ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.pharmascope.org/ijrps

Method Development and Validation of Famotidine Oral Suspension by RP-HPLC Method

Prakash chand T, Elancheziyan K, Yamini R, Aysha Jadeera K A, Vijey Aanandhi M, Binoy Varghese Cheriyan*

Department of Pharmaceutical Chemistry and Analysis, School of pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS) Pallavaram, Chennai-600117, Tamil Nadu, India

Article History:

Received on: 05 Jun 2020
Revised on: 13 Jul 2020
Accepted on: 22 Jul 2020

Keywords:

Famotidine,
Method development,
Method validation,
Reverse Phase HPLC

ABSTRACT

For perseverance of Famotidine a simple, fast and selective procedure were developed in drug substance and its pharmaceutical preparations. In the proposed project, a successful attempt has been made to develop a simple, accurate, economic and rapid method for the estimation and to validate the method. As a result, a simple, economical, precise and accurate method was developed and validated by Reverse Phase High Performance Liquid Chromatography (RP-HPLC). The main objective for that is to improve the conditions and parameters, which should be followed in the development and validation. The developed Reverse phase HPLC technique was done utilizing filtered and degassed pH-6.0 Acetate buffer as a Mobile phase-A and pH-6.0 Acetate buffer and organic mixture in the ratio of 30:70 as a Mobile phase-B. By using waters X-Bridge C_{18} (150*4.6mm), 3.5μm column chromatographic separation was achieved. The flow rate and run time was 0.8mL/min and 45minutes. The detection wavelength was 265nm.The average percentage recovery for Famotidine related compound-C was found to be 94.3%, 95.9%, 96.0% represents the accuracy of the method and for Famotidine related compound-D was found to be 95.8, 95.4 and 96.4. The %RSD for Famotidine related compound-C was found to be 5.576 and for Famotidine related compound-D was found to be 1.588 represents the precision of the method. The correlation coefficient square for Famotidne, Famotidine related compound-C and Famotidine related compound-D was found to be 0.999999, 0.9992 and 0.9991 respectively. Respective parameters met the acceptance criteria, from the results concluded that the developed method was precise and accurate.

*Corresponding Author

Name: Binoy Varghese Cheriyan
Phone: 9840677122
Email: lallybinoy@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i4.3250

Production and Hosted by

Pharmascope.org

INTRODUCTION

Famotidine is a competing suppressant or blocker of histamine H2-receptors. Famotidine is a propanimidamide and H2-receptor antagonist chemically called as 3-[[2-(diaminomethylideneamino)-1,3-thiazolyl-4]methylsulfanyl]-N'-sulfamoylpropanimidamide. It is white to pale yellow crystalline composite that is readily or amply solvable in glacial acetic acid, most moderately solvable in water, moderately solvable in methanol and almost insolvable in ethanol (Langtry *et al.*, 1989). Famotidine is a competing suppressant or blocker of histamine

H2-receptors, it hinder or prevent nocturnal gastric acid secretion and basal by competing blockage or prohibition of the activity of histamine at the histamine H2-receptors of the lateral cells and also hinder gastric acid secretion accelerated or excited by insulin, pentagastrin, food, caffeine, betazole and physiologic vagal reflex. Comparing to ranitidine famotidine is three fold high effective or dynamic and twenty times more effective when compared to cimetidine. Feeble inhibiting of hepatic cytochrome p450 mixed function oxidase system (Rockville and Convention, 1996), (Chicago, 1994). Famotidine is effective in boosting or facilitating the restoring of stomach and duodenal ulcers and additionally in diminishing ulcer agony (Kanayama, 1999) (Soga *et al.*, 1999). High doses are utilized for healing circumstances in which there are characterized enhance or rise in acid excretion called Zollinger-Ellison syndrome, when provided in low doses for prolonged periods of time it has been efficient in inhibiting or stopping repetition of ulcers (Borody *et al.*, 1995) , (Hu *et al.*, 2003). Famotidine additionally is utilized for healing heartburn and in treating or restoring ulceration and inflammation of the esophagus emerging from acid (Kirika *et al.*, 2004) (Fujiwara *et al.*, 2005). Prior or earlier operation famotidine provided to surgery patient (Escolano *et al.*, 1992) to diminish the chance of aspiration pneumonitis (Vila *et al.*, 1991) (Jahr *et al.*, 1991) .

Method Development

Documentation or authentication and method development plays crucial part in development analysis and production of pharmaceuticals. Method development needs a lot of efforts and implies functioning on several concepts or thoughts concurrently and therefore eventually choosing one of those (Sethi, 2001) (Shethi and Hplc, 1996). Method development employed to make sure or secure the efficiency of drug products, identification, potency and purity. There are several steps concerned in development process are:

1. Documentation of developed method
2. Development of test procedure
3. Method enhancement
4. Set up HPLC condition
5. Laboratory method authentication (Sankar, 2006) (Breaux *et al.*, 2003)
6. Documentation statement (Sankar, 2006) (Breaux *et al.*, 2003)

MATERIALS AND METHODS

Chemicals and Reagents

The utilized pharmaceutical preparation Famotidine Oral Suspension (Equivalent to 40mg) were formulated in-house. Famotidine API with a potency 99.68% were used. All reagents utilized were of an analytical grade. Methanol HPLC grade were procured from Finar Limited and Acetonitrile HPLC grade were procured from MerckLimited and water for HPLC ELGA purification system.

Instrumentation

Method development and validation was performed on HPLC instrument equipped with UV-detector using waters X-Bridge C_{18} (150*4.6mm), 3.5μm column chromatographic separation was achieved. The injection volume was 20μL. The run time was set 45minutes and flow rate 0.8mL/min and wavelength selected was 265nm. The Empower Software is used for processing data. Chromatographic parameters are shown in Table 1 and gradient program in Table 2.

Preparation of solution

Buffer Preparation

Acetate Buffer pH 6.0

The solution was prepared by dissolving 13.6 g of sodium acetate trihydrate in 1000 mL of water. Mixed well and then the solution adjusted to pH 6.0$\pm$0.05 with glacial acetic acid, then the solution filtered through 0.45 μm membrane filter and sonicated the buffer solution to degas.

Phosphate Buffer pH 7.0

The solution was prepared by dissolving 13.6 g of sodium dihydrogen phosphate monohydrate in a suitable container containing 1000 mL of water. Mixed well and then the solution filtered through 0.45 μm membrane filter and sonicated the buffer solution to degas.

Preparation of Organic Mixture

The organic mixture was prepared by mixing ACN: Methanol in the ratio of 80:20 and sonicated for 5 minutes to degas.

Preparation of Diluent

The diluents was prepared by mixing 900mL of pH 7.0 Phosphate buffer and 100mL of Organic mixture into suitable container and then sonicated to degas.

Mobile Phase - A

Used filtered and degassed pH 6.0 Acetate buffer as a Mobile Phase-A.

Mobile Phase - B

Table 1: Chromatographic parameters

Chromatographic Parameters	Conditions / Specifications
Column	Waters, X-Bridge C18; 150*4.6mm, 3.5μm
Mobile Phase-A	pH 6.0 Acetate Buffer
Mobile Phase-B	pH 6.0 Acetate Buffer : Organic Mixture (30:70)
Flow Rate	0.8 mL/min
Column Temperature	35°C
Sample Temperature	Ambient
Wavelength	265nm
Injection Volume	20 μL
Run Time	45.0 minutes

Table 2: Gradient Program

Time (min)	Mobile phase-A (%)	Mobile phase-B (%)
0.00	90.0	10.0
6.00	90.0	10.0
12.00	85.0	15.0
16.00	85.0	15.0
35.00	15.0	85.0
40.00	15.0	85.0
40.50	90.0	10.0
45.00	90.0	10.0

Table 3: Injection Sequence for Filter Validation

Solution Name	No. of Injections	Purpose
Centrifuged/Unfiltered	1	To verify the content of Famotidine related Compound-C and related compound-D
0.45μm Nylon/2mL discard	1	
0.45μm Nylon/4mL discard	1	
0.45μm Nylon/6mL discard	1	
0.45μm Nylon/8mL discard	1	

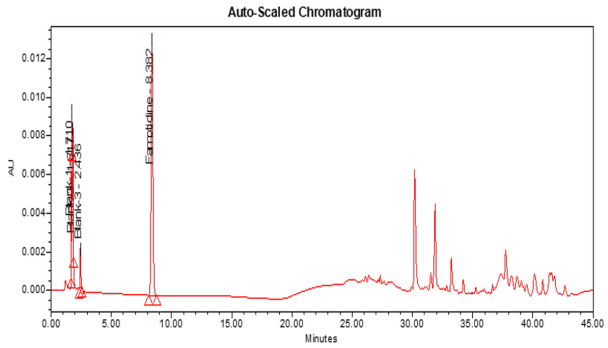

Figure 1: Optimized Chromatogram of Famotidine Standard Solution

The mobile phase was prepared by mixing 300 mL of pH 6.0 Acetate buffer and 700 mL of Organic mixture into a suitable container and thensonicated to degas.

Procedure

Standard Stock Preparation

40.37mg of Famotidine RS was weighed and transferred into a 250mL volumetric flask. To that 3/4th volume of diluent was added. Sonicated to dissolve, diluted to volume with diluent and mixed well.

Standard Preparation

Pipetted out 2mL of Famotidine Standard Stock solution into 100mL volumetric flask. Diluted to volume with diluent and mixed well. An optimized chromatogram is shown in Figure 1

Preparation of Sample Solution

Transfer 5.0mL of sample into a 250-mL volumetric flask and noted down the weight of sample in mg. (Equivalent to about 40 mg of Famotidine). Added 150mL of diluent and then spiked the 10mL of Impurity-C and Impurity-D stock solution into the same sample solution.Further sonicated to 15 min-

Table 4: System suitability parameters for Famotidine

S.No	Injection No	Peak Area for Famotidine	USP Tailing factor	USP Plate Count
1	1	199934	1.138	20264
2	2	197856	1.124	20142
3	3	198921	1.262	20584
4	4	195764	1.142	20873
5	5	196328	1.233	20285
6	6	199976	1.191	20589
Mean	-	198130	-	-
STDEV	-	1800.45	-	-
%RSD	-	0.9	-	-

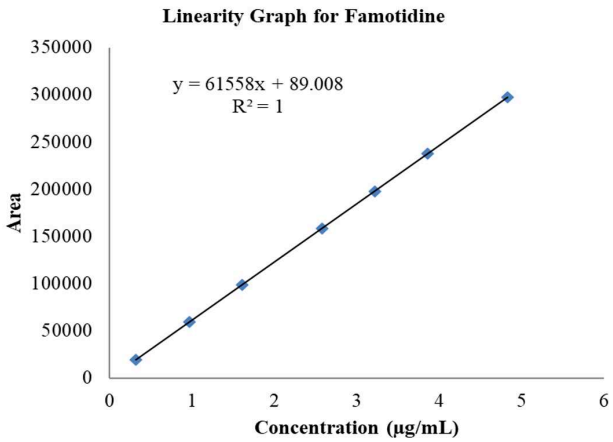

Figure 2: Linearity Graph for Famotidine

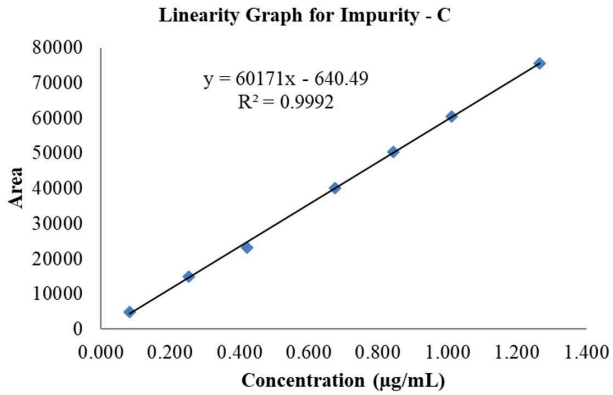

Figure 3: Linearity Graph for Impurity - C

utes with frequent intermittent shake. After the sonication, diluted to volume with diluent and mixed well. Centrifuged the sample for about 5 minutes and collected the supernatant. Filtered the clear aliquot through 0.45-μm Nylon syringe filter and collected the filtrate after discarded the first 4mL of filtrate. An optimized chromatogram of samples are shown in Figures 5 and 6.

Preparation of Placebo Solution

Transfer 5.0mL of sample into a 250-mL volumetric flask and noted down the weight of sample in mg. (Equivalent to about 40 mg of Famotidine). Added 150mL of diluent and further sonicated to 15 minutes with frequent intermittent shake. After the sonication, diluted to volume with diluent and mixed well. Centrifuged the sample for about 5 minutes and collected the supernatant. Filtered the clear aliquot through 0.45-μm Nylon syringe filter and collected the filtrate after discarded the first 4mL of filtrate.

Initialization of the Instrument

Initially the column was positioned on the instrument and switch on the instrument and column washed with distilled water for about 60min, then for stabilization of the column run the mobile phase for 30min.

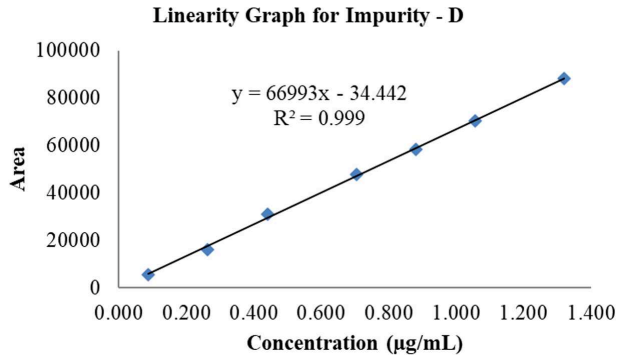

Figure 4: Linearity Graph for Impurity - D

Validation of Developed Method

As stated by ICH guidelines the optimized technique was validated. In accordance with above developed technique, the mobile phase were prepared and organized all parameters.

Evaluation of System Precision

System precision was tested by injecting 6 replicates of Famotidine standard.The %RSD of peak area of

Table 5: Linearity Data

	Famotidine		Impurity-C		Impurity-D	
Linearity Level (%)	Concentration (μg/mL)	Peak Area for Famotidine	Concentration (μg/mL)	Peak Area for Impurity-C	Concentration (μg/mL)	Peak Area for Impurity-D
LOQ (10%)	0.322	19864	0.084	5010	0.088	5749
30	0.966	59683	0.253	15015	0.264	16247
50	1.61	99164	0.422	23193	0.440	30998
80	2.576	158743	0.675	40108	0.704	47997
100	3.22	198130	0.844	50386	0.880	58432
120	3.864	237865	1.013	60463	1.056	70453
150	4.83	297543	1.266	75579	1.320	88234
Correlation Coefficient Square (r2)		0.999999		0.9992		0.9991

Table 6: Data of Method Precision

		Impurity-C		Impurity-D	
S.No	Sample	Peak Area	%Impurity	Peak Area	%Impurity
1	Method Precision-1	52286	0.495	51954	0.486
2	Method Precision-2	53256	0.455	52354	0.504
3	Method Precision-3	52785	0.520	50454	0.490
4	Method Precision-4	53443	0.515	50354	0.489
5	Method Precision-5	52081	0.460	50654	0.498
6	Method Precision-6	53506	0.501	50064	0.484
Mean	-	-	0.491	-	0.492
S.D	-	-	0.027	-	0.008
%RSD	-	-	5.576	-	1.588

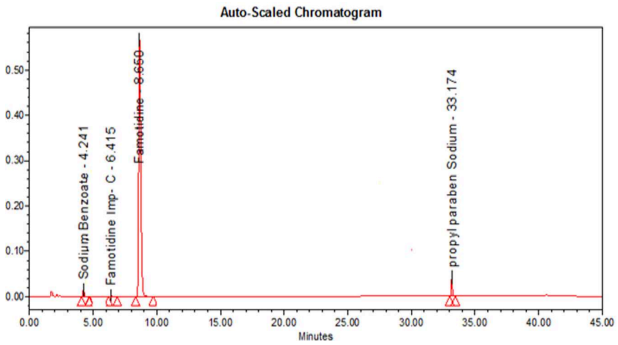

Figure 5: Optimized Chromatogram of Impurity - C Sample Solution

the respective peaks were calculated.

Acceptance criteria

The tailing factor for famotidine peak in standard preparation should not be more than 2.0. The theoretical plate count for famotidine peak in the standard preparation should not be less than 5000. The relative standard deviation for the area of famotidine peak from six replicate injections of standard solution should not be more than 2.0%.

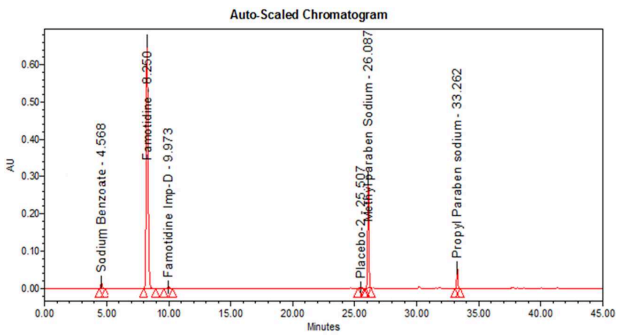

Figure 6: Optimized Chromatogram of Impurity - D Sample Solution

Linearity

Linearity was performed in the concentration of

LOQ(10%), 30%, 50%, 80%, 100%, 120%, 150% of working concentration of respective Famotidine, Famotidine related compound C and Famotidine related compound D average area for each level was recorded and slope, y-intercept & correlation coefficient was calculated. Graph was plotted for respective analyte peak concentration on x-axis and area response on y-axis. Linearity graphs are shown in Figures 2, 3 and 4.

Standard Stock Preparation

40.37mg of Famotidine RS was weighed and transferred into a 250mL volumetric flask. To that 3/4th volume of diluent was added. Sonicated to dissolve, diluted to volume with diluents and mixed well.

Standard Preparation

Pipetted out 4mL of Famotidine Standard Stock solution into 200mL volumetric flask. Diluted to volume with diluent and mixed well.

Acceptance criteria

The correlation coefficient should not be less than 0.98 for famotidine.

Famotidine Related Compound-C Stock Preparation

2.12mg of Impurity-C was weighed and transferred into a 100mL volumetric flask added 75mL of diluent and sonicated to dissolve. After sonication diluted to volume with diluent and mixed well.

Famotidine Related Compound-C Preparation

Pipetted out 4mL of Impurity-C Stock solution into 100mL volumetric flask. Diluted to volume with diluent and mixed well.

Famotidine Related Compound-D Stock Preparation

2.21mg of Impurity-D was weighed and transferred into a 100mL volumetric flask added 75mL of diluent and sonicated to dissolve. After sonication diluted to volume with diluent and mixed well.

Famotidine Related Compound-D Preparation

Pipetted out 4mL of Impurity-D Stock solution into 100mL volumetric flask. Diluted to volume with diluent and mixed well.

Acceptance criteria

The correlation coefficient should not be less than 0.98 for famotidine related compound-C and related compound-D.

Method Precision

Method precision was evaluated by injecting a blank, standard, six sample injection and one bracketing standard injection.

Acceptance Criteria

The %RSD for %Impurity from six (6) sample preparations should be NMT 10.0.

Solution Stability

Stability of standard and sample solution was demonstrated by injecting standard and sample solution with different time interval from the time of preparation. A solution was injected once in initial, 12 hours, 24 hours, 48 hours, 72 hours and 96 hours. The stability of solution shall be decided based on the area obtained at different time interval. If the results are not meeting the acceptance criteria within the time interval specified, the test can be discontinued and reported the hours up-to which the solution is found to be stable.

Acceptance Criteria

1. The %difference in area between initial and time points should be NMT 25.0 for Standard.
2. The %difference in %Impurity between initial and time points should be NMT 25.0 for sample.

Acceptance Criteria

The %difference in Peak area for Impurity between the centrifuged sample and filtered sample should be NMT 25.0. Injection sequence for filter study is shown in Table 3.

Specificity

No interference should be observed from diluents, placebo and all known Impurities at the retention time of Famotidine peak.

Accuracy

Accuracy shall be assessed using 3 concentrations 50%, 100%, 150% by preparing triplicate sets of sample solutions. The active can be added to placebo at 50%, 100%, 150% concentrations. At each concentration, the average result shall be expressed as a percentage.

Acceptance Criteria

1. Overall average recovery should be between 80.0-120.0%.
2. The %RSD for recovery of triplicate preparations at each level should be NMT 10%.

RESULTS

Inference

The system suitability parameters were within the acceptance criteria and the results are presented in

Table 7: Recovery Studies of Famotidine Related Compound - C

Accuracy Levels	Sample #	Peak Area of Impurity-C	Amount Added (μg/mg)	Amount Recovered (μg/mg)	% Recovery	Average % Recovery	S.D & %RSD
50%	Sample 1	26084	0.422	0.447	94.5	94.3	S,D 1.73
	Sample 2	26245	0.424	0.459	92.6		%RSD
	Sample 3	24385	0.394	0.411	96.0		1.8
100%	Sample 1	50027	0.809	0.837	96.6	95.9	S.D 1.02
	Sample 2	51856	0.839	0.869	96.5		%RSD
	Sample 3	50242	0.812	0.857	94.8		1.0
150%	Sample 1	75023	1.213	1.244	97.5	96.0	S.D 1.40
	Sample 2	74756	1.209	1.276	94.7		%RSD
	Sample 3	74647	1.207	1.260	95.8		1.5

Table 8: Recovery Studies of Famotidine Related Compound - D

Accuracy Levels	Sample #	Peak Area of Impurity-D	Amount Added (μg/mg)	Amount Recovered (μg/mg)	% Recovery	Average % Recovery	S.D & %RSD
50%	Sample 1	27321	0.449	0.478	93.8	95.8	S,D 2.35
	Sample 2	26536	0.436	0.459	95.1		%RSD
	Sample 3	26973	0.443	0.451	98.4		2.5
100%	Sample 1	52532	0.864	0.897	96.3	95.4	S.D 1.08
	Sample 2	51345	0.844	0.881	95.8		%RSD
	Sample 3	50951	0.838	0.889	94.2		1.1
150%	Sample 1	80127	1.318	1.348	97.8	96.4	S.D 1.39
	Sample 2	76587	1.288	1.356	94.9		%RSD
	Sample 3	76734	1.290	1.336	96.6		1.5

Table 9: Solution Stability of Famotidine at Room Temperature

Time Interval	Famotidine Peak Area	Difference in Area
Initial	195765	N/A
12 Hours	195542	0.11
24 Hours	195185	0.30
48 Hours	195042	0.37
72 Hours	194953	0.41
96 Hours	194596	0.60

Table 10: Solution Stability of Impurity-C and Impurity-D at Room Temperature

	Impurity-C		Impurity-D	
Time Interval	Impurity-C Peak Area	% Difference in Area	Impurity-D Peak Area	% Difference in Area
Initial	52263	N/A	57450	N/A
12 Hours	51467	1.52	57286	0.29
24 Hours	50987	2.44	57003	0.78
48 Hours	50663	3.06	56876	1.00
72 Hours	50221	3.91	56276	2.04
96 Hours	50021	4.29	56006	2.51

Table 11: Filter Study Data of Impurity-C and Impurity-D

	Impurity-C		Impurity-D	
Sample	Peak Area	% Difference	Peak Area	% Difference
Centrifuged/Unfiltered	53982	N/A	57450	N/A
0.45μm Nylon/2mL discard	53563	0.78	57386	0.11
0.45μm Nylon/4mL discard	53429	1.02	57245	0.36
0.45μm Nylon/6mL discard	53276	1.31	57213	0.41
0.45μm Nylon/8mL discard	53239	1.38	57126	0.56

Table 4. Hence the system was suitable to carry out the analysis for estimation of sample of Famotidine oral suspensions.

This method is to be employed on Famotidine oral suspensions for the purpose of determining the RS method.

Observation

The Correlation coefficient square (r^2) of Famotidine, Impurity-C and Impurity-D was found to be 0.999999, 0.9992 and 0.9991 respectively.

Report

The Correlation Coefficient Square (r^2) for Famotidine, Impurity –C and Impurity-D were met the acceptance criteria of not less than 0.998. The linear regression data shows that the method is linear over the entire concentration range (LOQ (10%)-150%) and it is adequate for its intended concentration range and results are shown in Table 5.

Observation

The S.D and %RSD of Impurity-C was found to be 0.027 and 5.576 then for Impurity-D 0.008 and 1.588 respectively.

Report

The %RSD for %Impurity from six (6)-sample preparations of Impurity-C and Impurity-D is less than 10 and the results are given in Table 6, hence the method is precise.

Report

1. Overall average recovery for Famotidine related compound-C is between 80.0-120.0%.

2. The %RSD for recovery of triplicate preparations at each level is NMT 10% and hence the method is accurate, results are presented in Table 7.

Report

1. Overall average recovery for Famotidine related compound-D is between 80.0-120.0%.

2. The %RSD for recovery of triplicate preparations at each level is NMT 10% and hence the method is accurate, results are presented in Table 8

Report

1. The %difference in area between initial and time points is NMT 25.0 for standard.

2. The %difference in %Impurity between initial and time points is NMT 25.0 for sample solution and results are reported in Tables 9 and 10.

All results met the acceptance criteria. Based on above results, it is concluded that standard and sample solutions were stable up to 96 hrs respectively when stored at Room temperature.

Specificity

No interference was observed from diluents, placebo and all known Impurities at the retention time of Famotidine peak.

Report

The %difference in Peak area for Impurity between the centrifuged sample and filtered sample is NMT 25.0. Datas are reported in Table 11.

DISCUSSION

In the proposed project, a successful attempt has been made to develop a simple, accurate, economic and rapid RP-HPLC method for the determination of Famotidine Oral suspension, Famotidine related compound-C and related compound-D in pharmaceutical formulations. The method has been validated as per the guidelines given by ICH requirements to assure that the method consistently meets the predetermined specifications and quality attributes. The average percentage recovery for Famotidine related compound-C was found to be 94.3, 95.9, 96.0 represents the accuracy of the method and for Famotidine related compound-D was found to be 95.8, 95.4 and 96.4. The %RSD for Famotidine related compound-C was found to be 5.576 and for Famotidine related compound-D was found to be 1.588 represents the precision of the method. The correlation coefficient square for Famotidne, Famotidine related compound-C and Famotidine related compound-D was found to be 0.999999, 0.9992 and 0.9991 respectively. Respective parameters met the acceptance criteria, from the obtained results concluded that the developed method was precise and accurate.

CONCLUSIONS

All respective validation parameters met the acceptance criteria and it was concluded that the Related substance determination of famotidine in oral suspension by using pH 6.0 Acetate buffer as mobile phase-A and pH 6.0 Acetate buffer: Organic mixture (30:70) as mobile phase-B. pH 7.0 Phosphate buffer: Organic mixture (90:10) is diluent. The separation is achieved by using column Waters, X-Bridge C18, (150*4.6mm), 3.5μm and flow rate is 0.8mL/min. Detection wavelength is 265nm. Hence this method can be used for related substance determination of famotidine in oral suspension formulation by precise and accurate manner. The final resultant of the established RS method for perseverance of Famotidine indicates that the technique or procedure was precise, simple, accurate and reproducible. The developed HPLC technique indicates satisfying outcome with precision, linearity, specificity and accuracy. Hence the method is precise and accurate.

ACKNOWLEDGEMENT

The authors are thankful to Novitium Labs Private Limited, Chennai for providing sample for research work. The authors are thankful for Vels Institute Science Technology and Advanced Studies (VISTAS), Chennai Tamil Nadu for providing all the facilities to make this work success.

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

REFERENCES

Borody, T. J., Andrews, P., Fracchia, G., Brandl, S., Shortis, N. P., Bae, H. 1995. Omeprazole enhances efficacy of triple therapy in eradicating Helicobacter pylori. *Gut*, 37(4):477–481.

Breaux, J., Jones, K., Boulas, P. 2003. Understanding and implementing efficient analytical methods development and validation. *Pharm Technol Anal Chem Test*, 5:6–13.

Chicago 1994. Council on Drugs. AMA Drug Evaluations Annual. pages 902–902.

Escolano, F., Castano, J., Lopez, R., Bisbe, E., Alcon, A. 1992. Effects of omeprazole, ranitidine, famotidine and lacebo on gastric secretion in patients ndergoing elective surgery. *British Journal of Anaesthesia*, 69(4):404–406.

Fujiwara, Y., Higuchi, K., Nebiki, H., Chono, S., Uno, H., Kitada, K., Satoh, H., Nakagawa, K., Kobayashi, K., Tominaga, K., Watanabe, T., Oshitani, N., Arakawa, T. 2005. Famotidine vs. omeprazole: a prospective randomized multicentre trial to determine efficacy in non-erosive gastro-oesophageal reflux disease. *Alimentary Pharmacology and Therapeutics*, 21(s2):10–18.

Hu, F. L., Jia, J. C., Li, Y. L., Yang, G. B. 2003. Comparison of H2-Receptor Antagonist-and Proton-Pump Inhibitor-Based Triple Regimens for the Eradication of Helicobacter Pylori in Chinese Patients with Gastritis or Peptic Ulcer. *Journal of International Medical Research*, 31(6):469–474.

Jahr, J. S., Burckar, G., Smith, S. S., Shapiro, J., Cook, D. R. 1991. Effects of famotidine on gastric pH and residual volume in pediatric surgery. *Acta Anaesthesiologica Scandinavica*, 35(5):457–460.

Kanayama, S. 1999. Proton-pump inhibitors versus H2-receptor antagonists in triple therapy for Helicobacter pylori eradication. *Nihon Rinsho. Japanese Journal of Clinical Medicine*, 57(1):153–159.

Kirika, N. B., Bodrug, N. I., Butorov, I. V., Butorov, S. I. 2004. Efficacy of different schemes of antihelicobacter therapy in duodenal ulcer. *Therapeutic archive*, 79:18–22.

Langtry, H. D., Grant, S. M., Goa, K. L. 1989. Famotidine. *Drugs*, 38(4):551–590.

Rockville, M. U., Convention 1996. *USPDI - Drug Information for the Health Care Professional*. Pharmaceutical Convention, Inc, U.S.

Sankar, S. R. 2006. *Text book of Pharmaceutical Analysis*. Rx Publications, Tirunelveli, 13-1, 2 edition .

Sethi, P. D. 2001. *High Performance Liquid Chromatography, Quantitative analysis of Pharmaceutical Formulation, Edn 1st*. CBS Publication, New Delhi.

Shethi, P. D., Hplc 1996. *Quantitative Analysis of Pharmaceutical Formulation*. CBS Publishers and Distributors, New Delhi.

Soga, T., Matsuura, M., Kodama, Y., Fujita, T., Sekimoto, I., Nishimura, K., Yoshida, S., Kutsumi, H., Fujimoto, S. 1999. Is a proton pump inhibitor necessary for the treatment of lower-grade reflux esophagitis? *Journal of Gastroenterology*, 34(4):435–440.

Vila, P., Vallès, J., Canet, J., Melero, A., Vidal, F. 1991. Acid aspiration prophylaxis in morbidly obese patients: famotidine vs. ranitidine. *Anaesthesia*, 46(11):967–969.