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# DEVELOPMENT AND OPTIMIZATION OF POLYMERIC GASTRORETENTIVE MICROSPHERES OF FAMOTIDINE WITH NATURAL BIOENHANCERS

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**Abstract:**

***Aim:*** *The aim of present work was to develop microspheres of Famotidine using natural bioenhancers to achieve sustained action for treatment of Peptic ulcer.*

***Method:*** *Ionotropic gelation method was used for the development of microspheres. During preliminary trials, optimum concentration of all the ingredients were selected through entrapment efficiency, dissolution studies method. An optimized formulation was prepared and evaluated for mean particle size, percentage buoyancy, dissolution studies, micromeritic studies. Microscopic characteristics of the optimized formulation were studied using Scanning electron microscopy. Stability studies and releae kinetics were studied for the optimized formulation.*

***Result:*** *After preliminary trials, F5, F9, F11 and F13 were selected on the basis of entrapment efficiency and dissolution studies and their concentrations were utilised for preparing optimized formulation. Optimized Formulation of famotidine containing bio enhancers showed excellent floatability, good buoyancy, better micromeritics properties and increment in drug release. It was observed that release follows first order kinetics and good stability was observed for 2 months during stability studies.*

***Conclusion:*** *Current results indicate a promising approach of Famotidine microspheres, as an alternative for treating Peptic ulcer.*

**Keywords:** *Famotidone, Bioenhancers, Dissolution studies, Microspheres, Peptic ulcer*

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## INTRODUCTION:

Controlled release drug delivery systems provide a uniform drug concentration at the target tissue and thus after absorption allow maintenance of plasma concentration within a therapeutic range which reduces the frequency of administration and also minimizes side effects and may improve the therapy of peptic ulcer. Peptic ulcer is an upper gastrointestinal disorder occurring due to excessive acid and pepsin secretion from the parietal cells. Gastric ulcer occurs due to hydrolytic and proteolytic digestion of gastric mucosa. Furthermore, it has been evidenced that there lies an imbalance between aggressive factors like, pepsin, Non-steroidal Anti-inflammatory Drugs (NSAIDS), etc. and various protective factors like Prostaglandins (PG), mucus, bicarbonate and blood flow to mucosa. Inhibition of Prostaglandins synthesis leads to decrease in mucus secretion which further protect gastric mucosa by acid and pepsin secretion leading to formation of gastric ulcers [8-13]. The multiple-unit (microspheres) floating drug delivery system has been designed to develop a reliable formulation which is devoid of all the disadvantages of single unit systems which includes release all or nothing during emptying process. On the other hand, multiple unit dosage system pass through Gastro-intestinal tract to avoid vagaries of gastric emptying and release the drug more uniformly leading to less local irritation, reduced intersubjective variability, low probability of dose dumping, site specific targeting increased absorption and bioavailability [1-7]. Bioavailabilty can be increased by adding bioenhancers, which themselves do not show typical drug activity but when used in combination with a drug molecule, they enhance its activity by increasing bioavailability or any other mechanism. They are also termed as absorption enhancers and act as functional excipients included in the formulation to increase absorption of drugs. Some examples are quercetin and kaempferol. Quercetin has shown to increase bioavailability, blood levels and efficacy of number of drugs including dilitiazem, digoxin and epigallocatechingallate. Dose dependent Kaempferol may also increase the bioavailability of etoposide [14][15]. The floating drug delivery system which results in delayed gastric emptying has several advantages. Drugs that have absorption window and also which is a reason for poor bioavailability can be delivered effectively. Treatment of all types of stomach and duodenal cancers can be done by buoyant formulation strategy. The floating strategy can also be beneficial in the development of various reflux formulations. Exploration of narrow spectrum antibodies using microspheres technique for the eradication of Helicobacter pylori was popularly accepted.

Therefore, the aim of this research work was to screen natural bio enhancers to enhance the activity of famotidine and develop microspheres for better gastro retention to achieve sustained action for the treatment of peptic ulcer, further optimized.

## MATERIALS AND METHODS:

Famotidine was obtained as a gift sample from Belco Pharmaceutical pvt. Ltd., Bahadurgarh, Harayana. All the other raw materials were of analytical grade and of high purity, purchased from local source. Instruments were validated and laboratory conditions were well maintained throughout the entire procedure.

Preformulation studies were done which involves solubility studies [16], physical compatibility as well as chemical compatibility studies [17]. The main excipients involved in preparation of microspheres include polymer, gas generating agent and bioenhancers. Sodium alginate was selected as polymer and calcium carbonate as a gas generating agent. However, the selection of bioenhancers is mainly done on the basis of their drug release enhancing property [18][19].

Ionotropic gelation method was used for the formulation of microspheres. Famotidine (200mg) was accurately weighed and made solubilized in water and dispersed in a solution containing sodium alginate, calcium carbonate (gas forming agent), Quercetin and kaempferol. The resulting solution was dropped through a needle into 100 ml of solution containing calcium chloride (gelling agent) with acetone and glutaraldehyde. The beads were allowed to remain in the solution for half an hour to improve their mechanical strength. On expiration of this period the solution of gelling agent was decanted and beads were filtered and washed with deionized water. The beads were there after dried in hot air oven at a temperature of 60ºC.

In preliminary trials, Formulations were formed with different excipients with varying concentrations. In formulation (F1-F5), varying concentrations of Sodium alginate were used with equiproportions of Calcium chloride (5%) and Famotidine (200 mg) as shown in Table 1. The effect of amount of Sodium Alginate on the entrapment efficiency and particle size of microspheres was evaluated [20].

**Table 1: Amount of polymer (Sodium alginate) in Formulation (F1-F5)**

| Sodium alginate concentration(mg) | Calcium chloride (%) | Famotidine(mg) |
|---|---|---|
| F1(200) | 5 | 200 |
| F2(400) | 5 | 200 |
| F3(600) | 5 | 200 |
| F4(800) | 5 | 200 |
| F5(1000) | 5 | 200 |

**Table 2: Amount of various ingredients in formulation (F6-F13)**

| Ingredients | Formulations | Calciumchloride (%) | Sodium alginate(gm) | Famotidine(mg) |
|---|---|---|---|---|
| **Calcium carbonate : Sodium alginate** | F6(0:1) | 5 | 1 | 200 |
| | F7(0.5:1) | 5 | 1 | 200 |
| | F8(0.75:1) | 5 | 1 | 200 |
| | F9(1:1) | 5 | 1 | 200 |
| **Quercetin (mg)** | F10(5) | 5 | 1 | 200 |
| | F11(10) | 5 | 1 | 200 |
| **Kaempferol (mg)** | F12(1) | 5 | 1 | 200 |
| | F13(2) | 5 | 1 | 200 |

In formulation (F6-F9), Calcium carbonate is mixed with sodium alginate at different ratios as shown in Table 2. A 'bio enhancer' is an agent which enhances the bioavailability and bio efficacy of a drug with which it is combined without any pharmacological activity of its own at the dose used such as Quercetin and Kaempferol. Quercetin has shown to increase bioavailability, blood levels and efficacy of number of drugs including dilitiazem, digoxin and epigallocatechingallate. Dose dependent Kaempferol may also increase the bioavailability of etoposide. In formulation (F10-F11), quercetin was added with 5 mg as well as 10 mg. Dose dependent Kaempferol may also increase the bioavailability of etoposide. In formulation (F12-F13), kaemferol was added at concentrations of 1 mg and 2 mg, as shown in Table 2. In all these formulations, equiproportions of Calcium chloride (5%) and famotidine (200 mg) were also added [21].

**Evaluation of formulation trials**

Evaluation of formulation trials were done by determining mean particle size [22], Entrapment efficiency [23][24], as well as Dissolution studies [25]. The particle size of bio enhancers loaded famotidine microspheres was measured by optical microscope and the mean size of particles was calculated using a calibrated ocular micrometer. To determine the entrapment efficiency 25 mg of microspheres were weighed and thoroughly triturated and dissolved in 25 ml of 0.1N HCL. This mixture was centrifuged at 4200 rpm for 30 minutes, filtered and analyzed spectrophotometrically 265nm against buffer as blank. The in-vitro release studies of drug loaded microspheres were carried out at 37ºC using pH 1.2 0.1 N HCL. Using Dialysis Sac method, 25 mg of microspheres were weighed and added to conical flask containing 50 ml of 0.1N HCL and kept on a magnetic stirrer at 50rpm. The samples were withdrawn at regular time intervals for 12hrs from the dissolution medium and analyzed at 265nm by using UV-spectrophotometer.

**Preparation and Characterization of optimized formulation**

From the above preliminary trials, optimum concentrations of all the excipients were selected and used for preparing an optimum formulation. After preparation of optimized formulation, characterization or evaluation of optimized formulation was done through various parameters.

**Mean particle size:** The particle size of bio enhancers loaded famotidine microspheres was measured by optical microscope and the mean size

of particles was calculated using a calibrated ocular micrometer [25][26].

**Percentage buoyancy**

The floating test was carried out to investigate the floatability of famotidine microspheres. To access the floating properties, few milligrams of microspheres were placed in 0.1N HCL containing 0.02% Tween 80 surfactant to simulate gastric conditions. The mixture was stirred at 100 rpm on a magnetic stirrer. After 12 hours, the layer of buoyant microspheres was pipetted out and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both the types were dried in hot air oven at 65 until constant weight. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles. Despite the solution being stirred for 12h, the hollow microspheres still floated indicating that the microspheres exhibit an excellent buoyancy effect [24][25].

**Micromeritic properties**

The microspheres were characterized by their micromeritic properties such as \particle size, tapped density, compressibility index, true density and flow property [26][27][28][29].

**Dissolution studies**

The in-vitro release studies of drug loaded microspheres were carried out at 37ºC using pH 1.2 0.1 N HCL. Using Dialysis Sac method, 25 mg of microspheres were weighed and added to conical flask containing 50 ml of 0.1N HCL and kept on a magnetic stirrer at 50rpm. The samples were withdrawn at regular time intervals for 12hrs from the dissolution medium and analyzed at 265nm by using UV-spectrophotometer. Equal volume of the dissolution medium was replaced in the vessel after each withdrawal to maintain sink conditions [26].

**Scanning Electron Microscopy**

The shape and surface characteristics of the optimized formulation was determined by Scanning electron microscope. Samples of microspheres were dusted onto a double adhesive tape. Afterwards the stub containing the sample was coated with gold using a cool sputter coater (Polaron SC 7640) to neutralize electrons and to obtain a clear morphology of the microspheres. Photomicrographs were taken at an accelerated voltage of 20Kv and chamber pressure of 0.6mm Hg [30].

**Release kinetics**

To analyze the mechanism of drug release and release rate kinetics from the dosage form, the data obtained were fitted to Zero order, First order, Higuchi release and Korsmeyer- Peppas release model as shown in Table 3 [31][32].

**Table 3: Drug release mechanisms**

| Drug transport Release exponent (n) | Drug transport mechanism |
|---|---|
| 0.45 | Fickian diffusion |
| 0.45<n<0.89 | Anamolous transport |
| 0.89 | Case-II transport |
| Higher than 0.89 | Super case- II transport |

**Stability studies**

Optimized (Fopt) formulation was stored at different temperatures for 2 months. Then the colour, physical stability and concentration of famotidine were investigated. For the estimation of drug content, UV spectrophotometer is used. Accelerated studies were done by subjecting samples to 25±2ºC/65±5%RH and 40±2ºC/75±5%RH respectively for 2 months. At the end of 0, 7, 15, 30 & 60 days samples were withdrawn and diluted with 0.1N HCL and analyzed with UV spectrophotometer [26][33].

## RESULTS:

The solubility study of the drug was carried in various different solvents using “Shake flask method. The solubility of famotidine was determined as 2.38 g/ml in water and 29.71 g/ml in 0.1 N HCL. There was no change observed in physical characteristics of samples containing drug, alone and in combination with sodium alginate in any ratio during the study when exposed to 40oC/75%RH and 25oC/60% RH (i.e. normal and accelerated conditions as per ICH guidelines). Therefore, the excipients were considered suitable on preliminary basis.

From the DSC thermogram of physical mixture of drug and excipients, peaks corresponding to the melting endotherm of pure famotidine were shown in Figure 1. There was no significant change in the melting point of the drug when compared against pure drug as well as there was no appreciable peak observed. This indicated that there is no interaction between the drug and the excipients. In other words, drug and excipients were said to be compatible.

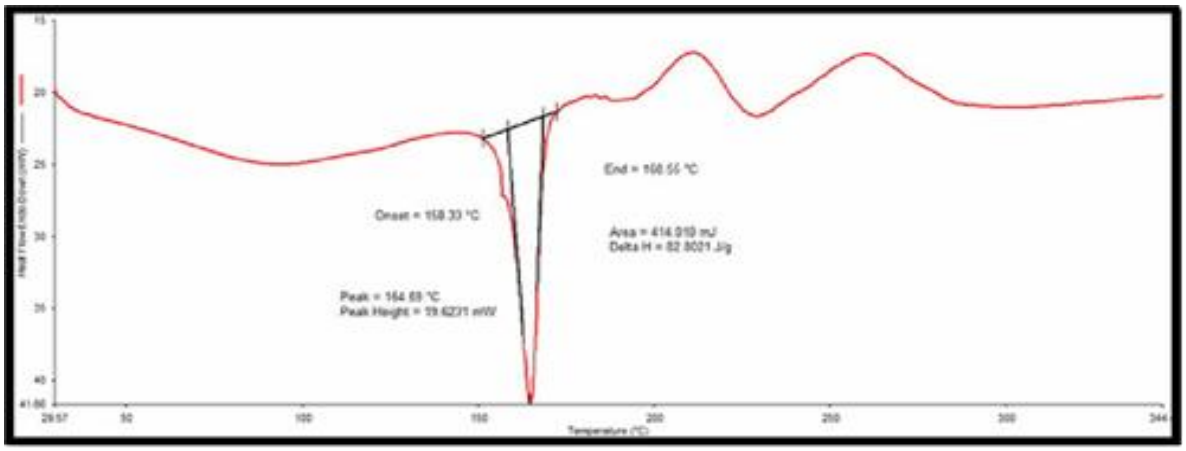
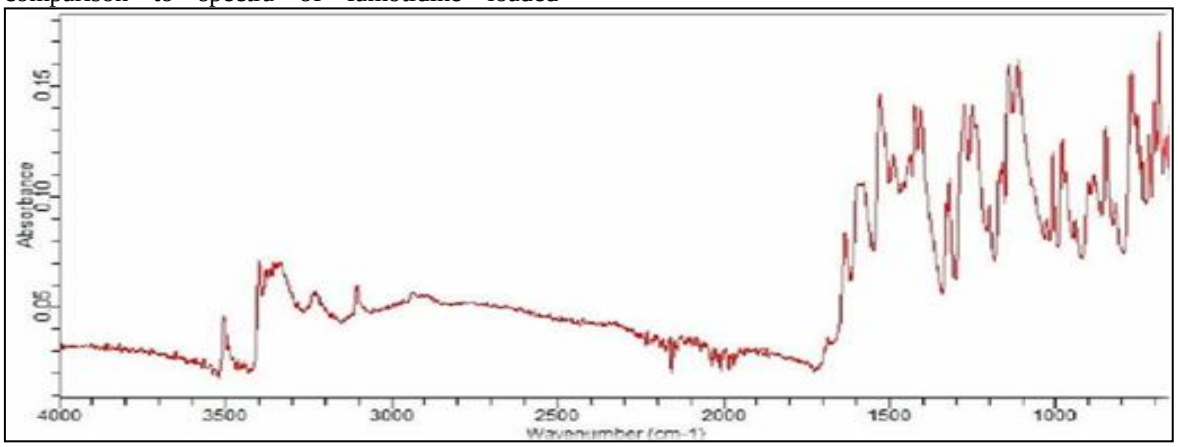
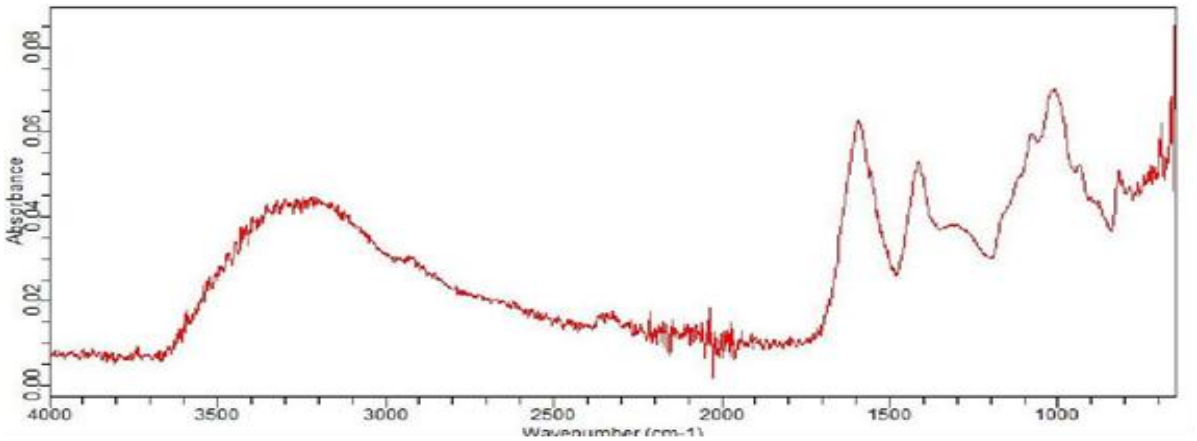



**Fig 1: DSC thermogram of drug and excipients**

The FT-IR spectra of optimized formulation is given in figure 2. No appreciable change was observed in peaks of famotidine spectra in comparison to spectra of famotidine loaded microspheres. Therefore it can be concluded that no chemical interaction has occurred between the drug and excipients.




**A**




**B**

**Fig 2: A: FTIR spectra of formulation B: FTIR spectra of famotidine**

**Evaluation of formulation trials**

Amount of sodium alginate significantly affects the particle size and entrapment efficiency of famotidine microspheres. The particle size was found to be increased when concentration of polymer was increased from F1 to F5 as shown in Table 4.

Amount of calcium carbonate significantly affects the entrapment efficiency of famotidine microspheres. On increasing the concentration 0:1(F6) (drug: polymer ratio) to 1:1(F9), it was noticed that entrapment efficiency decreases with its increasing concentration. On increasing the amount of calcium carbonate, it was found that microspheres floated for 24 hrs as shown in Table 5.

On increasing the amount of quercetin from 5mg (F10) to 10 mg (F11), it was found the drug release further increased at the end of 8 hrs. The values are given in Table 6, which indicates the increment in drug release by increasing the amount of quercetin.

**Table 4: Entrapment efficiency and particle size of microspheres**

| S. no. | Sodium alginate concentration (mg) | Entrapment efficiency (%) | Average Particle size (µm) |
|---|---|---|---|
| 1 | F1(200) | 38.5 | 706±1.23 |
| 2 | F2(400) | 46 | 773±1.45 |
| 3 | F3(600) | 53.5 | 813±1.28 |
| 4 | F4(800) | 59.5 | 879±1.83 |
| 5 | F5(1000) | 62.5 | 906±1.28 |

**Table 5: Decrease in entrapment efficiency on increasing calcium carbonate**

| S. no. | Calcium carbonate: Na alginate(mg) | Entrapment efficiency (%) | Floating ability(h) |
|---|---|---|---|
| 1 | F6(0:1) | 64 | --- |
| 2 | F7 (0.5:1) | 62.5 | 24 |
| 3 | F8(0.75:1) | 57.2 | 24 |
| 4 | F9(1:1) | 55 | 24 |

**Table No. 6: *in-vitro* dissolution profiles of Quercetin**

| Time(hrs) | 5mg(F10) | 10mg(F11) |
|---|---|---|
| 1 | 14.23±0.11 | 17.12±0.17 |
| 2 | 15.19±0.13 | 18.43±0.16 |
| 3 | 15.82±0.04 | 18.92±0.14 |
| 4 | 17.80±0.07 | 24.16±0.09 |
| 5 | 18.18±0.08 | 28.52±0.07 |
| 6 | 21.96±0.09 | 29.89±0.08 |
| 7 | 24.85±0.12 | 31.29±0.11 |
| 8 | 27.70±0.02 | 34.51±0.12 |

It was found that as the concentration of kaempferol increased from 1mg (F12) to 2mg (F13) drug release from famotidine microspheres also increased as shown in Table 7.

**Preparation and Characterization of optimized batch**

Following concentrations of polymer and excipients were taken for preparing the best batch (Fopt) of famotidine microspheres with higher entrapment efficiency and higher drug release based on the preliminary trials data as shown in Table 8.

**Mean particle size:** Microspheres were prepared with optimized parameters and particle size was calculated using optical microscopy and particle diameter of 50 particles was measured as shown in Table 9.

**Percentage buoyancy:** The optimized batch of microsphere was evaluated for percentage buoyancy effect. The microspheres remained buoyant for more than 12 hrs as shown in Table 9.

**Micromeritic properties:** Microspheres were prepared with optimized parameters and evaluated for micromeritic properties like angle of repose, compressibility index, tapped density and bulk density as shown in Table 9.

**Table 7: *In-vitro* dissolution profiles of Kaempferol**

| Time (hrs) | Kaempferol concentration | |
|---|---|---|
| | **1mg(F12)** | **2mg(F13)** |
| 1 | 14.70±0.07 | 15.23±0.12 |
| 2 | 14.96±0.11 | 15.59±0.23 |
| 3 | 15.30±0.10 | 16.19±0.32 |
| 4 | 15.95±0.08 | 16.52±0.22 |
| 5 | 16.25±0.20 | 16.70±0.41 |
| 6 | 16.65±0.30 | 16.91±0.35 |

**Table 8: List of ingredients**

| | |
|---|---|
| Quercetin | 10mg |
| Kaempferol | 2mg |
| Famotidine | 200mg |
| Sodium alginate | 1000mg |
| Calcium carbonate | 500mg |
| Calcium chloride | 5% |

**Table 9: Characterization of optimized formulation**

| | | |
|---|---|---|
| **Mean Particle Size** | Average particle size | 906µm |
| **Percentage buoyancy** | Weight of floating particles | 0.091g |
| | Weight of total particles | 0.024g |
| | Percentage buoyancy | 79% |
| **Micromeritic properties of the drug loaded hollow microspheres** | Angle of repose (degree) | 22.43º |
| | Compressibility index I (%) | 12 |
| | Tapped Density (g/cm3) | 0.15 |
| | Bulk Density (g/cm3) | 0.1333 |

**Dissolution studies:** Cumulative drug release profile of Famotidine microspheres was calculated by using pharmacokinetic parameters shown in Table 10. It can be seen that drug release rate of batch containing no bio enhancers (control formulation) was less by 2 times as compared to the microspheres batch with quercetin and kaempferol (optimized batch) as seen in Figure 3. As a result, there is some improvement in drug release and floating was also satisfactory.

**Scanning Electron Microscopy**

The morphology of microspheres was examined by scanning electron microscope using Zeiss EVO40. The view of the microspheres showed a fairly spherical structure with a rough surface morphology. The surface roughness may be due to incorporation of drug. The shell of the microsphere also showed some porous structure due to incorporation of calcium carbonate which is favorable for floating properties.

**Table 10: Cumulative drug release profile of famotidine microspheres**

| Time (hrs) | %Drug release |
|---|---|
| 1 | 15.50±2.89 |
| 2 | 16.24±2.76 |
| 3 | 16.30±2.45 |
| 4 | 17.00±2.23 |
| 5 | 20.00±2.13 |
| 6 | 22.00±1.14 |
| 7 | 25.00±1.11 |
| 8 | 27.80±1.44 |
| 9 | 34.50±1.46 |
| 10 | 42.80±0.92 |
| 11 | 52.00±0.87 |
| 12 | 60.40±0.86 |

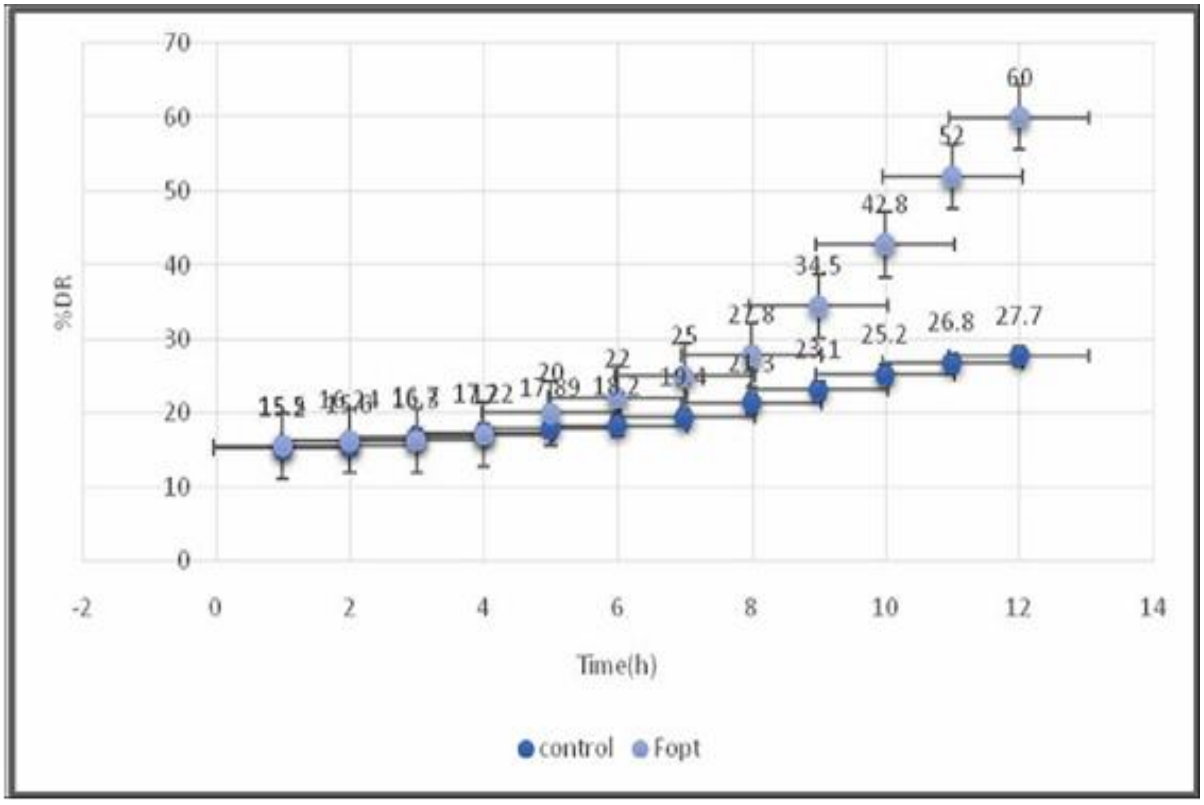



**Fig 3: Comparative dissolution profile of $F_{optimized}$ and control preparation**

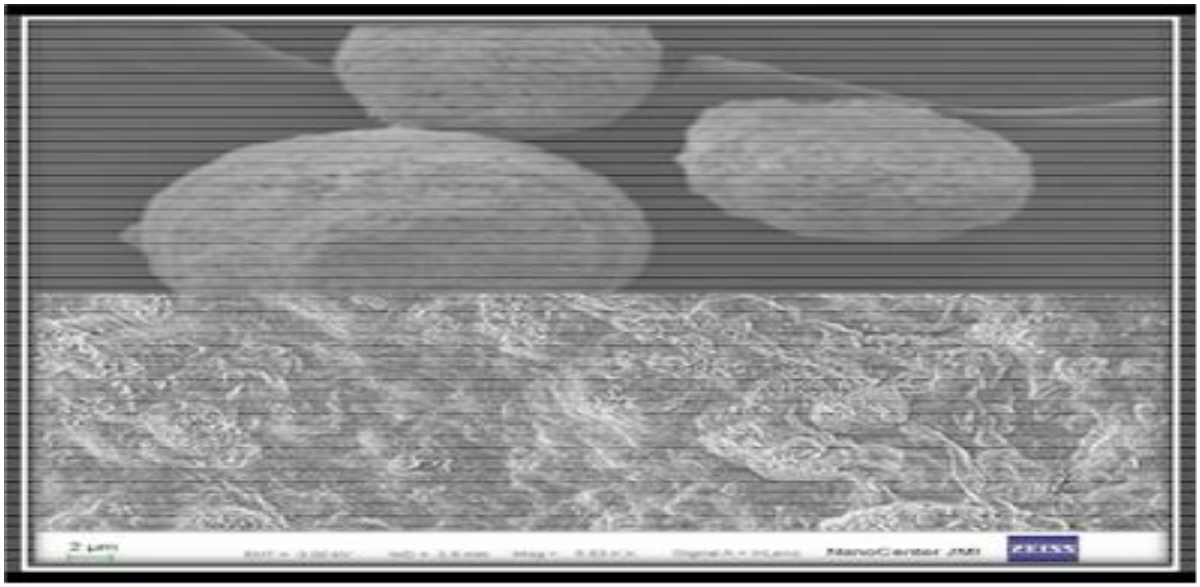


**Fig 4: SEM image of optimized formulation**

**Kinetic Modelling**

The in vitro release data obtained were fitted in to various kinetic equations. Correlation coefficients of individual batch with applied equation were given in Table 3. The value of $R^2$ was more in first order drug release as shown in Table 11. The value on n is 0.45<n<0.89 that is non ficckian diffusion.

**Stability studies**

The stability of famotidine microspheres formulations were evaluated at different conditions of room temperature (25±2°C) and under accelerated condition (40±2°C/75±5% RH). These were evaluated at regular intervals for 2 months. The results of stability studies showed that no change in physical appearance has occurred up to 2 months at all temperature conditions. After 2 months storage period, entrapment efficiency of microspheres was found to be 61.76±1.46 and 61.88±1.50 at room and accelerated temperature respectively. The drug content was found to be maximum at room temperature (Table 12). It was found that no remarkable change occurred in the entrapment efficiency and drug content of the microspheres. The change in drug content observed at accelerated storage condition was plotted against time using software.

**Table 11: Correlation Coefficients of drug release curves**

| Zero order | First order | Higuchi | Korsmeyer-peppas |
|---|---|---|---|
| $R^2$ | $R^2$ | $R^2$ | $R^2$ |
| 0.8582 | 0.9458 | 0.8597 | 0.7240 |

**Table 12: Accelerated analysis for chemical stability**

| | | CHEMICAL CHANGES | | |
|---|---|---|---|---|
| | 25±2/60%RH | | 40±2°C/75%RH | |
| | %EE±SD | %drug Content | %EE±SD | %drug Content |
| 0 | 62.50±1.20 | 100±0.90 | 62.5±1.09 | 100.90±0.3 |
| 7 | 62.20±0.92 | 99.80±0.23 | 62.16±1.20 | 99.79±0.43 |
| 15 | 62.16±1.44 | 99.79±0.41 | 62.08±1.45 | 99.77±0.26 |
| 30 | 62.04±1.38 | 99.76±0.35 | 62.00±1.43 | 99.75±0.41 |
| 60 | 61.76±1.46 | 99.69±0.45 | 62.88±1.50 | 99.58±0.49 |

**DISCUSSION:**

Oral controlled drug delivery has become a promising approach for those drugs having shorter half- life and high dosing frequency. It also reduces fluctuations in drug plasma concentration. The physical properties of the drug delivery system {density and size} as well as the contents and food in the stomach governs the *in-vivo* performance of a dosage form. To provide good floating behavior in the stomach the density of the formulation should be less than the stomach contents. Floating drug delivery systems are the systems which float or remain buoyant in the stomach for a longer duration of time and release drug at the target area which enhances bioavailability. These forms are expected to remain buoyant in gastric fluids for 3-4 hours without being effected by intrinsic rate of gastric emptying. The reasons of buoyancy are i) their low density as compared to gastric contents ii) formation of gaseous phase inside the stomach.

PUD or peptic ulcer disease, is an ulcer (defined as mucosal erosions equal to or greater than 0.5 cm) of an area of GIT that is exposed to acid in sufficient concentrations. The extent of the drug absorption in a segment of the GIT depends on the rate of absorption as well as on the exposed surface area and time available for the drug absorption. It is well documented that the stomach may be used as a depot for the controlled release dosage forms. It is widely used in the management of peptic ulcer, duodenal ulcer, gastric esophagitis, Zollinger-ellinson syndrome, etc. It has greater potency to eradicate H. pylori.

A 'bio enhancer' is an agent which enhances the bioavailability and bio efficacy of a drug with which it is combined without any pharmacological activity of its own at the dose used. They reduce the dose, cost, and minimize drug toxicity and adverse reactions. Some examples are quercetin and kaempferol. Quercetin has shown to increase bioavailability, blood levels and efficacy of number of drugs including dilitiazem, digoxin and epigallocatechingallate. Dose dependent Kaempferol may also increase the bioavailability of etoposide. The multiple-unit floating drug delivery system has been designed to avoid vagaries of gastric emptying and release the drug more uniformly leading to less local irritation, reduced inter subject variability ,low probability of dose dumping.

Ionic Gelation method was used in the preparation of floating microspheres of famotidine containing bio enhancers and it is the most common method to prepare alginate microspheres is to combine alginate with divalent ions.It was observed that amount of sodium alginate significantly affects the particle size and entrapment efficiency of famotidine microspheres. On increasing the amount of alginate from 200mg to 1000mg affected the entrapment efficiency. When the amount of alginate was 200mg, entrapment efficiency was found to be lower than that found in higher concentration of alginate that is 1000mg. The particle size was found to be increased when concentration of polymer was increased from 200mg to 1000mg. It was found that on increasing the amount of calcium carbonate (gas generating agent) with polymer in the preparation of microspheres it was found that entrapment efficiency decreases with increase in concentration of calcium carbonate. On increasing the concentration of calcium carbonate from 0.25:1 (drug: polymer ratio) to 2:1 it was noticed that entrapment efficiency decreases with its increasing concentration.

Floating ability of microspheres was also affected by the concentration of calcium carbonate. On increasing the amount of calcium carbonate it was found that microspheres floated for 24 hrs. It was seen that the amount of quercetin mainly affects the release profile of famotidine microspheres. On adding quercetin 5mg drug release from famotidine microspheres was higher as compared to the quercetin free microspheres. On increasing the amount of quercetin from 5mg to 10 mg it was found the drug release further increased at the end of 8 hrs. So 10 mg of quercetin was selected for optimal drug release. The amount of kaempferol also affects the drug release profile of famotidine microspheres. On adding 1 mg of kaempferol in the preparation of famotidine microspheres it was found that drug release was more as compared to the famotidine microspheres containing no kaempferol. Further it was found that as the concentration of kaempferol increased from 1mg to 2mg drug release from famotidine microspheres also increased.

The angle of repose value was found to be 22.43º indicating potential flow of microspheres. These results were further potentiated by I value 12%. The density values were obviously less than that of gastric fluid implying that these microspheres will possess a great buoyancy effect in vivo. It was noticed that drug release rate of batch containing no bio enhancers (control formulation) was less by 0.5 times as compared to the microspheres batch with quercetin and kaempferol (optimized batch). As a result there is some improvement in drug release and floating was also satisfactory. The morphology of microspheres was examined by scanning electron microscope using Zeiss EVO40. The view of the microspheres showed a fairly spherical structure with a rough surface morphology. The surface roughness may be due to incorporation of drug. The shell of the microsphere also showed some porous structure due to incorporation of calcium carbonate which is favorable for floating properties. The *in-vitro* release data obtained were fitted in to various kinetic equations. The value of

R2 was more in first order drug release. The value on n is 0.45<n<0.89 that is non ficckian diffusion.

The stability of famotidine microspheres formulation were evaluated at different conditions of room temperature (25±2°C) and under accelerated condition (40±2°C/75±5% RH). It was found that no remarkable change occurred in the entrapment efficiency and drug content of the microspheres.

## CONCLUSION:

The microspheres prepared by ionic gelation method and with natural bio enhancers had lower densities, greater floatability for over 24 hours and retained in the gastric environment for a longer period of time. Famotidine is having a less bioavailability due to poor absorption and drug release, so as to increase the release profile of drug natural bio enhancers were used. Gastric retention time of drug was also increased as the microspheres floated for a period of 24 hours in body. The present study demonstrated that the hollow microspheres showed satisfactory drug entrapment efficiency, particle size and floating ability on appropriate balance between polymer and calcium carbonate. It also showed the invitro drug release increased by 0.5 times by appropriate concentration of bio enhancers (quercetin and kaempferol). In-vitro obtained for the floating microspheres of famotidine containing bio enhancers showed excellent floatability, good buoyancy and increment in drug release. Thus major advantages of the system include ease of preparation, good buoyancy, high entrapment efficiency, increased in-vitro drug release.

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## ABBREVIATIONS

FT-IR: Fourier Transform Infrared Radiation; SEM: Scanning Electron Microscopy; PUD: Peptic ulcer disease; PG: Prostaglandins; NSAIDs: Non-steroidal anti-inflammatory drugs

## CONFLICT OF INTEREST

There is no conflict of interest/competing interest. This work is original and nothing has been plagiarised to the best of my knowledge.

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