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FORMULATION DEVELOPMENT AND CHARACTERIZATION OF FAMOTIDINE DRY SUSPENSION FOR ORAL USE

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ABSTRACT

Famotidine an H_2 receptor blocker is generally used to treat ulcers of stomach and intestine. Famotidine is available in liquid suspension that is unstable during shelf life. Degradation of the drug as well as bad smell and color change is major problem in liquid suspension. This problem may be solved by formulating the drug as a dry suspension. We prepared four different formulations of famotidine as dry suspension. Geometric mixing methodology was followed to prepare the formulations. IR-spectroscopy showed no incompatibility between excipients used and Active Pharmaceutical Ingredients (API). Tests performed to evaluate formulations include assay, pH, viscosity, flow property, sedimentation volume and re-dispersibility. Among all the developed formulations, F3 was most ideal having excellent flow property, 100% drug assay, optimum viscosity and pH. Other formulations displayed some problems like viscosity of F1 was high that caused difficulty in flow while assay of F2 was 94% and F4 had bitter taste and low pH value. Hence F3 formulation was selected for further studies and kept for six months in stability chamber at accelerated conditions having temperature 40 °C ±2 and 75% ±5 R.H. samples were taken at 0, 1, 2, 3, 4 and 6 months to evaluate stability of the dry formulation. Moreover formulation (F3) was reconstituted with water and placed at accelerated conditions for 28 days to check its stability. Samples were taken at 0, 1, 2, 3, and 4 weeks. Results showed that no change occurred in both dry and reconstituted suspension during stability studies. It can be concluded on the basis of these findings that F3 formulation was stable and can be used in future.

Keywords: Dry suspension, Famotidine, HPLC, Stability study, Viscosity.

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INTRODUCTION

Oral route is one of the most common forms of drug delivery due to its easy administration **[1]**. This route does not require strict sterile conditions for manufacturing and is least expensive and very convenient. However, poor bioavailability due to hepatic metabolism and rapid blood spikes (both high and low), which require frequent/higher dosing, makes this route cost prohibitive and inconvenient **[2]**. Pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are suspended uniformly throughout the suspending vehicle with the help of one or more suspending agents. [**3**]. Dry suspension is more suitable as compared to liquid suspension dosage form due to its improved chemical stability, bioavailability and masking bitter taste of drugs.

One of the major causes of enteric diseases is irregular production/secretion of gastric acid or retrograde/anterograde movements to the adjacent anatomical structures. This causes damage to epithelial lining of enteric system which lack natural defense system against the acid **[4]**. Over the years, various treatment strategies including acid neutralizing agents, mucosal protecting substances, and proton pump inhibitors have been discovered and innovated to relieve the symptoms of these agonizing conditions. Proton pump inhibitors including famotidine have always been the main stay of treatment and prevention of these pathological states **[5]**. Famotidine is H_2 (histamine) receptor blocker prescribed for short-term treatment of esophagitis and treatment of pathological hyper secretory conditions e.g., Zollinger-Ellison Syndrome, Famotidine is also well tolerated in acute duodenal ulcers **[6]**.

MATERIALS

Famotidine (API) was obtained from Aurik Pharmaceuticals Rawat, Islamabad; Pakistan.

Citric acid, titanium dioxide, sodium benzoate, xanthan gum, methyl paraben, aerosil, CMC sodium (carboxy methyl cellulose), propyl paraben and peppermint flavor were obtained from Sigma Aldrich and Merck KGaA, Darmstadt, Germany. Sugar (Granular) was purchased from local Market. All the reagents used were of analytical grade.

METHODS

Preparation of Famotidine Dry Suspension

Famotidine was mixed with the half quantity of sugar and sieved through mesh#20. The remaining half of the sugar fine was passed through mesh# 20. Sodium benzoate was mixed with citric acid and sieved through mesh# 30. Titanium Dioxide, methyl paraben and saccharin sodium were mixed separately and sieved through mesh# 30. Carboxymethyl Cellulose, Xanthan gum were mixed with each other separately and passed through mesh# 30. At the end aerosil was mixed with flavor and passed through mesh #60. After that all the sieved materials were mixed and sieved again through mesh#20. After sieving this powder blend was mixed continuously for 20 minutes **[7]**. All the formulations of dry suspension were prepared in the same manner. The composition of formulations is given in **Table 1**.

Evaluation of Dry Suspension

Flow Properties of Powder

Angle of Repose

Fixed funnel method was used for determination of angle of repose by setting the funnel in such a manner that its lower tip slightly touches the powder heap properly mixed dry powder (2gm) was added in the funnel and allowed to drop. Diameter of heap was then measured and angle of repose was calculated according to the equation given below **[8]**.

$Tan\ \theta = h/r$

Where,

θ = angle of repose

h = height of cone

r = radius of the cone base

Table 1: Composition of famotidine dry suspension formulations.

Ingredients (mg)	F1	F2	F3	F4
Famotidine	20	20	20	20
Sugar Fine	2010	2000	2000	2040
Carboxymethyl cellulose	20	8	8	10
Sodium Benzoate	7.5	7	10	-
Saccharin sodium	0.05	2.00	1.5	1.5
Sodium Citrate	0.005	-	-	-
Xanthan Gum	0.005	3	3	3
Aerosil-200	0.015	1	1	0.5
Flavor	0.08	2	2	1.5
Citric Acid	-	-	3	4
Microcrystalline cellulose	-	25	-	-
Methyl Paraben Sodium	-	-	-	4
Propyl Paraben Sodium		-	-	0.50
Titanium Dioxide	-	5	5	4

Bulk and Tapped Density

Bulk and tapped density were determined by adding 2gm of evenly mixed powder in 10ml graduated cylinder. Cylinder was placed on a flat hard surface and initial volume of powder was measured. Bulk density was calculated by using the following formula **[8]**.

$$Bulk\ density = weight\ of\ mixed\ powder / volume\ of\ mixed\ powder$$

Then cylinder was tapped gently over the hard surface until no change in volume occurred. Final volume of powder was measured. Tapped density was determined using formula given below **[9]**.

$$Tapped\ density = Weight\ of\ the\ blend / Final\ volume$$

Compressibility Index

Compressibility index (CI) was calculated by following formula [**10**].

$$CI = [(Tapped\ density - Bulk\ density) / tapped\ density] \times 100$$

Hausner's Ratio

It indicates flow properties of powder that was calculated with the help of following formula.

$$Hausner's\ Ratio = Tapped\ density / Bulk\ density$$

Drug Assay

To prepare standard dilution of drug, 50mg of famotidine was added into 100ml volumetric flask. 50ml of 0.1N NaOH was added in the flask

containing the drug and sonicated. After sonication, the volume was made 100ml with 0.1N NaOH. Same procedure was used to make the dilution of sample. The absorbance of sample and standard was recorded at 286nm after making suitable dilutions. For HPLC analysis buffer A (pH 6.0 ±0.1) and buffer B (pH 7.0 ±0.1) were prepared freshly. Standard solution was prepared with 0.16mg/ml famotidine while sample solution was prepared by transferring suspension to a 100ml volumetric flask that is equivalent to 40mg of famotidine. Add 10 ml of ethanol, sonicate for 5 minutes. Then add 70ml of diluent and sonicate for additional 5 minutes. Dilute 10ml of this solution with diluent to 25ml and filter it. Column used 4.6mm x 25cm x 5µm L1.

Physicochemical Characteristics

Four different formulations of famotidine were prepared that were evaluated according to the parameters given below relating to their physiochemical characteristics.

pH

pH of the formulation after reconstituting with water was determined using a digital pH meter at 25˚C [**11**].

Viscosity

Viscosity of suspension was determined at ambient condition. For viscosity measurement 30ml of suspension was taken in a small beaker in such a way that spindle (L3) having 10rpm was completely immersed in suspension. This test was carried out using Haake viscometer to observe any change in viscosity of formulation.

Sedimentation Volume

Formulation (50 ml) was placed in a measuring cylinder that was stoppered and stored undisturbed at room temperature. The separation in formulation was noted regularly at specific time intervals for 28 days. The sedimentation volume was noted at zero time (freshly prepared) on 7th day, 14th day then 28th day of storage and this was considered as final volume of sediment. The sedimentation volume F was calculated using the formula given in equation.

$$F = Vu/Vo$$

Where,

V_u is the volume of sediment

V_o is the original height of the sample.

It is expressed as a percentage. The redispersibility of the suspension was checked by moving the cylinder upside down until there was no sediment at the bottom of the cylinder. One inversion was considered as 100% easy to be redisperse. Every additional inversion decreased the percent ease of redispersibility by 5% **[12]**.

Fourier Transform Infrared Spectroscopy

FTIR spectroscopy of pure famotidine (API) and also for active ingredient along with excipients of four formulations was measured at 4000—650 cm^{-1} for spectra scanning [**13**].

Organoleptic Evaluation

Suspension after pouring in a beaker was checked for its color, taste and odor. Variation in color often indicate poor distribution, whereas change in particle size and crystal habit causes taste changes. Change in color, odor and taste are indication of chemical instability [**14**].

Stability Studies of Reconstituted Formulation

Stability studies were carried out according to ICH guidelines. Water reconstituted samples were properly covered with aluminum foil and kept in accelerated temperature and humidity condition of 40 ±2 °C and 75 ± 5% RH for 28 days in order to determine stability of formulations **[15]**. Sample was analyzed for drug content using HPLC. Both the sample were analyzed i.e. dry form for about 6 month stability studies and sample after reconstituted with water for 28 days placed in accelerated stability chamber.

Clarity Test

Clarity test was performed for 28 days during stability studies to check any particulate matter in the suspension.

Pourability

Suspension was reconstituted in water. Suspension was filled in bottles and poured from the bottles to evaluate its easy pouring **[16]**.

RESULT AND DISCUSSION

Flow Property of Dry Suspension

All the formulations had excellent flow property Value were in the limit of 0.37-0.42gm/ml and tapped density between 0.38-0.46gm/ml. Similarly angle of repose, Hausner ratio and compressibility index value were also in the limit of excellent flow property as shown in **Table 1 [17]**.

Compressibility index equivalent to 15% gives good flow properties. Value of Hauser's ratio less than 1.25 depicts good flow property. Stability of suspension depends upon sedimentation rate of dispersed phase which is dependent on viscosity of dispersion medium.

Physiochemical Evaluation of Dry Suspension

All formulations were evaluated for physiochemical properties. Average particle size was 20 mm. F1 formulation had higher viscosity as compared to other formulations. F2 formulation had pH. Flow rate in ml per second is shown in **Table 2**. Sedimentation volume after reconstitution with water was high in F1

formulation as compared to other formulations. The suspension was carefully evaluated for change in colour, odor and taste in order to determine any chemical instability during storage period **[13]**.

Drug Assay Content

Drug content analysis for all formulation was analyzed by UV-spectroscopy method (**Table 3**). Drug assay content was in official limit 90%-110 for all the formulations **[18]**. Fresh dilution was prepared for both sample and standard for analysis.

F3 formulation had most accurate drug content assay with in limit, good flow property, optimum viscosity, pH and also had low sedimentation volume as compared to other three formulations. So F3 was considered as optimized formulation and subjected to stability studies. So we selected F3 formulation for further studies. Stability studies were done for six months at accelerated condition of temperature and humidity i.e. 40°C and 75 % RH. Drug assay was done during stability studies at specific time intervals for six months and results are shown in **Table 5**. These results indicate that there is no significant change in drug assay during six months study period. Because dry suspension is used after reconstitution so we also perform studies to evaluate its stability after reconstituting with water, because it is used for 28 days after reconstitution so we evaluate the form for 28 days. Drug assay, organoleptic evaluation, pH, viscosity and sedimentation volume was done and results are shown in **Table 6-7** and **Fig. 1** and **Fig. 2**. Drug assay is showing that there is minute change occurs in it but that is not significant and within limit.

Table 2: Flow property of all dry suspension formulations.

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Angle of repose	Compressibility index
F1	0.39 ±0.06	0.46±0.04	1.16±0.04	23.55±0.02	12.68±0.07
F2	0.42±0.07	0.41±0.06	1.09±0.02	29.41±0.02	11.81±0.06
F3	0.37±0.03	0.43±0.03	1.11±0.03	23.67±0.04	12.08±0.05
F4	0.41±0.03	0.38±0.05	1.20±0.03	25.31±0.00	10.43±0.05

All results are represented as Mean ± SD (n=3)

Table 3: Physiochemical evaluation for all dry suspension formulations.

Formulation	particle size	Viscosity (cps)	pH	Volume of Sedimentation
F1	20mm ±0.05	1350±1.52	4.6±0.01	5ml±0.05
F2	20mm ±0.06	1580±0.57	4.2±0.01	3.6ml±0.02
F3	20mm ±0.08	1420±4.04	5.1±0.03	1.8ml±0.05
F4	20mm ±0.02	1700±3.60	5.20±0.05	2.5ml±0.10

All results are represented as Mean ± SD (n=3 experiments)

Table 4: Drug assay result of all dry suspension formulations.

Formulation	Absorption of standard	Absorption of standard	% content
F1	0.832nm	0.846nm	101.68
F2	0.832nm	0.782nm	93.99
F3	0.832nm	0.834nm	100.24
F4	0.832nm	0.828nm	99.51

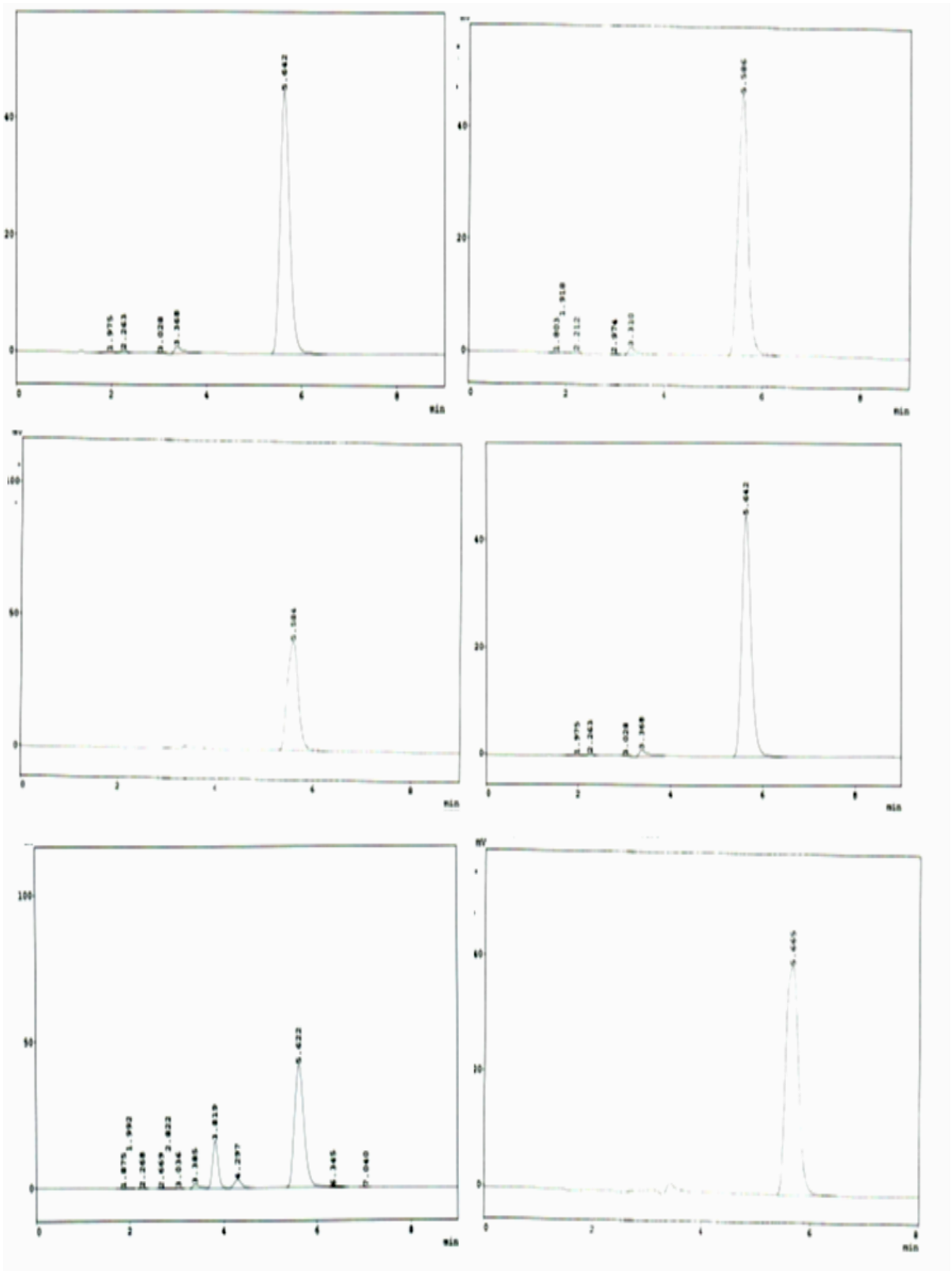

Figure 1: HPLC scans of F3 formulation a) Famotidine (Reference) scan b) F3 formulation at zero time c) F3 formulation after 1st week d) F3 formulation after 2nd week e) F3 formulation after 3rd week f) F3 formulation after 4th week**.**

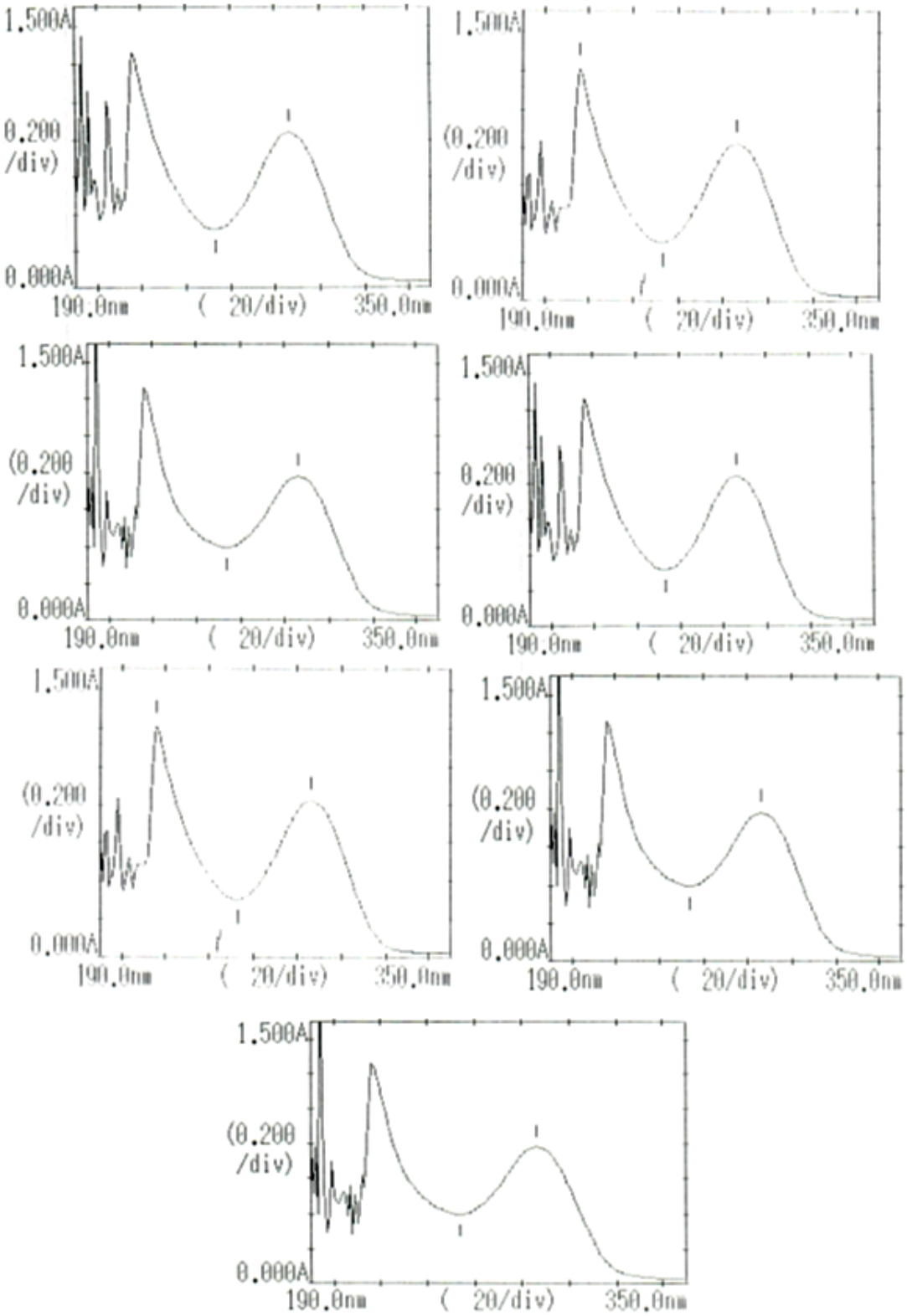

Figure 2: UV-Spectroscopy scans of F3 formulation in dry suspension form A) Famotidine (Reference) scan B) F3 formulation at zero time C) F3 formulation after 1st month D) F3 formulation after 2nd month E) F3 formulation after 3rd month F) F3 formulation after 4th month G) F3 formulation after 6th month.

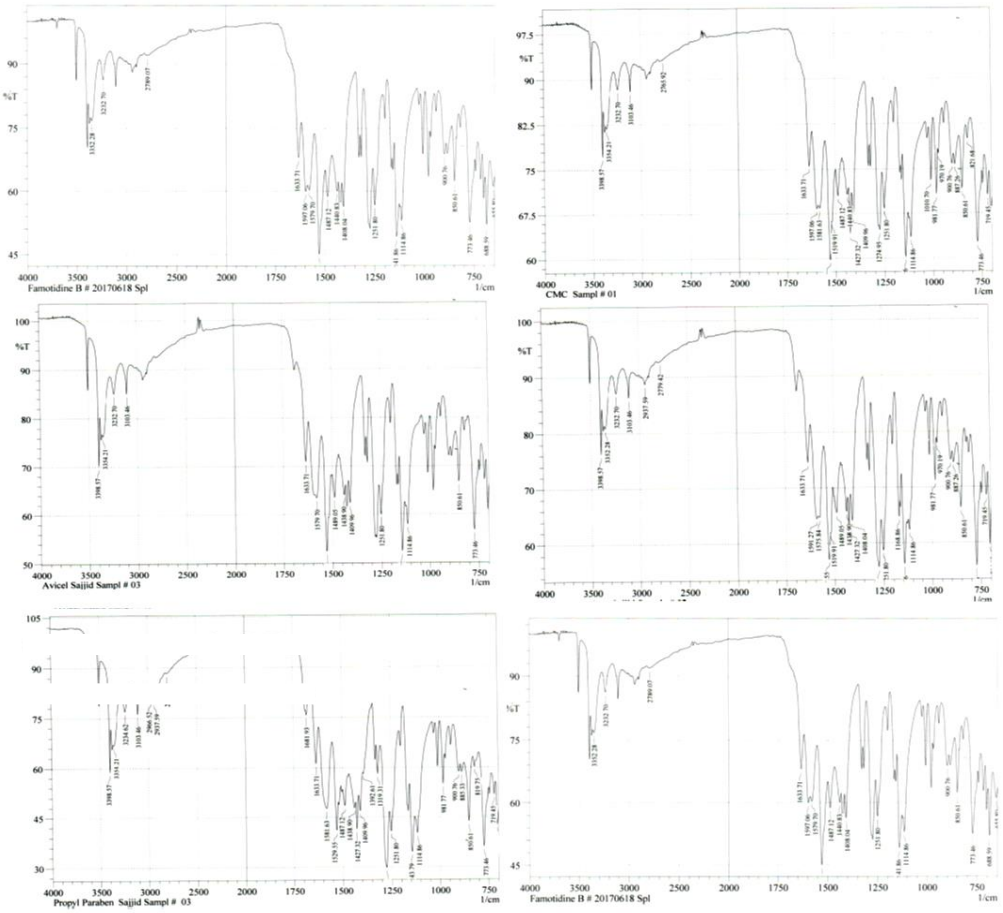

Figure 3: 1) IR spectra of Famotidine (Standard) 2) IR spectra of famotidine and saccharin sodium used in F3 formulation 3) IR spectra of famotidine and sodium benzoate used in F3 formulation 4) IR spectra of famotidine and CMC used in F3 formulation 5) IR spectra of famotidine and Sugar used in F3 formulation 6) IR spectra of famotidine and Citric acid used in F3 formulation.

Table 5: Assay of F3 dry suspension formulation.

Month	Absorption of standard	Absorption of standard	% content
1st	0.832nm	0.835nm	100.36
2nd	0.832nm	0.839nm	100.84
3rd	0.832nm	0.845nm	101.56
4th	0.832nm	0.833nm	100.12
6th	0.832nm	0.824nm	99.03

Table 6: Assay of formulation (F3) reconstituted with water at different time intervals

Week	AUC of Reference (Famotidine)	AUC of F3 Formulation	% contents
Zero	625129	649008	103.81
1st	625129	644730	103.13
2nd	625129	643568	102.94
3rd	625129	625129	100
4th	625129	607445	97.17

Table 7: Organoleptic evaluation of formulation (F3) at different time intervals

Weeks	Organoleptic characteristics (Color, Taste, Smell)	Viscosity (cps)	pH	Sedimentation Volume
1st	No Change	1445	5.1	0.5ml
2nd	No Change	1455	5.2	0.8ml
3rd	No Change	1460	5.4	1.1ml
4th	No Change	1485	5.5	1.8ml

CONCLUSION

Dry suspension formulations F1, F2, F3 and F4 were prepared and evaluated for physiochemical characteristics. F3 formulation was more suitable among all and was considered for further studies. Six months studies at accelerated conditions were performed for dry suspension by placing it in stability chamber and evaluated for physiochemical parameters. Stability studies of formulation after reconstituted with water were also performed for 28 days at accelerated conditions of temperature and humidity. Physical parameters for F3 formulation were studied after every week. And it was concluded that there is no visual change occurs in F3 formulation i.e. physical appearance, taste, drug content assay, pH and viscosity and hence concluded that F3 formulation is stable during stability studies.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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