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FORMULATION AND *IN VITRO - IN VIVO* EVALUATION OF BILAYER FLOATING-BIOADHESIVE FAMOTIDINE TABLETS

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ABSTRACT

Bilayer floating-bioadhesive drug delivery systems exhibiting a unique combination of floatation and bioadhesion to prolong gastric residence time were developed. Hydroxypropyl methylcellulose and sodium bicarbonate were added such that when immersed in 0.1N HCl, the tablet expands and rises to the surface and famotidine is gradually released without interference from gas bubbles. Effect of different ratios of drug: polymer on *in vitro* release profile was investigated. Developed tablets were evaluated for uniformity of weight, hardness, friability, drug content, buoyancy and floating lag time. Time buoyancy curve, detachment force and swelling index were evaluated. Antiulcer activity of famotidine tablets was assessed by inducing ulcers in fasted rats by ethanol and indomethacin. Measurement of gastric contents was carried out by ulcer induced pylorus liagated rats. Prepared tablets exhibited satisfactory physico-chemical characteristics. The tablet swelled radially and axially during *in vitro* buoyancy studies. From the buoyancy kinetic curve it was observed that bilayer tablet started floating in less than 10 minutes and remained buoyant for 12h. *In vivo* antiulcer studies exhibited that developed formulation showed comparable percent inhibition of ulcers to standard in both gastric ulcer models. Gastric pH was significantly reduced showing decreased acid output. Thus floating-bioadhesive systems exhibited independent regulation of buoyancy and drug release and *in vivo* studies showed good antiulcer efficacy confirming potential of floating-bioadhesive tablets as drug delivery system for prolonging gastric residence and enhancing local effect of famotidine.

Keywords: floating-bioadhesive tablets; buoyancy curve; sodium bicarbonate; gastric residence; antiulcer activity

INTRODUCTION

Famotidine is a histamine H_2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger- Ellison syndrome and gastroesophageal reflux disease. In the management of benign gastric and duodenal ulceration the daily oral dose is 40 mg at bedtime, for 4 to 8 weeks [1]. The low bioavailability (40-45%) and short biological half life (2.5-4.0 hours) of famotidine following oral administration favours development of a gastroretentive controlled release formulation. The gastroretentive drug delivery systems are retained in the stomach for prolonged periods and assist in improving the oral controlled delivery of drugs that have an absorption window in region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability [2].

It has been reported that the oral treatment of gastric disorders with an H_2 receptor antagonist like famotidine or ranitidine used in combination with antacids promotes local delivery of these drugs to the receptors of parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases efficacy of drugs to reduce acid secretion. Hence this principle may be applied for improving systemic as well as local delivery of famotidine, which would efficiently reduce gastric acid secretion [3].

Several approaches[4,5,6,7]. can be used to prolong gastric retention time, including floating drug delivery systems (i.e., hydrodynamically balanced systems), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric-emptying devices [8,9,10]. A dosage form that delivers famotidine in the stomach as a floating drug delivery system is one approach. A floating drug delivery system can be designed by incorporating at least one porous structural element that is less dense than gastric juice [11]. Research also has been done in making floating (effervescent-type) drug delivery system for gastroretention using famotidine [12]. A new type of multiparticulate floating drug delivery system consists of a highly porous carrier material (foam powder), drug, and polymer as low density microparticles [13, 14]. The material has a low density, large cavities interconnected by smaller pores (which give it a highly permeable structure), good compressibility, and good flowability.

In this study, an effervescent floating system and a bioadhesion system were used in combination. Floating dosage forms are meant to remain floating on the gastric fluid when the stomach is full after a meal. However, as the stomach empties and the tablet reaches the pylorus, the buoyancy of the dosage form may be reduced. It may be that the dosage form will then pass through the pylorus into the small intestine. Thus, the buoyancy of floating drug delivery systems in the stomach may be limited to only 3–4 h. Furthermore, floating systems do not always release the drug at the intended site. In a simple bioadhesive drug delivery system, it is quite likely that the system becomes dislodged from the stomach mucosa wall when the stomach is full and the semi-liquid contents are churning around due to the effect of peristalsis [15]. A floating-bioadhesive system would overcome these drawbacks of floating and bioadhesive systems and would have a significant effect on improving the therapeutic effect of the drug [16] .The purpose of this work was to develop a novel controlled release tablet with a unique combination of bioadhesion and floatation to prolong the gastric residence time of famotidine, which is absorbed from the gastrointestinal tract resulting in increased antiulcer effect.

EXPERIMENTAL METHOD

Materials: Famotidine was received as a gift sample from Microlabs, Chennai, India. Methocel K100 (100 cps apparent viscosity as a 2% solution) (HPMC K100M), Methocel K15M (15,000 cps apparent viscosity as a 2% solution) (HPMC K15M) and Starch 1500 were received as gift samples from Colorcon Asia Pvt. Ltd., India. Microcrystalline cellulose (MCC) and purified talc were obtained from E. Merck Ltd., India. Magnesium stearate, hydrochloric acid and sodium bicarbonate ($NaHCO_3$) were procured from S.D. Fine-Chem Ltd, India. All other ingredients were of analytical grade.

Preparation of bilayer and floating-bioadhesive tablets of famotidine: Famotidine bilayer tablet was formulated as effervescent-bioadhesive floating layer and a polymer controlled drug release layer. The floating layer constituted of sodium bicarbonate, methocel K100M and starch 1500. Controlled drug releasing layer consisted of famotidine, methocel K15M, microcrystalline cellulose and magnesium stearate. A series of formulations were prepared by varying the concentrations of drug and polymers (Table 1). All ingredients were passed through a sieve (60#) and mixed well in a mortar. Granules of the floating layer were prepared using 80 % ethanol. Weighed quantities of the controlled release layer equivalent to 150 mg were subjected to mild compression. Weighed granules of the floating layer equivalent to 140 mg were added to the compressed controlled release layer and both the layers were then compressed in a single station rotary press (Royal artist, Mumbai, India) using 8 mm diameter die.

Characterization of granules: The characteristic parameters of the granules were evaluated. The angle of repose and flow rate were determined by the funnel method. The bulk density and tapped density were determined by the cylinder method.

Drug content and physical evaluation: The drug content of the tablets was determined using 0.1N HCl as a solvent, and the samples were analyzed spectrophotometrically (JASCO, V-530, Japan) at 263 nm. Tablets were also examined for weight variation (n = 10), friability (n = 10) and hardness (n = 6). Results are given in Table 2.

Buoyancy lag-time studies: The buoyancy lag-time of the tablets was studied at 37 ± 0.5°C, in 100 ml 0.1N HCl (pH 1.2). The time required for the tablet to rise to the surface and float was taken as the buoyancy lag-time.

Dissolution studies: The release rate of famotidine from floating tablets was determined using USP Dissolution Rate Test apparatus II (Paddle type). The dissolution test was performed using 900 ml 0.1N HCl, at 37 ± 0.5°C and 50 r/min. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman filter paper and the absorbance of these solutions was measured at 263 nm. The cumulative percentage drug release was calculated using 'PCP Disso v2.08' Software.

Detachment stress test: The bioadhesive force of the bilayer tablet was determined by modified balance method. Pieces of sheep fundus tissue were stored frozen in saline solution and thawed immediately before use. The working of the double beam physical balance formed the basis of the fabrication bioadhesion test apparatus. The two pans of the balance were removed. The right pan of the balance was replaced with a lighter base and on the left side; Teflon ring was hung with a copper wire. The height of this total setup was adjusted to accommodate a glass container. The two sides were then balanced so that the right hand side was exactly 5 gm heavier than the left. The freshly excised sheep fundus tissue was tied tightly with the mucosal side facing upward direction. The formulation was then placed on to the cylinder containing tissue and the balanced beam raised with the 5 gm weight on the right pan removed. This lowered the Teflon cylinder over the tissue surface containing formulation with the weight of 5 gm. The balance was kept in this position for 10 min and then slowly weights were increased on the right pan, till the formulation just separated out from the tissue surface. The bioadhesive force, expressed as the detachment stress in dyne/cm^2, was determined from the minimum weight required to detach using the following equation [17].

Detachment stress (dyne/cm2) = $m \cdot g/A$

Swelling index: The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques. The water uptake study of the tablet was performed using USP dissolution apparatus Type II. The medium used was distilled water, 500 ml rotated at 50 rpm and maintained at 37 ± 0.5 °C, throughout the study. After selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed.

Time buoyancy kinetic studies: A special apparatus for determination of buoyancy was developed. The device composed of a balance (accuracy 1.0 mg) and a water bath maintained at 37ºC. In the measurement of resultant buoyancy, the tablet was placed in the basket. When it contacted with test medium freshly prepared from deareated water (SGF, pH 1.2, 37ºC), the tablet expanded, and the density decreased because of this expansion. The upward or downward force then was transmitted to the balance by the connecting line. By adjusting the balance weight set, the resultant buoyancy could be determined.

In vivo antiulcer activity assessment ethanol induced ulcers: *In vivo* studies on animals were carried our as per the protocol approved by the Animal Ethical Committee of Bombay Veterinary College, Parel (Protocol: IAEC Resolution no. 19/08 CPCSEA reg no. 230). Ulcers were induced by the oral administration of absolute ethanol (5 ml/kg) to 24 h fasted Wistar male rats, weighing 200 g [18]. The animals were divided in to three groups (n=6) negative controlled group (only ethanol treated), positive control group (pure drug treated) and treated group (developed formulation treated). Formulations (20 mg/kg of drug) were given 1 h before the administration of ethanol. After 2h of ethanol administration, animals were sacrificed; the stomachs were removed, opened along the greater curvature, and examined for lesion measurements.

Measurement of gastric acidity in pylorus ligated rats: The animals were divided into three groups (n = 6). After 24 h of fasting, the animals were anesthetized with ether the abdomen was incised and the pylorus was ligated. Immediately after pylorus ligature, positive control and treated group were administered with pure drug solution and formulation. Four hours later, the animals were sacrificed by cervical dislocation; the abdomen was opened and another ligature was placed at the oesophageal end. The stomachs were removed and the gastric content collected and centrifuged at 3000 rpm (8000×g, 250C, 10 min). The assay was performed using the method of Shay et al, with a few modifications. The amount of gastric acid (ml) and the pH values were determined. The total acid secretion in the gastric hen was determined in the supernatant volume by titration to pH 7.0 using a 0.01M NaOH solution, and phenolphthalein as indicator [19].

RESULTS AND DISCUSSION

Famotidine gastroretentive delivery system was prepared as bilayered tablets. The first layer contained a mixture of sodium bicarbonate, starch 1500 and HPMC K100M, with the HPMC K100M being used as a matrix material to retain the air bubbles. The first layer imparts buoyancy to the tablet. Sodium bicarbonate was added as a gas-generating agent. The ideal amount of both, effervescent mixture and polymer, for the floating layer was estimated by determining the onset time of floating. Short onset time was obtained by increasing the concentration of effervescent mixture, on the other hand, a lower concentration prolongs this. The CR layer provided controlled release of famotidine along with HPMC K100M as a hydrophilic matrix material (Table 1). Hence, the unique combination of floating and bioadhesion is likely to prolong the gastric retention time of famotidine, resulting in restricting GI absorption to the upper part of the small intestine. The granules of the floating layer were characterized with respect to the angle of repose, flow rate, bulk density, tap density and Carr's index (Table 2). The angle of repose was less than 25º for all the batches of granules indicating satisfactory flow behavior. Other physicochemical parameters were also determined and found to be within acceptable limits. Table 2 shows that, as the concentration of HPMC increased, the angle of repose and Carr's index increased while the flow rate decreased. The weight variation, friability, hardness and content uniformity were found to be within acceptable limits (Table 2). The formulations showed satisfactory floating lag time. Formulations F1 – F5 showed a floating lag time between 15 minutes to 6 minutes (Table 3). The buoyancy lag time depends on the amount of sodium bicarbonate responsible for CO_2 formation. For a floating system, the ideal matrix should be highly permeable to dissolution media in order to initiate rapid generation of CO_2 and allow release of CO_2 to promote floating. Both the layers contained HPMC resulting in a reduced buoyancy lag time. These results indicated that the buoyancy lag time was found to be satisfactory when a combination of 43 % sodium bicarbonate and 33 % of HPMC K100M.

The results for detachment stress test as shown in Table 3 indicated that the bioadhesive force increased significantly as the concentration of mucoadhesive polymer increased. All bilayer tablets showed mucoadhesive force in the range of 79.77 to 127. 82 dynes /cm^2. Bioadhesion is a surface phenomenon in which a material of natural or synthetic origin adheres or sticks to a biological surface, like mucus membrane. HPMC is a hydrophilic polymer that adheres to mucosal surface as it attracts water from the mucus forming a gel like layer adhering to the epithelial surface. Thus this hydration process causes the adhesion and this adhesion increases as the concentration of polymer increases and so does the detachment force.

The percent water uptake of the formulations ranged from 72 – 96 % (Table 3). The percentage water uptake was found to increase as the concentration of HPMC increased in the formulations resulting in increased water uptake capacity. Drug diffusion depends significantly on the water content of the tablet. Higher water content leads to greater penetration of the gastric fluid into the tablet leading to faster carbon dioxide gas generation, thereby reducing the floating lag-time. Consequently, faster and greater swelling of the tablet occur leading to an increase in the dimensions of the tablet resulting in an increase in diffusion pathways and thus reduction in diffusion rate.

On contact with the dissolution medium containing 0.1N HCl, the hydrochloric acid in the test medium reacted with sodium bicarbonate in the floating layer of the bilayer tablet, inducing CO_2 formation in the floating section. Because the gas generated is trapped in and protected by the gel formed by the hydration of HPMC, the expansion of the floating section keeps the whole tablet buoyant on the surface of the test medium for as long as 8 h, as shown in Fig 1. In the formulation of the floating layer, HPMC K100M was used to obtain a more sticky gel so as to prevent the air bubbles from rapture.

The results of the *in vitro* release studies are shown in Fig. 2. Formulation F1 containing lower concentration of release retarding polymer gave release of 96.7% of famotidine in 5 hrs. For formulations F2-F5 it was observed that as polymer increased the release was prolonged and controlled. Formulation F2 exhibited a release of 96.3 %, whereas 95.8% of drug was released for batch F3 for a period of 7 and 9 hours respectively. Formulation F4 showed 95.4% drug release in 12 hrs and 99.25% drug release was obtained for batch F5 at the end of 12h. The concentration of HPMC K100M in the release layer was the key factor governing drug release. In the bilayer tablet, the drug release layer included the gelling agent forming a gelatinous barrier which controls the drug release without interference from gas bubbles generated in the floating layer. As the concentration of HPMC K15M increases in the formulation the release rate was

found to decrease. Batch F5 showed controlled drug release for a period of 12 hrs (Fig 2)

The drug release data obtained by *in vitro* dissolution studies. The data for batch F5 was fitted in different kinetic models viz. zero order, first order, Higuchi and Korsemeyer's equation. The zero order plot was found to be fairly linear (Table 4) as indicated by its high regression values (r^2 = 0.9901). To confirm the exact mechanism of drug release from the tablets, the data were fitted according to Higuchi and Korsemeyer's equation [20,21] . Regression analysis was performed and regression value 'r^2' was 0.9821 and 0.9831 respectively for optimized batch indicating diffusion as mechanism for drug release.

The gastric ulcer indices were evaluated based upon degree of ulcers produced. In rats with ethanol induced gastric mucosal damage, linear hemorrhagic lesions were observed in the glandular portion of stomachs of negative control group. Pure drug treated and formulation administered groups showed significant decrease (p <0.05) in the ulcer index when compared with control group (Fig 3). Ethanol damages the plasma membrane and leads to intracellular accumulation of sodium and water by increasing the membrane permeability. These changes ultimately cause cell death and gastric mucosal exfoliation [22]. Ethanol is also known to release the endogenous ulcerogenic mediators. These could precipitate mucosal injury either by causing vascular changes like mucosal edema and increased mucosal permeability or by non-vascular effects like mucus depletion and enzyme release in the stomach [23]. In our study, famotidine floating-bioadhesive tablets significantly reduced mucosal damage induced by ethanol, which suggests that famotidine strengthens and protects the gastric mucosal barrier (Fig 4 A, B & C).

Gastric secretion plays an important role in gastric ulcer pathogenesis [25]. The rat treated with formulation (20mg/kg) produced significant (P<0.01) decrease free acidity, total acidity, Where as pH was significantly (P<0.01) increased when compared with control group. Pure drug solution also showed similar effects and was slightly more effective as compared with formulation (Fig 5). In the present study, famotidine floating-bioadhesive tablets showed reduction in gastric acid associated with inhibitory effect and showed suppression of aggressive factors like gastric acid secretion and thus helped in maintaining the integrity of gastric mucosal barrier.

CONCLUSION

In this study, we have developed optimized bilayer and floating-bioadhesive dosage forms which exhibit a unique combination of floatation and adhesion for prolonged residence in the stomach. The optimized F5 tablet formulation containing a combination of colloidal gel barrier HPMC K100M as well as gas generating agent $NaCO_3$ remained floating in the stomach for up to 12 h with a floating lag time of only 5 - 6 mins. The drug release from the tablets showed controlled drug release following diffusion mechanism. Enhanced antiulcer efficacy was obtained with reduction in gastric acid secrection.

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TABLE 1: FORMULATIONS OF FAMOTIDINE BILAYER FLOATING-BIOADHESIVE TABLETS

Ingredients	Floating layer (mg)	Controlled release layer (mg)				
		F1	F2	F3	F4	F5
Famotidine	_	20	20	20	20	20
HPMC K15M	_	40	50	60	65	70
HPMC K100M	50	_	_	_	_	_
MCC	_	44	39	25	30	15
Starch 1500	34	15	20	24	24	24
Sodium bicarbonate	65	_	_	_	_	_
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5

The floating layer contains lake brilliant blue FCF as a coloring agent.

TABLE 2: CHARACTERIZATION OF GRANULES AND TABLETS OF FAMOTIDINE

Preparations	**Parameters**	**F1**	**F2**	**F3**	**F4**	**F5**
	Angle of repose (°)	25 ± 1.3	25 ± 0.7	29 ± 2.8	31 ± 1.8	32 ± 1.2
	Flow rate (g/min)	25.6 ± 0.6	25.9 ± 0.3	26.5 ± 0.5	26.64 ± 0.6	25.43 ± 0.2
I. Granules	Bulk density (g/ml)	0.589	0.567	0.570	0.577	0.588
	Tap density (g/ml)	0.690	0.650	0.654	0.690	0.714
	Carr's index	14.5 ± 2.0	12.7 ± 2.3	12.3 ± 1.6	12.2 ± 2.2	12.86 ±1.7
Preparations	**Parameters**	**F1**	**F2**	**F3**	**F4**	**F5**
	Weight variation (%)	± 1.0	± 3.0	± 2.0	± 4.0	± 2.0
II. Tablets	Friability (%)	0.721	0.754	0.785	0.723	0.715
	Hardness (kg/cm^2)	5.2 ± 0.2	4.3 ± 0.4	5.6 ± 0.1	4.5 ± 0.5	4.9 ± 0.4
	Drug content (%)	97.5 ±1.6	98.6 ± 2.5	98.4 ± 2.7	97.3 ± 1.2	98.5 ± 1.4

Each sample was analyzed in triplicate (n = 3)

TABLE 3: EVALUATION OF FLOATING-BIOADHESIVE BILAYER TABLETS OF FAMOTIDINE

Formulation	**Buoyancy lag time (min)**	**Detachment force (dynes/cm^2)**	**Swelling Percent (%)**
F1	10.56 ± 1.43	79.22	72
F2	9.23± 1.13	88.47	78
F3	7.12 ± 1.21	93.65	85
F4	6.73 ± 1.86	114.71	89
F5	5.94 ± 1.57	127.82	92

TABLE 4: DRUG RELEASE KINETICS AND DISSOLUTION PARAMETERS OF BATCH F5

Formulation	**Regression Coefficient (r^2)**				**$T_{50\%}$ (h)**
	Zero order	**First order**	**Korsmeyer-Peppas**	**Higuchi model**	
Batch F5	0.9901	0.8316	0.9831	0.9821	6

Each sample was analyzed in triplicate (n = 3)

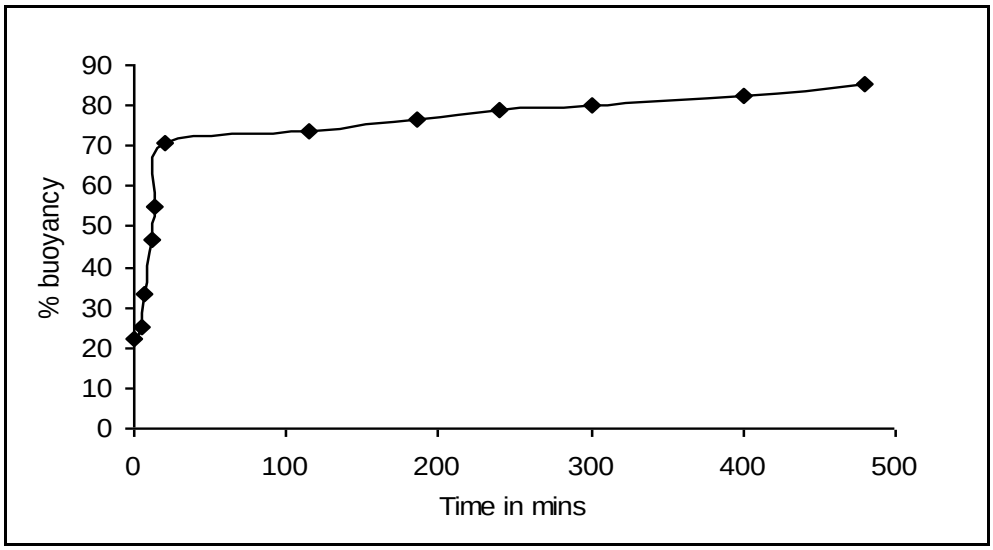


Figure 1: Time buoyancy kinetic curve for floating-bioadhesive bilayer tablets of famotidine

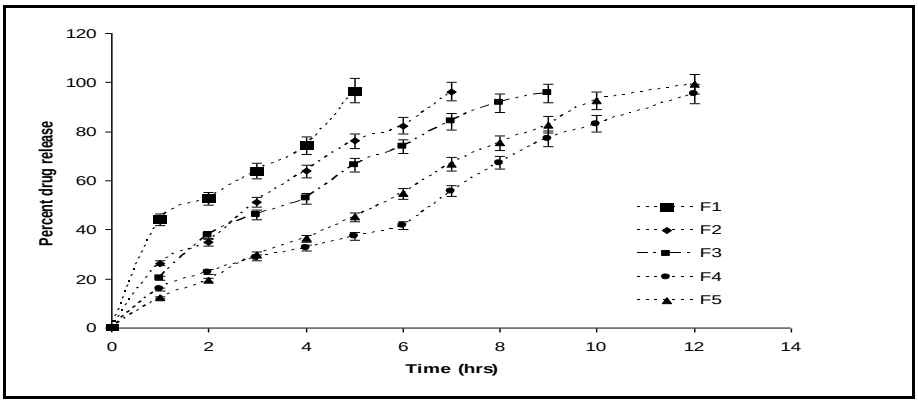


Figure 2. *In vitro* drug release profiles of famotidine floating-bioadhesive bilayer tablet formulations

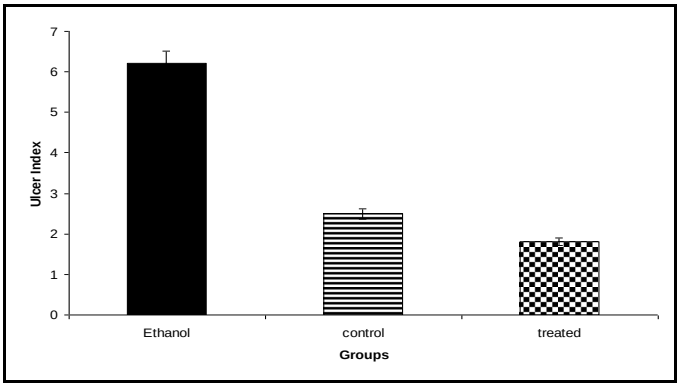
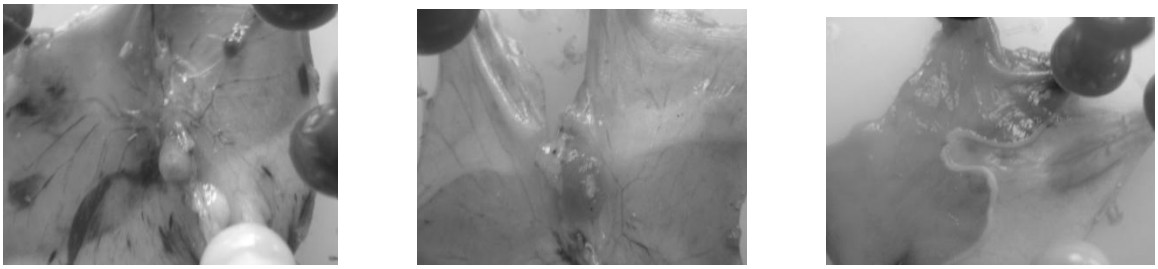


Figure 3. Effect of famotidine formulation ulcer index in ethanol induced ulcer model



(A) **(B)** **(C)**

Figure 4. Photographs of in vivo antiulcer activity (a) ethanol group (b) control group (c) formulation treated group

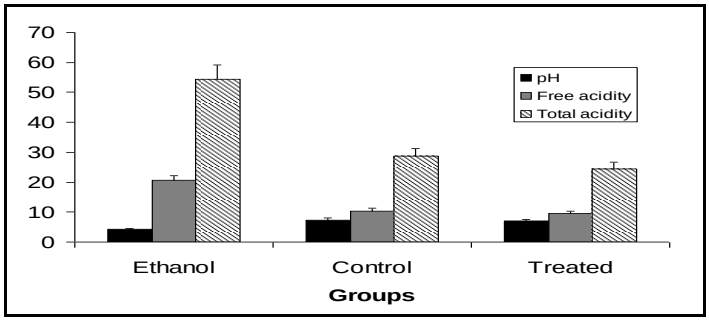


Figure 5. Effect of famotidine formulation on pH, free acidity and total acidity in pylorus ligation induced ulcer model.

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