

Floating tablets of Famotidine with natural polymer: An approach for gastric treatment

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Abstract:

A novel floating controlled release drug delivery system of famotidine was formulated in an effort to increase the gastric retention time of the dosage form and to control drug release. The present work investigates the *In vivo* buoyancy and pharmacological activity of prepared floating tablets of famotidine as model drug delivery system. The floating tablets were prepared with isolated chitosan by wet granulation technique. The best formulation was selected based on *in vitro* characteristics and was used *In vivo* radiographic studies by incorporating BaSO₄. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The *In vivo* buoyancy study was performed in beagle dogs to evaluate intra-gastric retention performance in different time intervals by X-ray radiographic method. Followed by the floating tablets were evaluated for its pharmacological activity in New Zealand white albino rabbits by immobilization stress induced ulcer in comparison with commercially available standard. The floating formulation shows excellent buoyancy and better gastric cytoprotection when compared with conventional dosage form.

Key words: *In vivo buoyancy; anti ulcer activity; floating dosage forms; immobilization stress induced ulcer.*

Introduction:

Floating tablets were used to increase the gastric residence time of dosage forms. Floating drug delivery system has been developed to identify the merit over a conventional dosage form. Such dosage forms are better because they reduce the inter-subject variability in absorption and lower probability of dose dumping by reducing frequency of dosing. [1] Many polymers that have been used to prepare floating tablets are HPMC, SCMC, etc. Famotidine was used as a model drug and was widely used for treating gastric and duodenal ulceration. [2] It is an anti-histaminic drug, which has been widely used in treating gastric and duodenal ulceration and also in the treatment of Zollinger Ellison syndrome and reflux esophagitis. It is poorly absorbed from the lower gastrointestinal tract and has a short elimination half life (2.5-4 h) [3]. The objective of this study was to develop floating tablets of famotidine using natural polymer having desirable properties in order to achieve an extended retention in the upper gastrointestinal tract, which may result in enhanced absorption and thereby improved bioavailability.

Materials and Methods:

Famotidine was obtained as a gift sample from Micro Labs, Hosur. Chitosan-I was isolated from marine sources. NaHCO₂, Citric acid and MCC were obtained from S.D. Fine Chemicals Ltd., Mumbai. All

other chemicals or reagents used were of analytical grade.

Preparation of placebo floating tablets for In vivo buoyancy study

For *In vivo* buoyancy study the placebo floating tablets with 250 mg weight were prepared for model dosage form of famotidine in accordance with formulation Table 1 by wet granulation method. The amount of the X-ray opaque material in these tablets was sufficient to ensure visibility by X-ray, but at the same time this amount of BaSO₄ was low enough to enable tablets to float [4].

To make the tablet X-ray opaque, incorporation of BaSO₄ was necessary. For this purpose, placebo floating tablets were prepared with BaSO₄ and all other ingredients were kept constant [5,6]. The tablets were characterized for hardness, floating lag time and floating duration as described in reported articles [7].

Preparation of floating tablets of famotidine for anti ulcer activity study

Floating granules were prepared by wet granulation technique [8,9,10]. Dose of 0.62mg/kg of famotidine was used according to body weight of the animal. The active ingredient and excipients such as citric acid, sodium bicarbonate and polymer were weighed accurately and mixed homogeneously according to geometric proportions as per formulation Table 1 in which 2% w/v alcoholic solution of respective polymer was used as a

Table 1: Composition of floating tablets for *In vivo* studies

| S.No | Ingredients | For buoyancy study mg/Tab | For Anti ulcer study mg/Tab |
|------|--------------------|------------------------------|--------------------------------|
| 1 | Drug | -- | 0.62/kg |
| 2 | BaSO ₄ | 4 | 4 |
| 3 | Chitosan-I | 60 | 60 |
| 4 | NaHCO ₃ | 60 | 60 |
| 5 | Citric acid | 10 | 10 |
| 6 | MCC (3%) | 7.5 | 7.5 |
| 7 | Lactose | 108.5 | 107.88 |
| 8 | Total | 250 | 250 |

Table 2: Ulcer index of all treatment groups

| Treatment Groups | Dose in mg/kg | Ulcer Index |
|------------------|--|-------------|
| Control | 5ml water | 8.6 ± 1.2 |
| STD | 0.62mg equivalent weight as powdered tablet | 0.68 ± 0.04 |
| TEST | Floating tablet containing 0.62mg/kg of drug | 0.64 ± 0.12 |

granulating agent. The coherent mass was sieved through mesh no. 16 and then dried in hot air oven at 50°C for 45 min. The dried granules were passed through sieve no. 20 to get uniform granules. The granules were blended with 3% MCC for 2-3 minutes and which was used as a lubricant to improve flow property. Citric acid and sodium bicarbonate were incorporated as a stabilizing and gas-generating agent respectively.

The granules were evaluated for its derived and flow properties followed by compressed into floating tablets weighing about 250mg using 6.8 mm shallow biconcave punches in Chamunda rotary tablet punching machine to a hardness of 4-5 kg/cm². The tablets were characterized for hardness, drug content, floating lag time, floating duration and percentage of drug released as described in reported articles [11].

In vivo radiographic study using dog as animal model

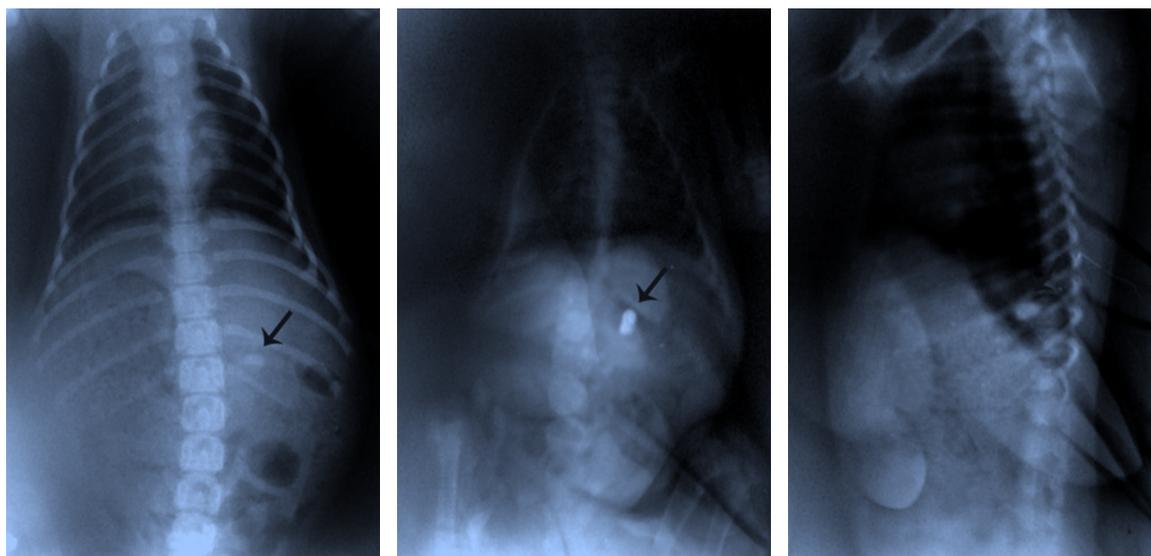
Unlike other formulations, determination of GRT is very important factor for FDDS throughout GIT. In most cases, it requires an imaging technique that can locate the FDDS in stomach. The following method

has been utilized to assess gastroretentivity.

Even though there are number of studies reported, the present work makes use of the Radiology study (X-Ray) for the determination of anatomical location and behavior of floating tablets in the gastrointestinal tract [12].

The *in-vivo* buoyancy study was carried out by administering placebo floating tablet to the dog and monitoring them through a radiological method. The study was approved by the Ethical Committee of Annamacharya College of pharmacy, Rajampet, Andhra Pradesh, India with Reg. No.1220/a/08/CPCSEA/ ANCP/06.

The study was conducted in dogs, weighing between 4-5 kg. The tablets prepared for radiography were administered orally. During the study, the animal was fasted but allowed free access for water. After ingestion of floating tablets containing barium sulphate, the animal was exposed to X-ray photography in the abdominal region. The X-ray photographs were taken at 4th, 8th and 12th h after administration of the floating tablet is shown in Figure 7.1.



At 4th hr

At 8th hr

At 12th hr

Figure 1: X-ray photographs showing *In vivo* buoyancy of placebo floating tablets of F14 at 4th, 8th, 12th hrs

In dog the position of the floating tablet was monitored by X-ray photographs (Konica Minolta, Siemens, Karlsruhe, Germany) of the gastric region at determined time intervals. All X-ray films were taken in different positions.

Anti ulcer activity study

Purpose and rationale

Psychogenic factors, such as stress, play a major role in the pathogenesis of gastric ulcers in man. The first report of the use of restraint as stress factor was published by Selye (1936) [13], Hanson and Brodie (1960) [14] described methods to study the effect of anti-ulcer drugs on immobilization stress in rats. The pharmacological activity of best formulations has been evaluated by the same method with some modification like rabbit were used instead of rat.

Procedure for Stress ulcer through immobilization stress

Three groups of male and female New Zealand Rabbit per dose of standard, test drug of Famotidine and for controls weighing 1.5–2 kg were used. Food and water were withdrawn 24 h before the experiment. After oral administration of the test tablets to the animals were slightly anesthetized with ether. Both lower and

upper extremities are fixed together and the animals were wrapped in wire gaze. They are horizontally suspended in the dark at 20°C for 24h and finally sacrificed in Phenobarbitone sodium anesthesia. The stomach was removed, fixed on a cork plate and the number of ulcers per stomach were noted and severity of the ulcers were observed microscopically and scoring was done as follows: 0 for normal coloured stomach, 0.5 for red colouration, 1 for spot ulcer, 1.5 for hemorrhagic streaks, 2 for ulcer between > 3 but < 5mm and 3 for ulcer > 5mm. Mean ulcer score for each animal was expressed as ulcer index [15].

Results and Discussion:

In vivo buoyancy study: The radiographic images shown in Figure 1 were made every 4 hours time interval after administration of placebo floating tablets, they were observed in the animal's stomach. The significant changes in positions were detected, which provide evidence that the tablets did not adhere to the gastric mucosa but, on the contrary, floated on the gastric fluid. The major limitation to the upper gastrointestinal residence time of solid single unit dosage forms administered in the fasted state is the third phase of the migrating

myoelectric complex (MMC), which occurs approximately every 2h in humans and approximately every 1h in dogs.



Figure 2: Normal stomach obtained from rabbit of control group



Figure 3: Ulcer induced stomach obtained from rabbit of ulcerated group



Figure 4: Famotidine treated stomach obtained from rabbit of STD group



Figure 5: Floating tablets of Famotidine treated stomach obtained from rabbit of Test group

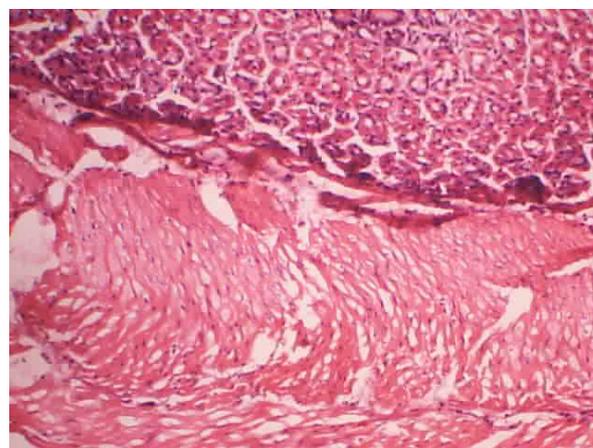


Figure 6: Section of normal stomach obtained from rabbit of control group

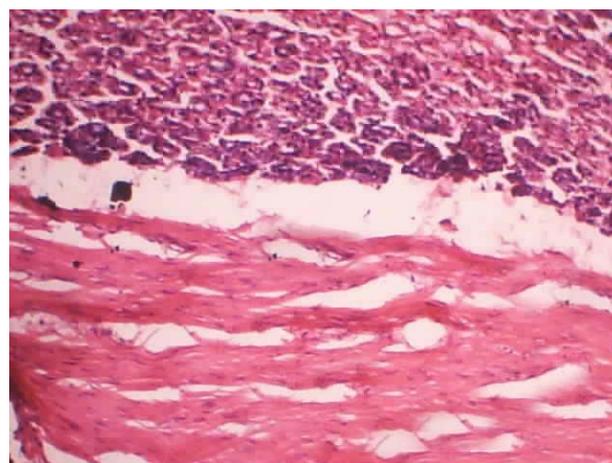


Figure 7: Section of ulcer induced stomach obtained from rabbit of ulcerated group

As the results have shown that the mean gastric residence time for the developed floating tablets was more than 6 h in dogs, this means that the floating formulation withstands four of these phases without emptying. It was expected that the gastric residence of this formulations in human beings would be even longer.

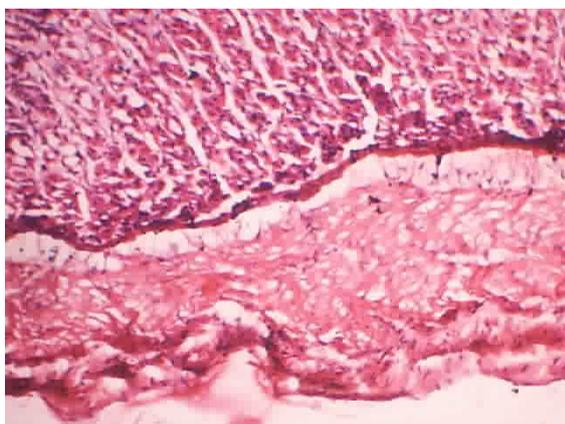


Figure 8: Section of Famotidine treated stomach obtained from rabbit of STD group

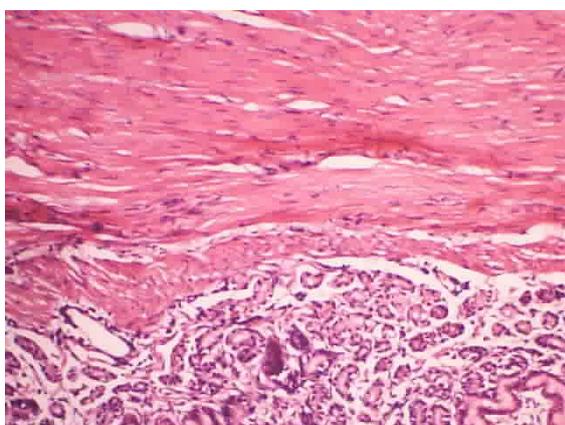


Figure 9: Section of Floating tablets of Famotidine treated stomach obtained from rabbit of Test group

Macroscopical and histopathological evaluation: Macroscopical changes of stomach of rabbits in immobilized stress induced ulcer model were shown in Figures from 2 to 5. Histopathological changes on this model showed the degeneration, hemorrhage, and inflammation in the gastric tissue whereas treatment by using floating tablets of famotidine reduced dramatically the changes. The histopathological changes on

these models were also shown in the figures from 6 to 9. The etiology of peptic ulcer is unknown in most of the cases, yet it is generally accepted that it results from an imbalance between aggressive factors and the maintenance of mucosal integrity through the endogenous defense mechanisms which is supported by Piper and Stiel, 1986 [16]. To regain the balance, different therapeutic agents are used to inhibit the gastric acid secretion or to boost the mucosal defense mechanisms by increasing mucosal production, stabilizing the surface epithelial cells or interfering with the prostaglandin synthesis. Dose administered to the treatment groups and their respective ulcer indexes are given in Table 2.

Conclusion:

As a conclusion, it was obvious that the floating formulations were able to delay the gastric emptying of Famotidine tablets in beagle dogs. Knowing that the dogs undergo gastric migrating myoelectric complexes than humans, the significant delay in the gastric emptying observed with the floating tablets when compared to the control is expected to be even longer in humans. This would maximize absorption by allowing the slowly released drug in the stomach to reach the upper small intestine (i.e. the sight of absorption) in a form ready for absorption. In present study the floating tablets of Famotidine showed better gastric cytoprotection when compared with conventional dosage form. This may be due to its extended duration of release and action.

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