 174.54 ℃ (Peak II). As shown in **Error! Reference source not found.**6,**Error! Reference source not found.**7 &**Error! Reference source not found.**8, the peak of Ibuprofen was observed intact in all condition but peak of Famotidine was non-intact when analysed in combination with Ibuprofen. Hence, we have concluded that DSC method is not feasible method for compatibility study of Famotidine.

Flow property parameters of powder blends and post compression parameters of tablet showed satisfactory results and were within standard limit.

Dissolution study

Increasing the concentration of disintigrants in the separating layer improves the disintegration time and separate the tablet immediately without affecting the dissolution of both the layer. As showed in Figure&Figure-10, Tablet shows similar dissolution pattern with the marketed formulation. Layers are separated by an inert layer, hence degradation of Famotidine is negligible and the product is stable.

Stability Study

Trilayer tablet was placed in the modified stability chamber for accelerated stability study at 40°C ± 2°C and 75± 5 % RH for 3 month (Table-3). After a period of one month, the samples were observed for any change in physical appearance. Tablets were analysed for percentage drug content and in vitro drug release studies. It was observed that surface was devoid of any change in colour or appearance of any kind of odour in it. Results also revealed that, there were no significant changes in percentage drug content or In vitro drug release.

CONCLUSION:

- Bilayer tablet on stability study fails in 2 Month – 40°C/75%RH, hence there is a need of intermediate or barrier layer to avoid direct contact between incompatible drugs. Intermediate barrier layer as platform technology was used to prepare tri-layered tablet. Increasing the concentration of disintegrant in the separating layer improves the disintegration time and separate the tablet immediately without affecting the dissolution of both the layer. Layers are separated by an inert layer, hence degradation of Famotidine is negligible and the product is stable. It was also observed chemical incompatibility between two drugs in a single tablet can be prevented without hampering dissolution profile of both immediate release part of Ibuprofen and Famotidine.

Conflict of Interest: The authors declare that they have no competing interest

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Table -1: Formulation Trials with intermediate layer or separating layer

Ingredients	Rationale	IF1		IF2	
		%w/w	mg/tab	%w/w	mg/tab
Ibuprofen Layer					
Ibuprofen	Active Ingredient	69.57	800.0	69.57	800.0
Microcrystalline Cellulose (Avicel PH 101)	Diluent	5.09	58.5	5.09	58.5
Croscarmellose Sodium	Disintegrant	2.09	24.0	2.09	24.0
Starch Paste (Maize Starch)	Binder	4.26	49.0	4.26	49.0
Purified Water	Granulating Solvent	--	q.s	--	q.s
Croscarmellose Sodium	Disintegrant	2.09	24.0	2.09	24.0
Colloidal Silicon Dioxide	Glidant	0.85	9.8	0.85	9.8
Magnesium Stearate	Lubricant	1.28	14.7	1.28	14.7
Ibuprofen Part (mg)		**85.22**	**980.0**	**85.22**	**980.0**
Intermediate Layer / Separating Layer					
Lactose Monohydrate (Pharmatose 200M)	Diluent	3.85	44.3	3.63	41.8
Povidone K30	Binder	0.22	2.5	0.22	2.5
Croscarmellose Sodium	Disintegrant	0.22	2.5	0.43	5.0
Magnesium Stearate	Lubricant	0.04	0.5	0.04	0.5
Brilliant blue FCF aluminum lake (E133)	Colouring Agent	0.02	0.2	0.02	0.2
Intermediate Part (mg)		**4.35**	**50.0**	**4.35**	**50.0**
Famotidine Layer					
Famotidine	Active Ingredient	2.31	26.6	2.31	26.6
Lactose anhydrous	Diluent	6.45	74.2	6.45	74.2
Pregelatinized Starch	Disintegrant	1.04	12.0	1.04	12.0
Starch Paste (Maize Starch)	Binder	0.42	4.8	0.42	4.8
Purified Water	Granulating Solvent	--	q.s	--	q.s
Colloidal Silicon Dioxide	Glidant	0.10	1.2	0.10	1.2

Ingredients	Rationale	IF1		IF2	
		%w/w	mg/tab	%w/w	mg/tab
Magnesium Stearate	Lubricant	0.10	1.2	0.10	1.2
Famotidine Part (mg)		**10.43**	**120.0**	**10.43**	**120.0**
Total Tablet Weight (mg)		**100.00**	**1150.0**	**100.00**	**1150.0**

Table-2: Drug Excipients Compatibility Results with Ibuprofen API by Assay & RS Method

Ingredients*	Ratio	Initial				4 Weeks (Close) 40°C/75%RH			
		I-C	Any Ind.	Total Imp.	%Assay of API	I-C	Any Ind.	Total Imp.	%Assay of API
	Limits	NMT 0.3%	NMT 0.1%	NMT 0.8%	95% - 105%	NMT 0.3%	NMT 0.1%	NMT 0.8%	95% - 105%
API	NA	0.02	0.01	0.15	100.2	0.18	0.03	0.28	99.8
API + Ibuprofen	1:1	0.11	0.05	0.22	99.1	1.77	0.57	3.89	94.7
API + Avicel PH 101	1:3	0.07	0.01	0.11	100.6	0.19	0.03	0.34	99.2
API + Avicel PH 102	1:3	0.06	0.03	0.12	98.7	0.18	0.05	0.36	99.4
API +Avicel PH 112	1:3	0.08	0.04	0.14	99.4	0.22	0.05	0.39	98.7
API + Pharmatose 200M	1:3	0.05	0.01	0.09	99.1	0.16	0.03	0.24	99.2
API + Hypromellose E3	1:2	0.03	0.01	0.06	99.7	0.17	0.04	0.31	99.6
API + Hypromellose E5	1:2	0.02	0.01	0.06	99.3	0.19	0.03	0.34	99.4
API + Ac-Di-Sol	1:0.5	0.03	0.02	0.07	99.8	0.22	0.05	0.42	99.6
API + Sodium bicarbonate	1:0.5	0.01	0.01	0.05	99.7	0.17	0.03	0.37	99.9
API + Magnesium Stearate	1:0.25	0.02	0.02	0.03	99.9	0.19	0.05	0.42	98.7
API + Talc	1:0.25	0.02	0.03	0.07	100.4	0.17	0.07	0.39	99.5
API + Aerosil 200	1:0.25	0.03	0.01	0.08	98.9	0.18	0.08	0.43	99.4
API + HPMC K4M	1:0.5	0.04	0.03	0.09	99.4	0.21	0.06	0.37	99.3
API + HPMC K15M	1:0.5	0.05	0.01	0.10	99.3	0.23	0.04	0.39	99.1
API + HPMC K100M	1:0.5	0.04	0.02	0.09	99.4	0.20	0.07	0.42	99.6

*API = Famotidine

I-C = Impurity C (Famotidine Sulfamoyl Propanamide)

Table-3:Stability Data

Stability Condition	40°C/75%RH	**Pack Details**		Blister pack		
Batch No.	IF2					
Test	**Specification**	**Initial**	**1M**	**2 M**	**3 M**	**6 M**
Description	Oval, Biconvex, uncoated tablet, Plain on both the side.	Complies				
Average Weight of 10 Tablets	1150.0 mg ± 3%	1143.7	1152.4	1151.4	1150.7	1157.4
Ibuprofen Part						
Dissolution	NLT 80% (Q) of the labeled amount is dissolved in 30 Mins	98%	100%	99%	98%	99%
Assay	90.0% to 110%	99.5%	99.7%	98.9%	100.2%	99.8%
DSC Curve	Single peak between79°C – 81°C	Complies				
Famotidine Part						
Dissolution	NLT 80% (Q) of the labeled amount is dissolved in 30 Mins	95%	97%	96%	99%	98%
Assay	90.0% to 110%	99.9%	100.4%	98.7%	98.9%	98.2
Related Substances	**Famotidine Sulfoxide:** NMT 0.3%	0.04%	0.09%	0.14%	0.16%	0.21%
	Impurity C: NMT 0.3%	0.02%	0.03%	0.02%	0.05%	0.08%
	Impurity D: NMT 0.3%	0.01%	0.03%	0.02%	0.02%	0.05%
	Impurity F: NMT 0.3%	ND	ND	0.02%	0.05%	0.09%
	Any Unknown Impurity: NMT 0.2%	0.07%	0.09%	0.08%	0.11%	0.15%
	Total Impurities: NMT 1.5%	0.22%	0.41%	0.52%	0.61%	0.95%

*US = Under Stability

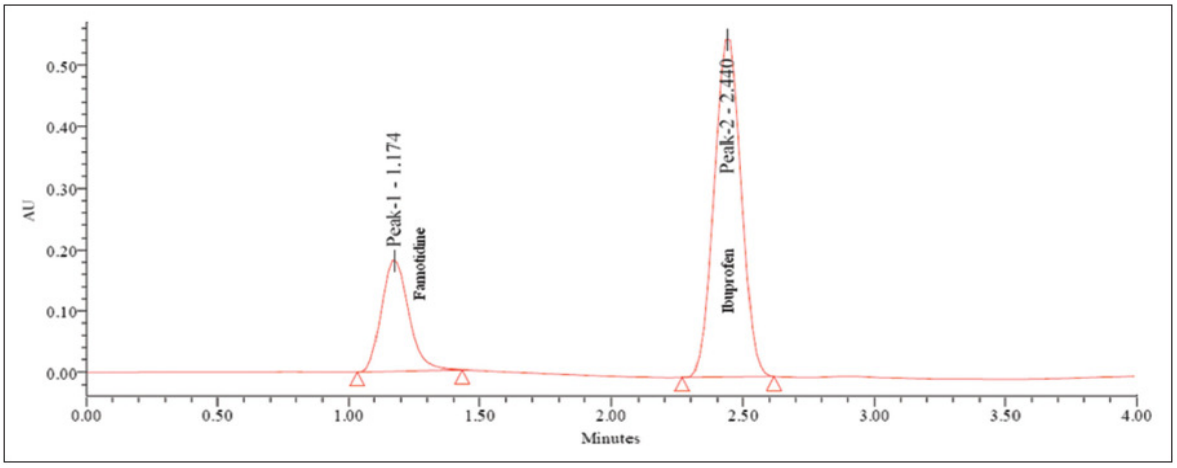

Figure -1: Chromatogram of standard solution of Ibuprofen and Famotidine

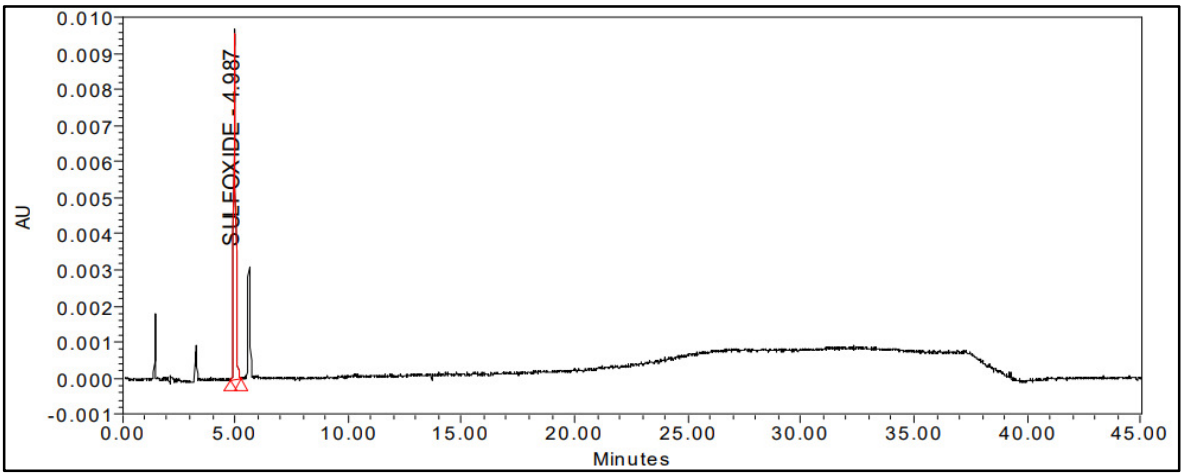

Figure-2: Chromatogram of Famotidine Sulfoxide Impurity

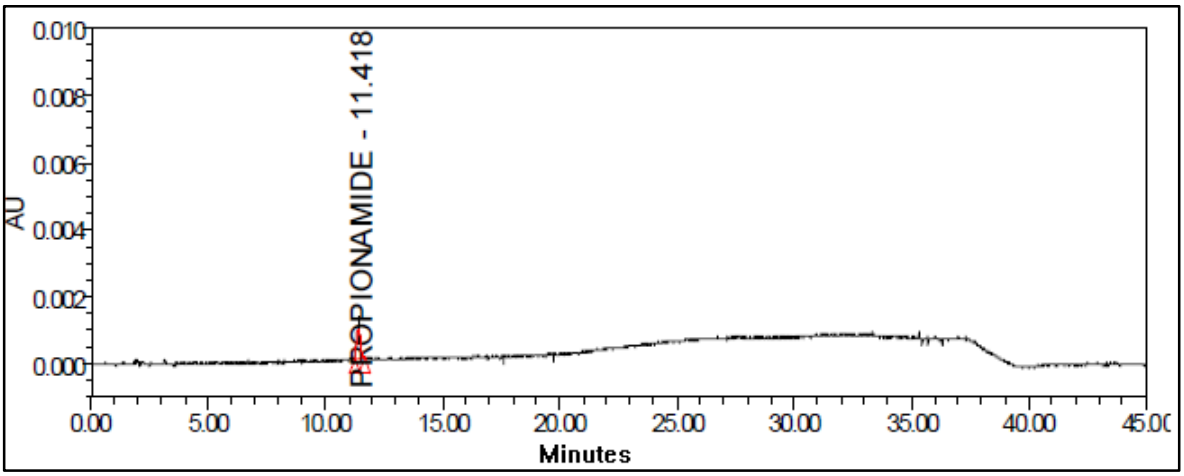

Figure-3: Chromatogram of Famotidine Propionamide Impurity

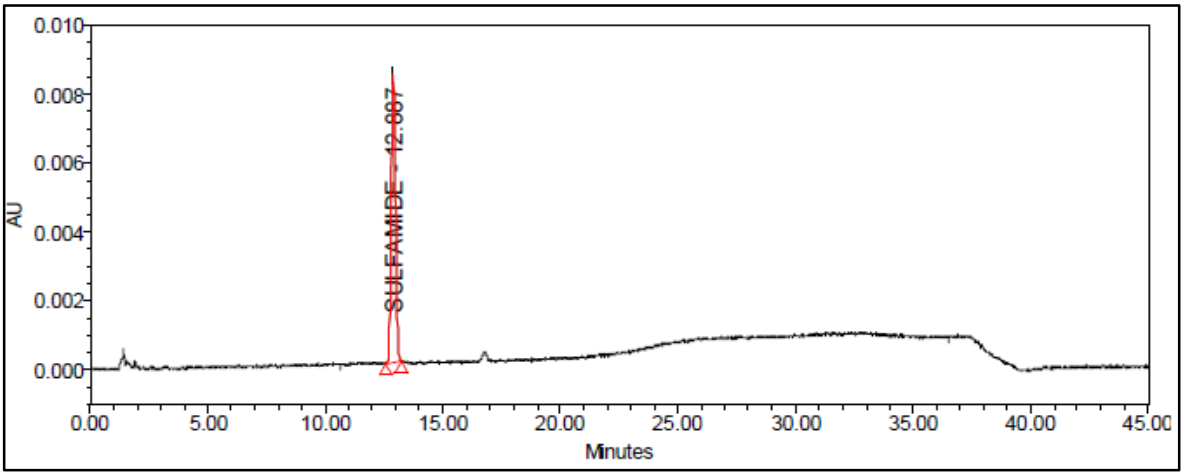

Figure-4: Chromatogram of Famotidine Sulfamide Impurity

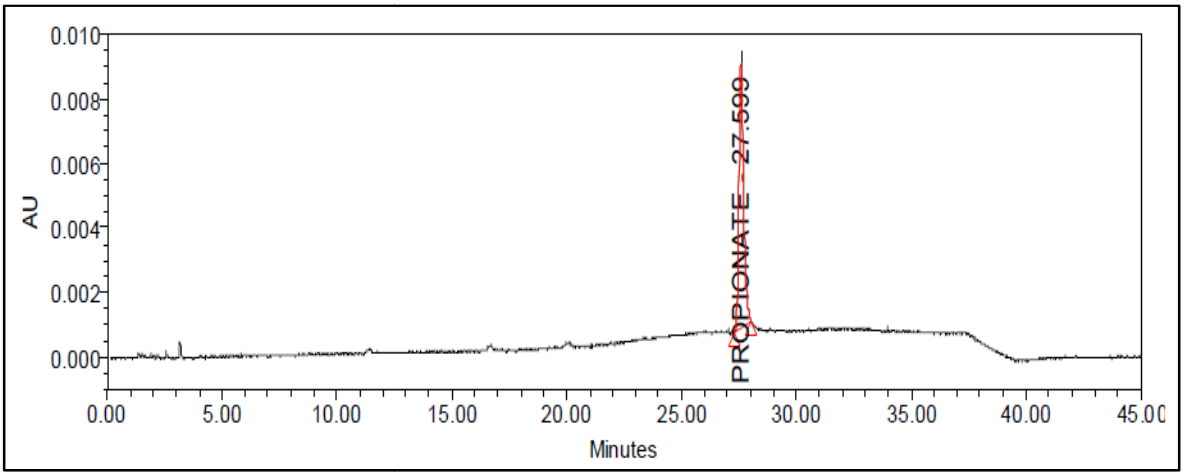

Figure-5: Chromatogram of Famotidine Propionate Impurity

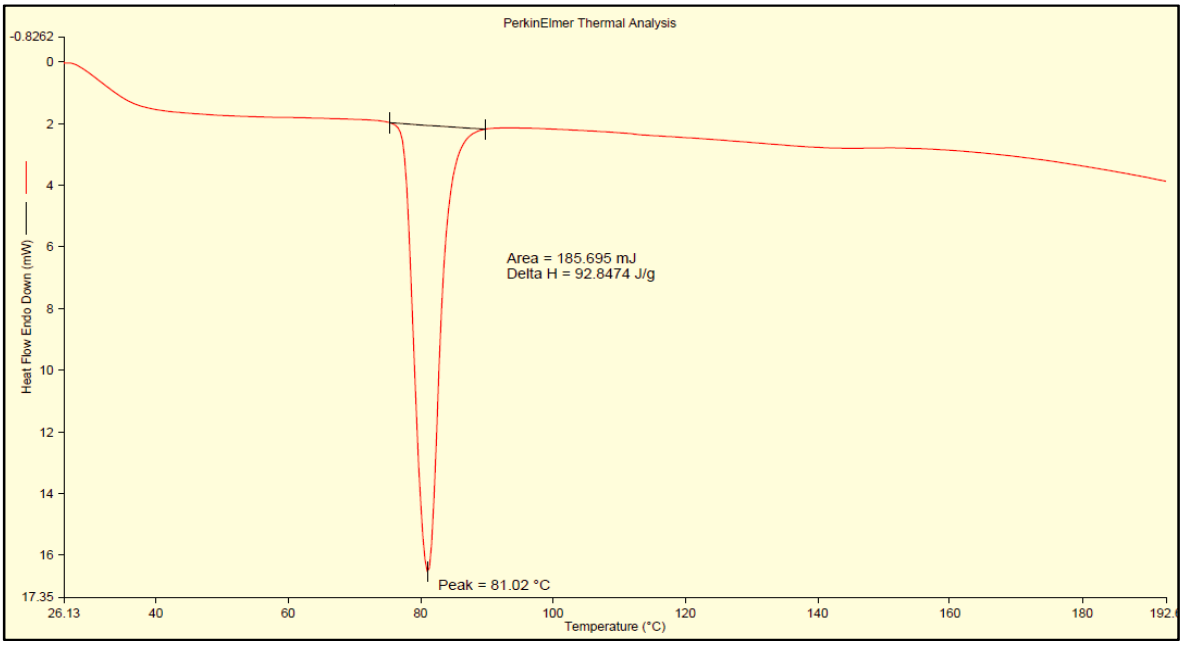

Figure-6: DSC Curve for Ibuprofen API

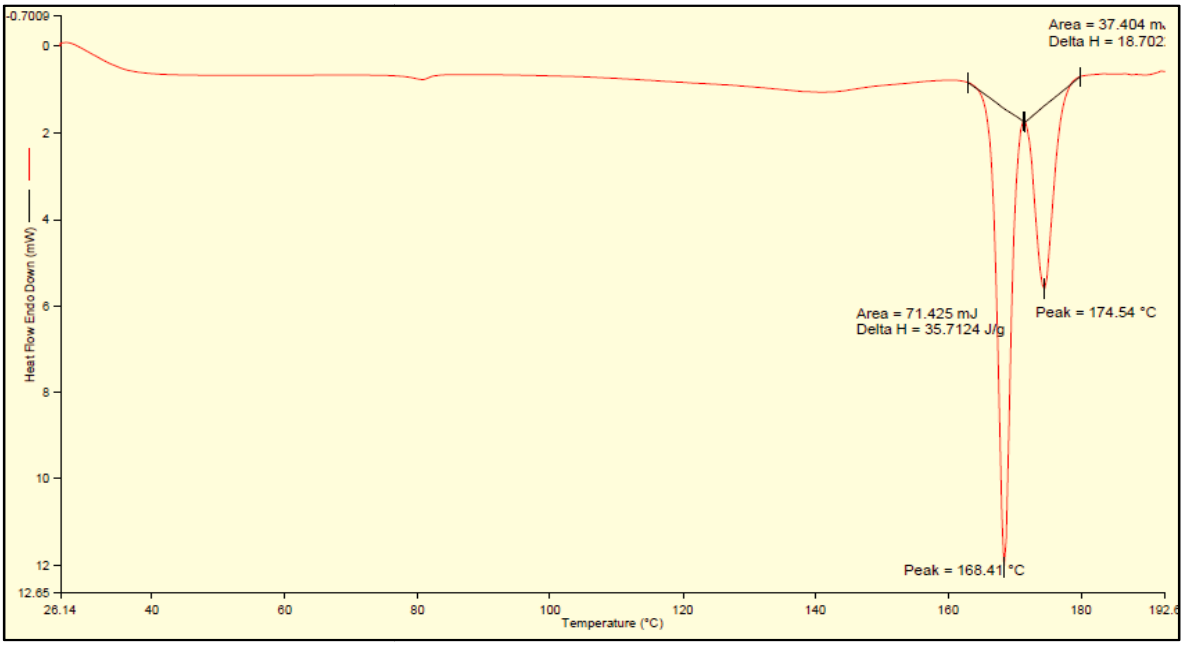

Figure -7: DSC Curve for Famotidine API

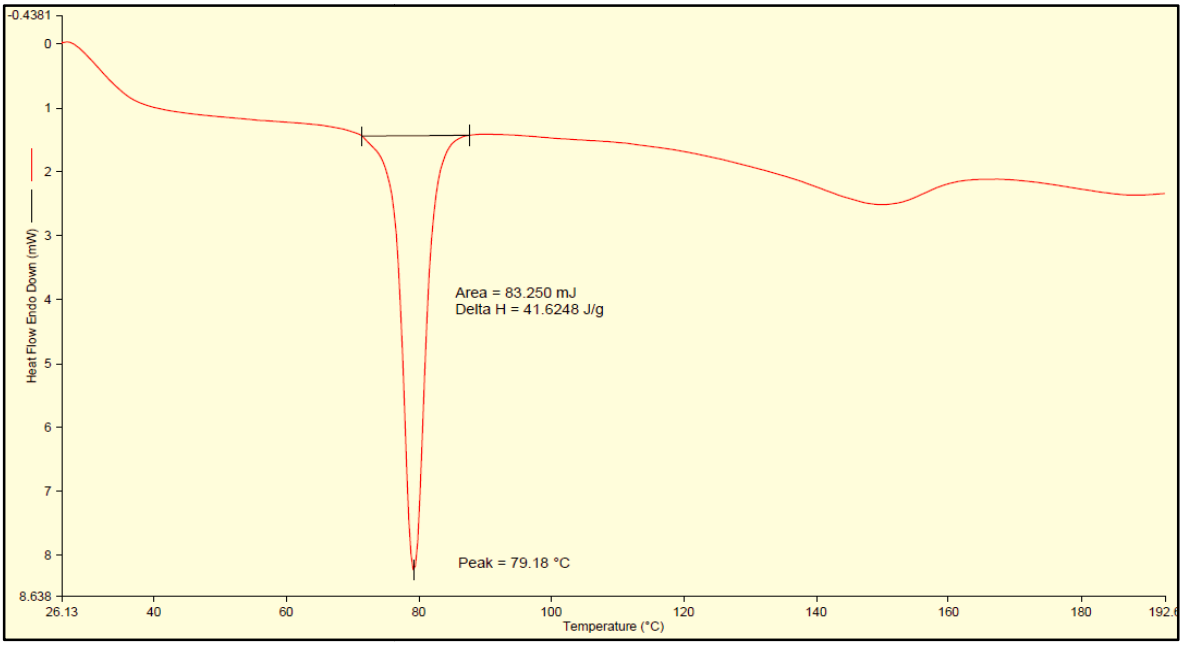

Figure-8: DSC Curve for mixture of Ibuprofen API and Famotidine API

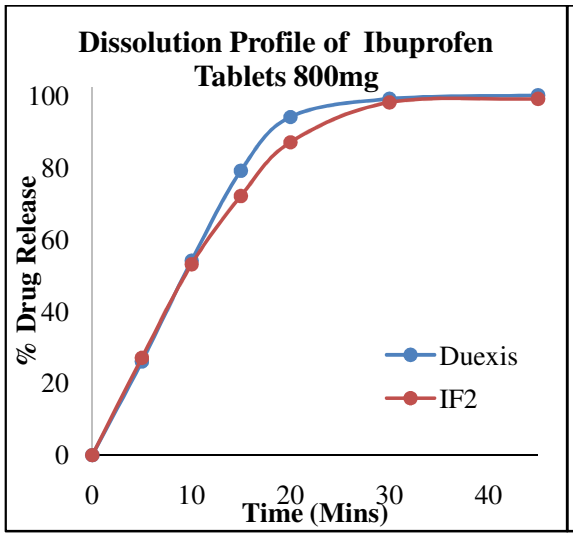

Figure-9:Dissolution Profile of Ibuprofen Tablets 800 mg in trilayer tablet

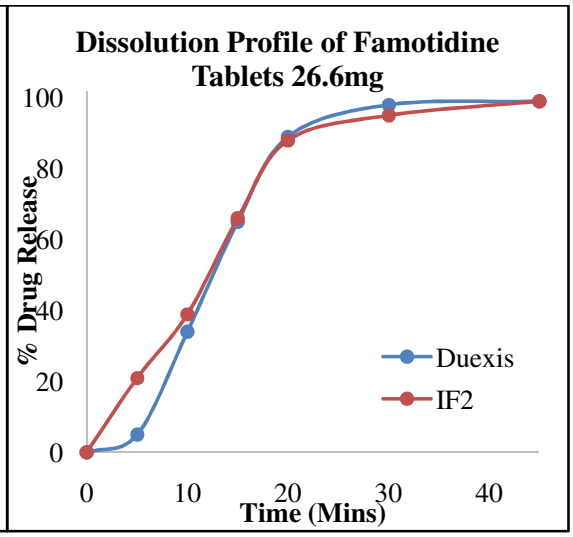

Figure-10:Dissolution Profile of Famotidine Tablets 26.6mg in trilayer tablet