Original Article

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Ion-exchange complex of famotidine: sustained release and taste masking approach of stable liquid dosage form

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Summary **A stable controlled release resinate-complex for the highly bitter taste famotidine (FAM) was developed to allow once-daily administration and improve patient compliance especially in pediatric and geriatric medicine. The drug-resinate complexes were prepared in different drug to resin (Amberlite IRP-69) ratios by weight (1:1, 1:2, 1:3, 1:4, 1:5 and 1:6). The optimized drug-resinate complex resulted from 1:6 drug to resin ratio experienced maximum drug loading and sustained release property. Hence, it was subjected to physicochemical characterizations by differential scanning colorimetry (DSC), x-ray diffractometry (XRD), Fourier transform infrared spectroscopy (FTIR) and scanning electron microscope (SEM). The optimized complex was further dispensed in the prepared syrup and the suspension was subjected to accelerated stability study, as mentioned in the International Conference on Harmonization (ICH) guidelines. Furthermore, the gustatory properties of the complex were evaluated on humans. The syrup complied successfully with ICH guidelines and sufficiently alleviated the bitterness of famotidine.**

Keywords: Famotidine (FAM), amberlite IRP-69, complexation, physicochemical characterizations, gustatory test

1. Introduction

Famotidine (FAM) is 3-([2-(diaminomethyleneamino) thiazol-4-yl] methylthio)-N'-sulfamoylpropanimidamide (*1*). It is very slightly soluble in water and in dehydrated alcohol, freely soluble in glacial acetic acid, and highly dissolvable in dilute mineral acids. It has been reported that poor lipophilicity, poor aqueous solubility and susceptibility to gastric degradation may contribute to the low and variable oral bioavailability (*2*). FAM is classified as a competitive inhibitor of histamine H2-receptors on the basolateral membrane of parietal cells. It reduces stomach acid production by 90% or more when given in single oral doses of 20 or 40 mg and promotes healing of duodenal ulcers (*3*). It is useful in treating heartburn, healing ulceration and inflammation of the esophagus resulting from acid (gastroesophageal reflux disease (GERD)). High doses are used for treating conditions characterized by marked increase in acid secretion such as Zollinger-Ellison syndrome. The current commercially marketable dosage forms for FAM are tablets, capsules and chewable tablets for adults. Additionally, FAM powder for oral suspension was prepared, evaluated and marketed to harmonize pediatric and geriatric patients, but its stability is limited to 30 d after reconstitution (*4*). FAM has extremely bitter taste which would be highly noticeable when administered as an oral liquid that also suffers from poor stability. Hence, researchers tried several approaches to mask the bitter taste (*5*).

Ion exchange resins (IER) are cross-linked water insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium reversibly and stochiometrically (*6*). Drugs can be loaded onto the resins by an exchanging reaction, and hence, a drug resinate complex is formed.

Amberlite IRP-69 resin is strong cation exchange resin derived from a sulfonated copolymer of styrene and divinylbenzene. It is supplied as sodium salt in the form of dry and fine powder. In addition to taste masking, it is employed as a carrier for cationic drugs and controlled release excipient (*7-9*).

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The present work aims at assessing the possibility of FAM-resinate complex formation with Amberlite IRP-69. The prepared and optimized drug-resinate complex would be subsequently suspended in the prepared syrup. Stability study of this syrup according to International Conference on Harmonization (ICH) guidelines would be of special concern. Previous research by the authors reported an optimized liquid dosage form for an essential drug for pediatric and geriatric medicine (*10*). The prepared and optimized drug-resinate complex that experienced maximum drug loading would be subjected to physicochemical characterization immediately after preparation by differential scanning colorimetry (DSC), x-ray diffractometry (XRD), Fourier transform infrared spectroscopy (FTIR) and scanning electron microscope (SEM). In addition, accelerated stability study would be performed for the complexes in the dry state and in the prepared syrup.

2. Materials and Methods

2.1. *Materials*

FAM was kindly supplied by Memphis Chemical Company, Cairo, Egypt. Amberlite IRP-69 and benzalkonium chloride were purchased from Sigma-Aldrich (Saint Louis, MO, USA). Sorbitol and glycerin were obtained from El-Nasr Pharmaceutical Chemical Co., Cairo, Egypt. Sucrose was purchased from United Company for Chemicals, Cairo, Egypt.

2.2. *Preparation of drug-resinate complexes*

In highly acidic conditions (*e.g*. 0.1 N HCl, pH 1.2), FAM was demonstrated to be extremely unstable. The degradation process of FAM was reported to be highly dependent on the pH of the solution, although a relatively stable profile for the drug was achieved at pH 4.0 (*11*).

Drug-resinate complexes were prepared by a single batch process. The time required for constant amount of the drug to react with the resin was taken as the equilibrium time. This was achieved by assaying the supernatant during preparation of the resinate complex. Amberlite resin (50, 100, 150, 200, 250, and 300 mg) was soaked overnight each in a beaker containing 50 mL of HCl (pH 4.0) and stirred with magnetic stirrer (Heidolph, U S A) to facilitate swelling and activation of the resin (*12*). Fifty mL of FAM solution (1 mg/1mL) in HCl (pH 4.0) was added to each beaker containing the calculated and activated amberlite resin to prepare 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 drug to resin ratios by weight complexes. The high drug to resin ratio (1:6) was based on its cationic exchange capacity (5 meq/g) (*13*). The resultant solutions were stirred at room temperature for 24 h.

The FAM-resinate complexes were separated by decantation, and washed two times with deionized water to remove unassociated drug and other ions. The complexes were then dried in hot air oven (Heraeus GS model B 5042, Germany) for 5 h at 45°C to a constant weight (*14*) and stored in a tight glass vial.

2.3. *Characterization and optimization of the prepared complexes*

Complexes of FAM and amberlite were characterized and optimized based on the drug content and *in vitro* drug release using the following methods.

2.3.1. *Estimation of FAM content*

Samples of the powdered complexes in triplicates were analyzed for FAM's content. Twenty mg samples were weighed and diluted with 10 mL 0.1 N HCl with vigorous shaking followed by sonication in an ultrasonic bath (Sonix USA, SS101H230) for 5 h in order to release and dissolve the drug from complex. The filtered samples were further diluted with 0.1N HCl, and then analyzed for FAM content spectrophotometrically using a UV–Vis double beam scanning spectrophotometer (Labomed, INC, UVD-2950, USA) at 263 nm. The drug-resinate complex with maximum drug content was the optimized one.

2.3.2. *In vitro drug release studies*

The dissolution profiles of untreated pure drug and the drug-resinate complexes were examined using USP type II paddle dissolution apparatus (Six-jars, USP rotating basket, dissolution test apparatus, DA-6D, India) at 37 ± 0.5°C and 50 rpm. The dissolution medium was 900 mL 0.1 N HCl (pH 1.2). Twenty mg sample of the pure drug or dry complex containing a known amount of FAM equivalent to the pure drug were weighed and each introduced to the dissolution tester cells. At predetermined intervals, 5 mL of the dissolution medium were taken and replaced with an equal volume of fresh dissolution medium in order to maintain the sink condition throughout the experiment. The collected aliquots were filtered and the absorbance of FAM was recorded using a UV-Vis spectrophotometer at 263 nm. Each experiment was done in triplicate and the average percentage released was calculated at each time interval.

2.3.3. *Kinetic analysis of the drug release data*

To examine the kinetics of drug release, the release data were fitted to models representing zero-order, first-order, Higuchi's square root of time (*15*) and Korsmeyer-Peppas equation (*16*). The coefficients of determination (r^2) were determined from regression plots of m *vs*. t, log (m_o – m) *vs*. t and m *vs*. $t^{1/2}$, for zero-

order, first-order, and Higuchi's model respectively. In these plots, m represents the cumulative percent of drug released at time t, and $m_o - m$ is the percentage of the drug remained after time t. For Korsmeyer-Peppas, the equation was:

$$M_t/M_\infty = kt^n \quad (1)$$

Where M_t/M_∞ is the fraction of the drug released after time t and n is a characteristic exponent for the release mechanism. Based on Korsmeyer-Peppas equation, values of the n exponent equal to or less than 0.5 were characteristic of Fickian or quasi-Fickian diffusion, whereas values in the range of 0.5 to 1 were an indication of an anomalous mechanism for drug release (*16*). On the other hand, a unity value for n would be expected for zero-order release. Models were evaluated using GraphPad Prism 5 software (GraphPad Software Inc., San Diego, CA, version 5.03) computer program.

2.4. *Evaluation of the optimized complex*

Since complex resulted from 1:6 drug to resin ratio experienced maximum drug loading, the drug-resinate were subjected to physicochemical characterization immediately after preparation by DSC, XRD, FTIR, and SEM. Evaluating molecular properties of drug-resinate complex and comparing them to the drug alone, the resin and their corresponding physical mixture was essential to reveal formation of complex. Furthermore, accelerated stability study was performed for the optimized complex in the dry state and in the prepared syrup for a period of six months. Gustatory test for the fresh suspension of the resinate complex in the prepared syrup was fulfilled.

2.4.1. *Differential scanning colorimetry*

Differential scanning colorimetry (DSC) was performed for the optimized complex using a Perkin-Elmer Differential Scanning Colorimeter model DSC-4 (New York, USA). It was calibrated with indium (99.99% purity, melting point 156.6°C). Eight mg samples of each of FAM, amberlite IRP-69, physical mixture and dry optimized complex were crimped in standard aluminum pans and heated from 30 to 350°C at a heating rate of 10°C/min under constant purging of dry nitrogen at 30 mL/min. An empty pan, sealed in the same way as the sample, was used as a reference.

2.4.2. *X-ray diffractometry*

X-ray diffraction patterns (XRD) of FAM, amberlite IRP-69, physical mixture of both and dry optimized complex were obtained using a Diano X-ray diffractometer equipped with Co Kα (USA). The tube operated at 45 kv, 9 mA.

2.4.3. *Fourier transform infrared spectroscopy*

Spectroscopic studies of FAM, amberlite IRP-69, their corresponding physical mixture and dry optimized drug-resinate complex were done by using Mattson 5000 FTIR Spectrophotometer (Madison Instruments, Middleton, Wisconsin, USA). KBr discs were prepared by means of hydrostatic press. The scanning range was 400 to 4,000 cm^{-1}.

2.4.4. *Scanning electron microscope*

The surface morphology of the samples was examined using scanning electron microscope (SEM) (JSM-6510LV, JEOL, Japan). The powders were fixed on a brass stub using double-sided adhesive tape and then made electrically conductive by coating, in a vacuum, with a thin layer of gold (approximately 150 Å) for 30 s.

2.4.5. *Accelerated stability studies of optimized complex*

Preparation of syrup The prepared syrup consisted of sucrose 54%, glycerin 5% and sorbitol 4% to retard crystallization of sucrose. The polyols were Generally Recognized as Safe (GRAS) and are listed in the Food and Drug Administration (FDA) (*17*). Benzalkonium chloride 0.01% was added as a preservative (*18*). This prepared syrup containing drug-resinate complex has a great advantage of having pH of about 6. At this pH value, the corresponding degradation rate of FAM was reported to be significantly decreased (*11*).

Accelerated stability study according to the ICH Accelerated stability study as mentioned in ICH guidelines was followed to evaluate physical changes and drug content of the optimized drug-resinate complex on storage (*19*). The stability study was performed for the complex in the dry state and in the prepared syrup dosage form. Dry resinate complex (137.07 ± 7.23 mg) containing the adult dose (20 mg) was either packed in glass bottles wrapped with aluminum foil, or suspended in 15 mL of the prepared syrup and then placed at ambient conditions (28 ± 2°C/40 ± 5% RH) for 6 months. Others for accelerated stability study were placed in humidity chamber at (40 ± 2°C/75 ± 5% RH) for the same period. Relative humidity (RH) was maintained at 75% using saturated solutions of sodium chloride. The RH (75% and 40%) were measured periodically. Drug content of the dry complex as well as the complex suspended in the prepared syrup was analyzed every three-month period as previously described and statistically analyzed.

Special stability experiment was performed monthly for the prepared syrup preparation. Sample of the supernatant was withdrawn, filtered through a Millipore filter (0.45 μm) and analyzed for drug released from the complex, if any. In addition, the pH change of the prepared syrup was monitored at the stipulated

times using digital pH-meter (Beckman Instruments Fullerton, CA 92634, Germany). Re-dispersibility of the prepared syrup preparation was also assessed monthly. The closed glass bottle was inverted through 180° and the number of inversions required for restoration was noted. If uniformity attained in one inversion, then it has 100% re-dispersibility. Every additional inversion decreases the % of ease of re-dispersibility by 5% (*20*).

2.4.6. *Gustatory sensation test*

Gustatory test reported by Mady *et al*. (*2*) for evaluating the taste masking ability of the ternary complexation of FAM was fulfilled for the fresh optimized drug-resinate complex suspension in the prepared syrup with slight modification. Twelve healthy human volunteers, of either sex; in the age group of 23-30 years were selected. The volunteers signed the protocol of the investigation before starting the study. This study was approved by the Scientific Research Ethical Committee at Faculty of Pharmacy, Mansoura University and all the procedures were performed under the terms and conditions of such committee.

Before testing, the volunteers (n = 12) were asked to retain the reference solution in their mouths for 10 s, and provide information on its bitterness intensity. Reference solution of the drug suspended in the prepared syrup was used (20 mg pure FAM suspended in 15 mL of the prepared syrup). The determination of the threshold was carried out as follows: immediately after the preparation, each volunteer held about 3 mL of the reference solution in their mouths for 10 s; the volunteers were then requested to recognize this taste and consider it as score 6. After expectoration, the bitterness value was recorded. A numerical scale was used with the following values: 0 = bitterless, 1 = very slightly bitter, 2 = slightly bitter, 3 = moderately bitter, 4 = moderate to strong bitter, 5 = strongly bitter, 6 = very strongly bitter.

Sample consisting of the optimized dry resinate complex (154.3 ± 4.92 mg) containing the adult dose (20 mg) and suspended in 15 mL of the prepared syrup. The volunteers were asked to repeat the same procedure as with the reference solution and to assign a bitterness score for it. The oral cavity was rinsed with distilled water three times to avoid bias. The wash out period between testing different samples was 10 min.

3. Results and Discussion

Taste is considered an important parameter in liquid dosage forms since the taste is perceived in mouth. IER works as a complexing agent and thus eliminates the bitter taste of drugs. For preparation of resinates, batch method was preferred because of its convenience. As the reaction is an equilibrium phenomenon, maximum efficiency in shorter time is best achieved in batch process. Also, higher swelling efficiency in batch process resulted in more surface area for ion exchange (*21*). The time to reach equilibrium for drug loading was found to be 24 h. The dissolved drug existed in the protonated ion could displace the hydrogen counter-ion (H^+) of the sulfonic acid functional group on the ion exchange resin, as depicted in the following equation:

$$Re–SO_3^-H^+ + FH^+ \rightarrow Re–SO_3^-FH^+ + H^+ \qquad (2) \quad (7)$$

Where Re is an insoluble portion of the resin and FH^+ is FAM ion.

3.1. *Characterization and optimization of the prepared complexes*

3.1.1. *Estimation of FAM content*

A linear increase in FAM loading has been recorded with increased resin ratio (Figure 1). The loading of the drug onto the resin was more than (80%) of the drug added for 1:6 drug to resin complex.

3.1.2. *In vitro drug release studies*

Figure 2 illustrates the *in vitro* release characteristics of FAM from different drug-resinate complexes in 0.1 N HCl. For the pure drug, the maximum percentage release reached 100% in 20 min as it is freely soluble in 0.1 N HCl. The existence of hydrogen ions in the dissolution medium (H^+) acted as a cationic counter-ion and could exchange for the drug in the resinate complex resulting in its liberation. About 60% of the drug was released from the complexes in about one and half h and near total in about 5 h. The sustained release property of strongly cationic exchange resin, with various drugs has been reported by Ngawhirunpat *et al*. (*22*). This technique may be of value for the

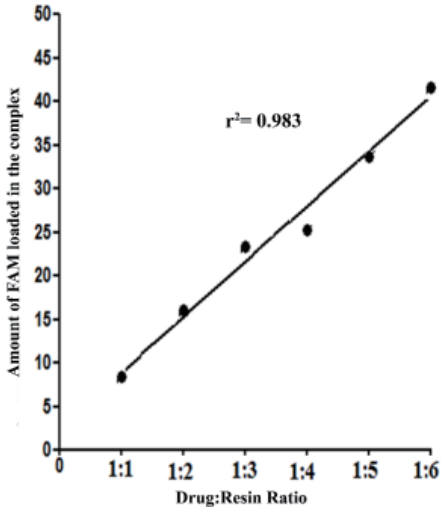

Figure 1. Effect of different drug: resin ratios (1:1 to 1:6) on the amount of FAM loaded in the complex.

pharmaceutical industries, especially in preparing palatable liquid dosage form of FAM with sustained release properties.

3.1.3. *Kinetic analysis of the drug release data*

The coefficient of determination of the drug release kinetics (r^2) and the exponent "n" for Korsmeyer-Peppas equation were presented in Table 1. The results revealed that there was a linear relationship between the percent drug released from all drug-resinate complexes and the square root of time indicating a typical release pattern according to Higuchi's equation. Mild deviation was noticed with 1:2 drug to resin complex but this will not influence the final conclusion. Since the exponent "n" values were found to be in the range of 0.2107-0.3675 for all the drug-resinate complexes, the result could be described as a quasi-Fickian diffusion mechanism (*23*). Untreated FAM showed a linear relationship between log percent of drug remaining to be released and time thus following first-order kinetics.

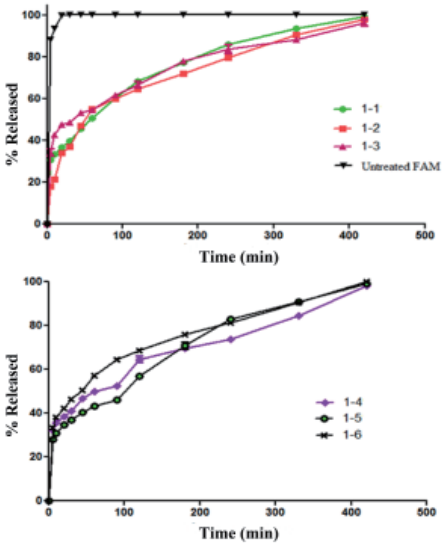

Figure 2. *In vitro* release profiles of untreated FAM and FAM from drug-resinate complexes prepared from different drug: resin ratios (1:1 to 1:6) in 0.1 N HCl. The values were the average of three determinations ± standard deviation (S.D.).

3.2. *Evaluation of the optimized complex*

Since complex resulted from 1:6 drug to resin ratio experienced maximum drug loading (Figure 1), the drug-resinate were subjected to physicochemical characterization immediately after preparation by DSC, XRD, FTIR, and SEM. Meanwhile, accelerated stability study was performed for the optimized complex in the dry state and in the prepared syrup. Gustatory test for the fresh suspension of the resinate complex in the prepared syrup was fulfilled.

3.2.1. *Differential scanning colorimetry (DSC)*

Figure 3 shows the DSC curves of FAM, resin, physical mixture and drug- resinate complex. FAM has an endothermic peak at 166.7°C, indicating the temperature of drug melting, whereas no peak over the range 150-350°C was observed in the DSC curves of the drug-resinate (Figure 3a and d). This indicates that the entrapped drug in the resinate changed from the crystalline to the amorphous state.

The thermal trace shown by the resin was characterized by a broad endothermic peak at 105.5°C as a result of the partial dehydration process of the resin (Figure 3b) (*24*). The thermogram of the physical mixture of both showed the same peaks of FAM and the resin indicating the absence of complexation among them on physical mixing (Figure 3c).

3.2.2. *X-ray diffractometry (XRD)*

The XRD patterns of the samples are shown in Figure 4. It appears that the molecular state of FAM is crystalline as it shows several sharp and narrow peaks between 10° and 40° (2Θ) with the maximum peak intensity at 2Θ = 23.973° (d = 3.70898 A°) (Figure 4a). The resin x-ray diffractogram displayed diffused peak due to their amorphous state (Figure 4b) (*24*).

It was noted that, FAM-resinate physical mixture diffractogram was simply the superimposed spectra of the two components, indicating that no complexation occurred upon physical mixing (Figure 4c). The complete disappearance of crystallinity in case of drug-resinate complex compared to the drug alone or its

Table 1. Kinetic analysis for the percentage drug released from FAM-resinate complexes*

Drug: resin ratio	Coefficient of determination "r^2"			Korsmeyer-Peppas		Main transport mechanism
	Zero-order	First-order	Higuchi model	r^2	n**	
Untreated FAM	0.9367	0.9595	0.9367	--------	--------	--------
1:1	0.9198	0.9066	0.9895	0.9652	0.2727	Fickian
1:2	0.8662	0.9170	0.9712	0.9818	0.3675	Fickian
1:3	0.9129	0.8961	0.9818	0.9692	0.2107	Fickian
1:4	0.9579	0.8128	0.9860	0.9523	0.2303	Fickian
1:5	0.9662	0.8475	0.9789	0.9265	0.2703	Fickian
1:6	0.9203	0.7170	0.9922	0.9847	0.2393	Fickian

* Analyzed by the regression coefficient method. ** Diffusional exponent indicative of the mechanism of drug release.

physical mixture, confirmed the complex formation between FAM and the resin (Figure 4d).

3.2.3. *Fourier transform infrared spectroscopy (FTIR)*

The FTIR spectroscopic analysis was performed to augment the results obtained from DSC and XRD (Figure 5). From (Figure 5a), the strong infrared shoulders at 3,505-3,237 cm^{-1} and 1,640-1,534 cm^{-1} region are assigned to the stretching and bending vibrations of NH_2 groups in both guanidine and sulfamoyl parts in FAM, respectively (*25*). The asymmetric and symmetric stretching modes of SO_2 group are generally assigned in 1,325 and 1,146 cm^{-1}, respectively.

The spectra of the physical mixture (Figure 5c) did not show any significant change in the position of the characteristic absorption bands. These spectra appeared to be consistent with that of FAM and the resin indicating that there was no appreciable interaction between the drug and resin in the physical mixture, which is in accordance with the results from DSC and XRD.

In the FTIR spectra of the resinate complex, however, the absorption bands at 3,505-3,237 cm^{-1} and 1,640-1,534 cm^{-1} region disappeared, probably owing to a restriction of the vibration related to complexation process (Figure 5d).

3.2.4. *Scanning electron microscope (SEM)*

The scanning electron photomicrographs for FAM, the resin, FAM/resin physical mixture and FAM-resinate complex were presented in Figure 6. It appeared that most of the drug crystals are elongated tabular form (Figure 6a), while amberlite resin is irregular in

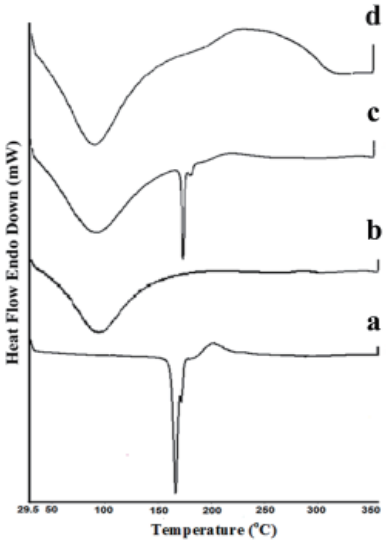

Figure 3. DSC of pure FAM (a), Amberlite IRP-69 resin (b), physical mixture of FAM and the resin (c) and optimized drug-resinate complex (d).

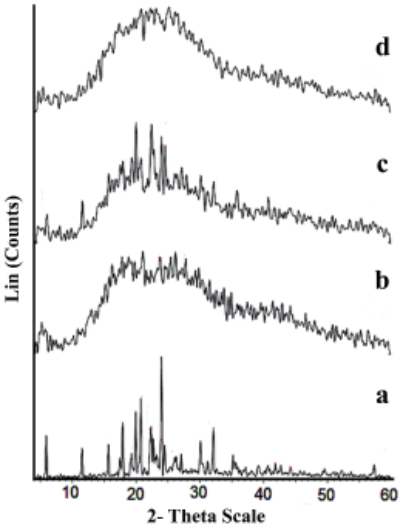

Figure 4. XRD diffractograms of pure FAM (a), Amberlite IRP-69 resin (b), physical mixture of FAM and the resin (c) and optimized drug-resinate complex (d).

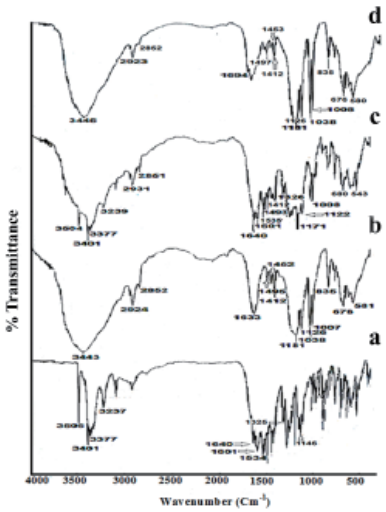

Figure 5. FTIR spectra of pure FAM (a), Amberlite IRP-69 resin (b), physical mixture of FAM and the resin (c) and optimized drug-resinate complex (d).

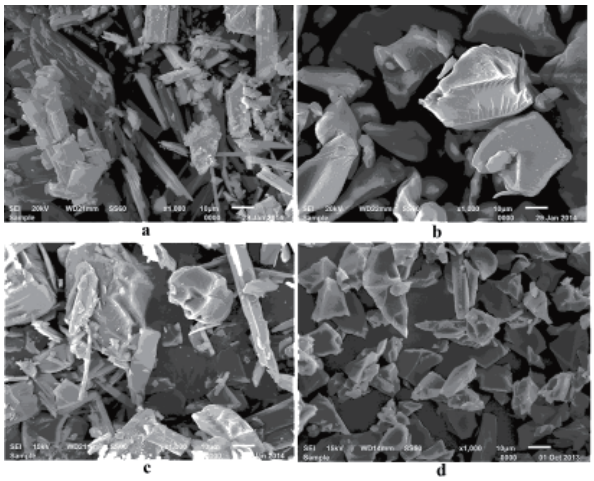

Figure 6. SEM ofpure FAM (a), Amberlite IRP-69 resin (b), physical mixture of FAM and the resin (c) and optimized drug-resinate complex (d).

shape and appears as separate pieces (Figure 6b) (*24*). Physical mixture was observed as a mixture of drug and the resin where it was easy to identify the individual component of FAM and resin (Figure 6c). Meanwhile, FAM-resinate looked different in appearance from the drug, the resin or their physical mixture. The features of drug crystals were not easily detectable indicating formation of a different compound (Figure 6d).

3.2.5. *Accelerated stability studies of optimized complex*

The stability study was performed for the complex in the dry state and in the prepared syrup dosage form. Both of them did not experience any physical changes at ambient and accelerated stability study conditions for a period of six months. The supernatant of the suspension was nearly free of the drug during the six months period stability study indicating absence of drug leaching into the vehicle after storage. This was assessed by UV scanning of the filtered syrup monthly at 263 nm, using prepared syrup without suspended complex as a blank (Figure 7). From Table 2 it may be concluded that no significant difference, ($p > 0.001$) by one- way analysis of variance (ANOVA) (Tukey's test), in drug content was experienced during storage at the two different temperatures.

Furthermore, the pH of the suspension in the prepared syrup originally equal 6 reached values of 5.76 and 4.93 at ambient and accelerated stability conditions, respectively. The number of inversions required to completely re-disperse the suspension ranged from 1-4 times along the stipulated intervals, indicating good re-dispersibility.

The drug-resinate complex prepared to achieve taste masking has the potential to affect the product performance beyond this objective, that is, stability during shelf-life, as well as in the stomach (*5*).

3.2.6. *Gustatory sensation test*

The results concerning the bitterness evaluation using consensual volunteers are listed in Table 3. The mean score of 0 for the sample indicated that the optimized complex resulting from 1:6 drug to resin ratio sufficiently alleviated the bitterness of FAM, compared with the reference solution containing the drug alone suspended in the prepared syrup. The complexation with the resin impeded the interaction of FAM with the taste buds. Similar masking effects of the bitter taste of cefetamet pivoxil hydrochloride (an oral third generation cephalosporin antibiotic) using amberlite IRP-69 and amberlite IRP-64 were obtained previously by Sateesha *et al*. (*26*).

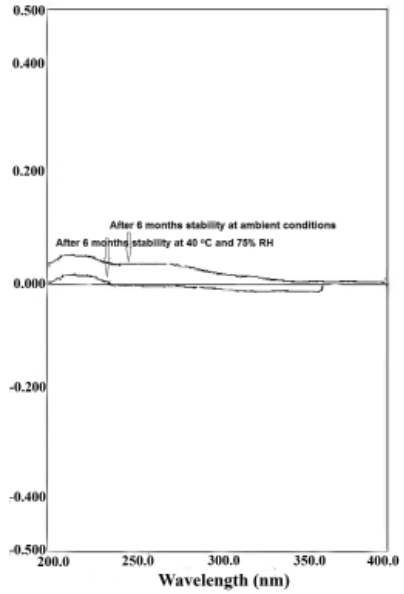

Figure 7. UV scan of the filtered syrup containing the suspended complex after six months of storage at ambient conditions and humidity chamber at (40 ± 2°C/ 75 ± 5% RH).

4. Conclusions

Famotidine has an extremely bitter taste and is unstable in acidic medium. A novel controlled release complex with amberlite resin was prepared. The complexation

Table 3. Bitterness score evaluation by a panelist of 12 human volunteers

Formulations	Number of volunteers rating the preparation as						
	0	1	2	3	4	5	6
Reference		7	2	3			
Sample	11	1					

Table 2. Stability studies of dry optimized FAM-resinate complex (1:6 drug to resin ratio) and suspended complex in the prepared syrup

Time	A- Dry complex		B- Suspended complex in prepared syrup	
	Drug content (mg)		Drug content (mg)	
	40 ± 2°C/75 ± 5% RH	28 ± 2°C/40 ± 5% RH	40 ± 2°C/75 ± 5% RH	28 ± 2°C/40 ± 5% RH
0 Months	20 ± 0.166 mg (100%)	20 ± 0.166 mg (100%)	20 ± 1.694 mg (100%)	20 ± 0.716 mg (100%)
3 Months	19.351 ± 0.251 mg (96.753%)	19.318 ± 0.426 mg (96.658%)	19.442 ± 0.579 mg (97.209%)	19.347 ± 0.532 mg (96.736%)
6 Months	18.989 ± 0.179 (94.947%)	19.070 ± 2.048 (95.342%)	19.298 ± 1.401 (96.488%)	18.898 ± 1.517 (94.493%)
p Value*	0.0013	0.6438	0.7624	0.4507

* Insignificant at $p > 0.001$.

with the resin impeded the interaction of famotidine with the taste buds and sustained its release in the acidic medium. Moreover, complexation was investigated using various physical characterization methods namely differential scanning colorimetry, x-ray diffractometry, Fourier transform infrared spectroscopy and scanning electron microscope. The complex in the dry state and in the prepared syrup dosage form complied with ICH guidelines for stability. Gustatory test on human for drug-resinate complex in the prepared syrup, as well, indicated that the preparation is palatable. Thus, the "patient friendly dosage form" of bitter drug, especially for pediatric, geriatric, bedridden, and non-cooperative patients, was successfully formulated using this technology.

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