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Research Article

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Fabrication of a Novel Device Containing Famotidine for Gastro Retentive Delivery Using Carbohydrate Polymers

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Abstract

The drug delivery systems that inflate in the gastric region are more appropriate for the local treatment of proximal parts of gastro intestinal tract (stomach and/or duodenum) and also drugs that are degraded in the colon, drugs with narrow absorption window and so on. The existing devices are compressible to a size suitable for swallowing and expandable to a size which will prevent passage through the pylorus. However, they put on certain trivial problems namely, composed of at least one insoluble/non-erodable synthetic polymer and one cellulosic polymer; don't explain the mechanism of disintegration or their exit from the stomach causing toxicity. Hence the present investigation was concentrated with an objective to develop a simple and novel device with carbohydrate polymers like gellan gum and guar gum containing famotidne a H_2 receptor antagonist. A simple film casting technique using a silicon mould was employed to fabricate the device. Sodium bicarbonate was added as gas generating agent to maintain buoyancy and to maintain microbial stability methyl paraben was also incorporated into the formulation. The developed devices were evaluated for mechanical and physicochemical properties before and after inserting into empty gelatin capsule. The thickness, diameter and weight were in the range of 1.2 ± 0.3 and 2.2 ± 0.8 mm, 2.2 ± 0.2 and 2.6 ± 0.5 cm, and 0.31 ± 0.06 gm and 0.404 ± 0.06 gm respectively. The devices took 20 ± 0.5 to 25 ± 2 min for self un-folding and become buoyant and the cumulative percent of drug released was in the range of 60.2 ± 5.1 to 98 ± 3.8, zero order drug release kinetics, anomalous non-fickian diffusion were observed and no drug excipient interactions were found. In conclusion the fabricated device was given a new sight in the development of FDDS (floating drug delivery systems) with natural polymers, fewer excipients and processing steps and shorter period of time.

Keywords: Guar gum; Gellan gum; Famotidine; Self unfolding; Inflatable

Introduction

The oral route is the preferred route for the administration of the therapeutic agents mainly due to the following reasons: ease of administration, patient compliance and cost effectiveness [1]. Among the orally administered dosage forms, gastro retentive delivery systems have long been recognized for the controlled/ or sustained release of a drug(s) over an extended period of time in the gastric region. These dosage forms are suitable for local action in the proximal parts (stomach and duodenum) of gastro intestinal tract (GRT), drugs that degrade in colon, drugs with narrow absorption window and drugs which are poorly soluble in alkaline pH. However, gastric emptying of dosage forms is an extremely variable process, and the ability to prolong and control emptying time is a valuable asset for dosage forms that reside in the stomach for a longer period of time than conventional dosage forms. Several challenges have been faced in designing controlled release systems for better absorption and enhanced bioavailability [2,3] e.g., the inability to confine the dosage form in the desired area of the gastrointestinal tract being one such challenge. Among the gastro retentive systems, floating drug delivery systems (FDDS) have gained much importance in recent years due to the fact that they enhances the gastric residence time without affecting the intrinsic rate of gastric emptying. However, they put on certain trivial problems namely, composed of at least one insoluble/non-erodable synthetic polymer and one cellulosic polymer; don't explain the mechanism of disintegration [4-7] and also their unpredictable and unreliable exit [5] from the stomach cause serious bioavailability, local irritation and toxicity problems. Hence the present investigation was concentrated to fabricate a simple and novel device with carbohydrate polymers like gellan gum and guar gum [8,9]. It is hypothesized that the selected gums are of natural origin, hydrophilic, swellable, biodegrable and hence non toxic. Hence, being hydrogels, they imbibe water, and expand to a predictable size, swell and form into a matrix and hence release the entrapped drug slowly for a specified period of time. Peptic ulcers are defects in the gastrointestinal mucosa that extend through the muscularis mucosa [10,11]. They persist due to the acidic or peptic activity of gastric juice. In a particular study, it was reported that peptic ulcer is an important cause of morbidity, and health care costs were estimated to be 5.65 billion dollars per year in the United States [12]. Hence for the present investigation famotidine a H2 receptor antagonist widely prescribed in gastric ulcers, duodenal ulcers and gastro esophageal reflux diseases was selected as a model drug. It is also effective in the treatment of peptic ulcers in patients with arthritis and those who are on long- term NSAIDs. The primary objective of the present work was to develop a formula for fabricating in to a single unit with multi layered drug-containing scaffolds that can self-unfolded, float in the stomach and release the drug over a predictable time, using carbohydrate polymers such as guar gum and gellan gum. The secondary objective was to evaluate the devices for various physicochemical properties such as swelling index, floating lag time, floating time, drug content, drug release and so on.

Materials and Methods

Materials

Famotidine was procured as a gift sample from Natco Lab Ltd, Hyderabad, India. Empty gelatin capsules were purchased from Akhil health care private limited, vadodara, India. $HPMCK_{15}$ was purchased from NSB pharmaceuticals, Vijayawada, Andhra Pradesh, India. Guar gum and gellan gums were received from Nishka labs Pvt. Ltd, Hyderabad, India as gift samples. Castor oil and methyl paraben were purchased from Sri Maha lakshmi oil and mill, Hyderabad, India, and

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Molychem, Mumbai, India, respectively.

Methods

Preparation of standard calibration curve of famotidine by UV spectroscopy: A reported UV-Visible spectroscopic method [13] for the estimation of famotidine was established in 0.1 N hydrochloric acid buffer, at λ_{max} 260 nm and calibration curve was constructed using Elico SL 210 double beam spectrophotometer.

Formulation and fabrication of scaffolds

Method 1: The device was fabricated using the film casting technique in three steps. Initially polymer solution was prepared by using two carbohydrate polymers (gellan gum and guar gum) in different ratios and concentrations. In the first step to the polymer solution plasticizer and preservative were added and mixed thoroughly with the help of a magnetic stirrer and sonicated for 5 minutes using an ultra bath sonicator to remove entrapped air. Then the polymer solution was divided into two equal parts. The first half of the solution was casted as film layer A on a silicone mould of 2.5cm diameter and kept in a hot air oven at 50°C for a period of 40 min. In the second step over the surface of the partially dried film layer A, a mixture of a unit dose of drug, matrix forming polymer and weighed quantity of gas generating agent (sodium bi carbonate) was kept in the center and then the second half of polymer solution was poured over this mixture covering the entire film layer A, to fabricate the scaffold. Then the mould was kept in the hot air oven at 50°C till the device dried. The dried fabricated device was folded and inserted into a 000 size capsule and preserved until analysis. The compositions of devices are given in Table 1. Silicone mould and photographs representing the method of preparation were showed in Figures 1 and 2.

Method 2: In this method a unit dose of drug was dispersed into polymer solution along with other excipients and a gas generating agent was placed in the center of the device. The compositions of devices are given in Table 1.

Evaluation of the devices

Weight variation, thickness and diameter of the devices: Three devices (n=3) were fabricated for each composition and the total weight of each device was determined using digital balance and the average weight was calculated. Average thickness and diameter were measured using a vernier calipers and a scale, respectively.

***In vitro* buoyancy studies**: The device was enclosed in a hard gelatin capsule and placed in 900 ml of 0.1 N hydrochloric acid buffer. The overall time taken for the device to release from the capsule, to self-unfold and to float was noted, and is referred to as the floating lag time. The floating duration was also measured simultaneously by visual observation during dissolution studies [14].

Determination of swelling index: Swelling index (SI) describes swelling behavior of the device in vivo and measured in terms of weight gain when it is placed the dissolution medium. In order to measure the SI, the device was kept in a beaker containing 100 ml of 0.1 N hydrochloric acid buffer at room temperature. The device was taken out at predetermined time intervals such as 1, 2, 4, 6 and 8 hrs, blotted with tissue paper to remove the adhering excess moisture and weight was determined [15]. The procedure was repeated thrice for each composition and average increase in weight was calculated. The SI was calculated from this data using the following equation:

$$SI = \frac{(\text{Weight of device at each time interval} - \text{initial weight of the device})}{\text{initial weight of the device}} \times 100$$

Determination of tensile strength: Tensile strength gives the information about the deformity of materials. The maximum stress required to break the film is known as tensile strength [16]. Tensile strength was determined by using a tensile strength apparatus. The initial length of the device was measured using a scale, and weight was gradually increased, and the corresponding increase in length was measured. This was repeated so as to increase the pulling force until the device broke. Percentage elongation was calculated and plotted against stress in pounds per square inch. From the graph, tensile strength was measured.

Drug content: The device cut into small portions and transferred to a volumetric flask containing methanol, shaken for few minutes and sonicated for 10 minutes using an ultrasonic bath sonicator to extract the drug completely. Then the solution was filtered using Whatmann filter paper, appropriate dilutions were made with methanol, and the absorbance was measured using a UV-Visible spectrophotometer.

***In vitro* dissolution studies:** *In vitro* drug dissolution characteristics were determined by performing *in vitro* dissolution studies in 0.1N hydrochloric acid buffer, at 37°C, 50 rpm using USP dissolution apparatus type II [Labindia dissolution tester DISSO 2000]. At periodical time intervals, the samples were withdrawn by replacing with equal volume of fresh dissolution medium in order to maintain sink conditions. The drug content in the samples was analyzed using the above described spectro photometric method and cumulative percent drug released was calculated.

Drug release kinetics: The *in vitro* drug dissolution data was fit into various mathematical models like zero order, first order, Higuchi and peppas models, and the rate of drug release and mechanism of drug release were determined [17].

Zero order drug release rate is independent of concentration of

S.NO	Name of the Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
1	Famotidine (mg)	40	40	40	40	40	40	40	40
2	Guar gum (mg)	150	200	225	225	100	133.2	150	200
3	Gellan gum (mg)	150	100	75	75	100	66.6	150	100
4	Castor oil (ml)	5	5	5	5	5	5	5	5
5	$NaHCO_3$ (mg)	10	10	10	10	10	10	10	10
6	$HPMCK_{15}$ (mg)	20	20	20	30	-	-	-	-
7	Methyl Paraben (mg)	15	15	15	15	15	15	15	15
	Total weight (mg)	390	390	390	400	270	269.8	370	370

Table 1: Composition of the self-unfolding floatable scaffolds.

Figure 1: Silicone mould used for the fabrication of the device.

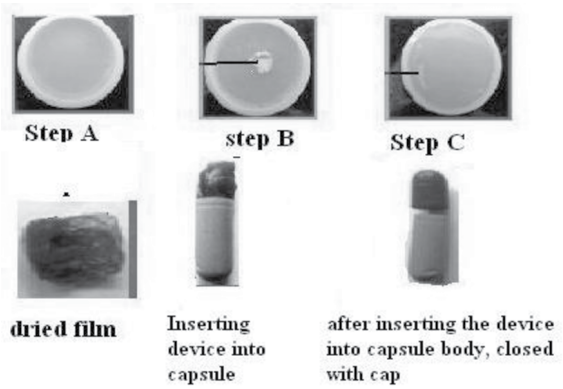


Figure 2: Preparation of formulation.

drug present in the device and it is mathematically represented as

$$Q_t = Q_0 + K_0 t$$

Where, Q_t = amount of drug dissolved in time "t"

Q_0 = initial amount of drug in the solution

K_0 = Zero order release constant

First order kinetics describes the drug release rate from the dosage forms is concentration dependent.

$$\text{Log } Q_t = \text{Log } Q_0 - Kt/2.303$$

Where, Q_t = amount of drug release in time "t"

Q_0 = initial amount of drug in the solution

Higuchi and Korsemeyer–Peppas power law equations explain the mechanism of drug release patterns from the dosage forms and mathematically they are represented as

$F_t = K^*\sqrt{t}$ and $M_t / M_\infty = k^*t^n$ respectively.

Where F_t = fraction of drug released at time t

K = release rate constant

$\sqrt{t}$ = square root time

M_t = amount released at time 't'

M_∞ = amount released at infinite time

n= release rate exponent

Drug-excipient compatibility studies

Differential scanning calorimetry (DSC): The test was carried out beyond the melting point of the pure materials and their mixtures. Any change in the thermograms of mixtures of drug and carrier compared to pure material thermo grams indicates incompatibility. The DSC thermogram of famotidine was run in the range of 0-400^{0}c under a controlled nitrogen purged environment and the thermograms of pure drugs and optimized composition were recorded using METTLER with STAR SW 9.01 software.

Fourier Transform Infrared Spectroscopy (FTIR): FTIR Spectrometry was found to be most reliable technique for predicting the possible interaction between the drug and excipient. The spectra were recorded for famotidine (pure drug) and for optimized formula using FTIR (bruker), model 10048657 Alpha T AT-001opus software. The samples were scanned from 1000 to 3500 cm^{-1} and the obtained spectra were evaluated for drug excipient interactions.

Results and Discussion

Gastro retentive drug delivery devices consisting of famotidine were fabricated and evaluated. The most commonly employed analytical technique in pharmaceutical field is UV-Visible spectrophotometry. It involves the measurement of absorption of ultraviolet or visible radiation by a substance present in solution. The median concentration was scanned using a UV-Visible spectrophotometer, and λ_{max} was determined at 260 nm. The absorbencies were measured for all the working standards at the $\lambda_{max,}$ and the calibration curve was constructed by plotting concentration *vs* absorbencies. Standard graph was plotted with concentration on the X-axis and absorbancies on the Y-axis. The linear regression coefficient was found to be 0.999. The limit of detection and limit of quantification were calculated as 0.634 and 1.92 µg/ml respectively.

Formulation and fabrication of scaffolds

For the present investigation two polymers guar gum and gellan gum were selected, as these polymers are non-synthetic and non-toxic. Guar gum is a natural polysaccharide made from kernel seeds of the guar plant Cyamopsis tetragonoloba and extensively investigated for biomedical applications as polymer for matrix dosage forms [18]. Gellan gum is produced through fermentation of various carbohydrates by Sphingomonas elodea. It is used as a thickening agent in various food products such as confectionaries, dairy products and jelly desserts. Recently it has been explored in the preparation of pharmaceutical formulations such as oral soluble films. Gellan gum has good film forming properties and guar gum has drug release retarding properties. Hence, a combination of these polymers has been used for fabrication of devices. But these polymers are of natural origin and may be prone to bacterial growth. Therefore, to enhance the stability against microorganisms, methyl paraben was used as a preservative. The films were fabricated in three steps by the film casting technique using silicone mold. Silicone moulds are stable at higher temperatures, inert, and polymers will not stick to the surface of these moulds. Initially the devices were fabricated using Method1in which a mixture of HPMCK 15, drug and gas generating agent were mixed and sandwiched between two polymer layers that acts as a drug reservoir. In this approach, the fabricated devices were thick at the center, which makes it difficult to insert into the gelatin capsule. Therefore, second approach was considered. In this approach

the devices prepared were thin and could be easily inserted into the capsule as the drug was uniformly distributed in the polymer matrix. Hence Method 2 was chosen and formulation was optimized for the fabrication of these devices.

Evaluation of fabricated devices

The fabricated devices were evaluated for various physicochemical properties, and the results shown in Table 2. The weight and thickness of the device were increased with increase in the concentration of the polymer. The diameter and floating lag time were relatively similar in all the devices. The floating duration was observed to be more than 12 hours in all formulations. Each formulation was assayed for drug content and content uniformity in triplicate spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The results are shown in Table 2.

Tensile strength

Mechanical strength is very important for any pharmaceutical dosage forms to withstand the mechanical rigors that occur during the processing and transportation. Tensile strength determines the mechanical and elastic properties of the devices. The tensile strength varied between 0.17 P/SI and 0.36 P/SI [19]. Therefore, it was confirmed that the fabricated devices were flexible enough and processable to insert in to the capsule.

Swelling index

Drug release from device depends on its swellability [20]. Therefore the hydration ratios of all the prepared formulations were determined and shown in Figure 3. The formulation F5 had shown better hydration ratio than other formulations. Thickness of the device also affects the hydration ratio of the film. With an increase in the thickness of the film, the time taken to complete hydration also increases, and so decrease in film thickness immediately leads to complete hydration of the film within seconds.

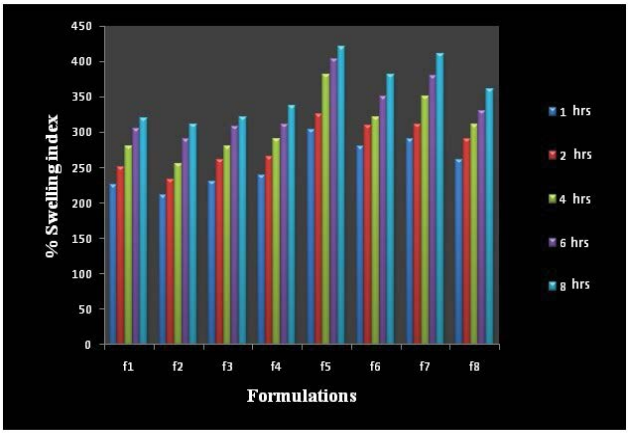


Figure 3: Swelling behavior of Famotidine self unfolding floatable scaffolds.

In vitro dissolution studies

In vitro dissolution studies were carried out for all the formulations and the results were showed in Figure 2. Cumulative percent drug released varied between 60.2 ± 5.1 and 98 ± 3.8. It was observed that with increasing guar gum concentration the cumulative percent drug released was decreased. During the dissolution process, as the dosage form was not disintegrated and the shape of the device was not altered it was assumed that the area was not changed. Therefore the rate of drug release was constant and no equilibrium conditions were obtained. This was confirmed by zero order plots. From all the devices, the rate of drug release followed zero order kinetics and is indicated by the regression coefficient. The drug release also followed Higuchi model confirming that during the process of dissolution the devices did not undergo any significant alteration in their surface and the shape of the device and this may be due to the presence of guar gum in the formulations. It is reported that guar gum formulations are not affected by stirring speed during the process of dissolution [21]. According to Peppas plot it is confirmed that from formulations F1, F4, F5, F6 and F8 the drug was released by Fickian diffusion as the 'n' values for all the formulations were between 0.298 and 0.440, but the formulations F2, F3 and F7 showed non – Fickian anomalous diffusion as 'n' values were greater than 0.5 but less than 1. It was also confirmed that drug release was concentration independent. Based on *in vitro* drug release studies, it was confirmed that the rate of drug release followed zero order kinetics; drug release was prolonged over a period of 12 hours, predictable and constant. The data is depicted in Figure 4.

Drug- excipient compatibility

The DSC thermo grams and FTIR spectra of pure drug famotidine and optimized composition are given in Figures 5, 6 and 7. The DSC thermogram of famotidine was run in the range of 0-40°C. The endothermic peak (melting point) was obtained at 164°C and the exothermic peak was obtained at 210°C. The formulation showed retention at this point of famotidine. The melting point of the famotidine did not change after fabrication of the film and no characteristic exothermic peaks were observed in DSC thermograms**.** The FTIR spectra showed characteristic peaks at 1602.24, 1288.87, 3331.61, 1165.97, 3236.87 due to C=N, S=O, N-H, C-N and C-H functional groups. The fabricated self-unfolding and float able scaffolds of famotidine clearly showed the retention of these

Code/physical property	Weight of the device (g)	Diameter of the device (cm)	Thickness (mm)	Floating lag time (min)	Percent drug content
F1	0.390 ± 0.06	2.46 ± 0.4	1.9 ± 0.5	23 ± 2	87.2 ± 4.8
F2	0.389 ± 0.07	2.5 ± 0.3	1.89 ± 0.6	24 ± 1	89.6 ± 3.4
F3	0.404 ± 0.06	2.52 ± 0.5	2.2 ± 0.8	23 ± 3	88.9 ± 4.5
F4	0.372 ± 0.04	2.5 ± 0.4	1.79 ± 0.4	25 ± 2	91.2 ± 2.5
F5	0.315 ± 0.05	2.4 ± 0.6	1.2 ± 0.3	20 ± 0.5	99.76 ± 2.3
F6	0.34 ± 0.07	2.2 ± 0.4	1.7 ± 0.4	21 ± 1	98.68 ± 3.1
F7	0.31 ± 0.06	2.4 ± 0.2	1.2 ± 0.5	23 ± 2	96.6 ± 4.7
F8	0.34 ± 0.2	2.2 ± 0.2	1.7 ± 0.4	22 ± 3	80.2 ± 5.6

Table 2: Physical and chemical properties of famotidine self unfolding floatable devices (n=3 ± SD).

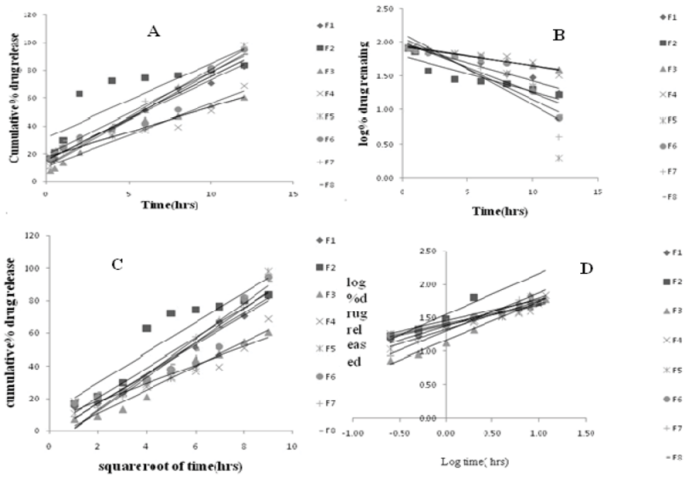


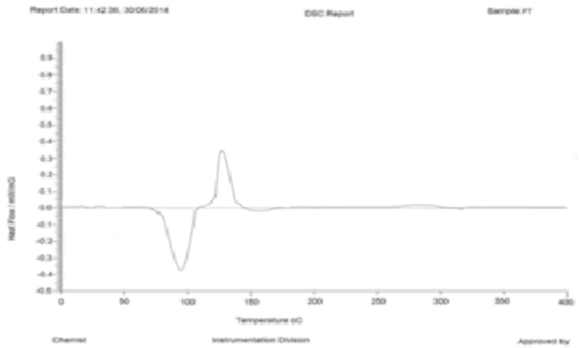
Figure 4: Dissolution profiles of famotidine from the device in 0.1 N HCl (n=3 ± SD).

A. Cumulative percent drug released *vs* time

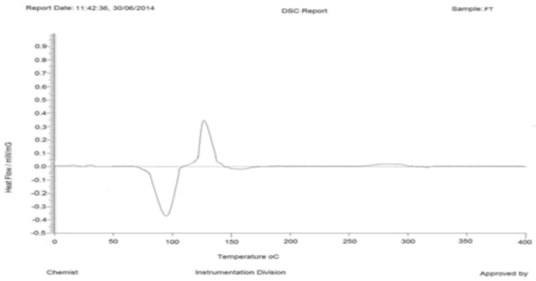
B. Log percent drug remaining to be released *vs* time

C. Higuchi plot of *in vitro* drug release data

D. Peppas plot of *in vitro* drug release data



A. Pure drug famotidine



optimized formula

Figure 5: DSC thermograph.

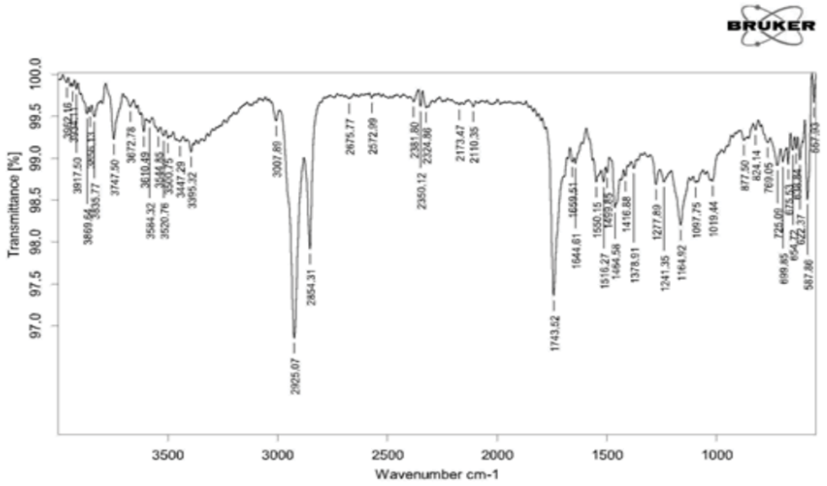


Figure 6: FTIR spectra of pure drug famotidine.

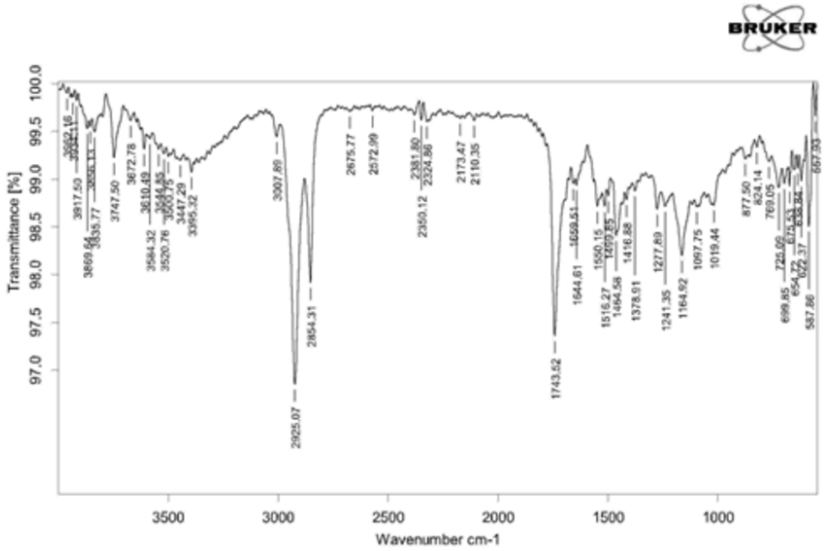


Figure 7: FTIR spectra of optimized formula.

characteristic peaks of famotidine. Thus from FTIR and DSC studies it was confirmed that there was no drug excipient interaction.

Conclusions

The present investigation was carried out systematically to formulate and fabricate multi layer scaffolds of famotidine using gellan gum and guar gum to increase bioavailability and to avoid local irritation and toxicity problems. The composition F_5 was considered as optimized formulation as it showed good drug loading efficiency, better drug release profiles, tensile strength etc. After fitting the data into various mathematical models, zero order drug release rate and diffusion controlled release mechanisms were observed. FTIR and DSC studies showed the absence of drug and excipient interactions.

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