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Formulation and Biopharmaceutical Evaluation of Gastro-Retentive Drug Delivery System of Anti-Ulcer Drugs (floating microspheres of famotidine) (Research Article)

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ABSTRACT:
The floating drug delivery system or hydrodynamically balanced systems are among the several approaches that have been made developed in order to increase the gastric transit time of drug. The microspheres are characteristically free flowing powders consisting of natural or synthetic polymers and ideally having a particle size less than 200m. Microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug.[1]
Microspheres are one of the multiarticulate delivery system and are prepared to obtain controlled the drug release from the dosage form to improve bioavailability, reduces the adverse action and prolong the action of drug, reduce absorption difference in patients, reduce the dosing frequency and adverse effects during prolong treatment. It is needed to formulate in long-acting dosage form, reaching to effective biological site rapidly.[2,3]
Famotidine is H2 receptor antagonist which is used for ulcers thus by formulating it in the form of floating microspheres it will not only show targeted action but also shows sustainability and reduced dosing interval. Thus, by formulating it as a floating microsphere the targeted action can be achieved. Famotidine is formulated as floating microspheres by Solvent evaporation method is the preparation technique that is widely preferred for the preparation of controlled release microspheres. To prepare emulsion by adding the dispersed phase consisting of drug, polymer and appropriate dispersion agent in organic solvent to dispersion medium which is immiscible with the dispersed phase and Mini matrix forms are obtained by removing the solvent used at the dispersed phase from the droplets which are formed in the emulsion[5, 6].The obtained microspheres of famotidine were subjected to various analytical techniques like Particle size analysis, SEM analysis, invitro dissolution studies and stability studies.

Key words: Famotidine, Floating microspheres, Solvent evaporation technique, Stability Studies.

I. INTRODUCTION:

Oral drug delivery system is the most preferable system because of ease in administration, patient compliance and flexibility. To develop an oral drug delivery system, it is necessary to optimize both the residence time of system within the gastrointestinal tract and release of drugs from the system. Drugs that are easily absorbed from the gastrointestinal tract and have short half life are eliminated quickly from the blood circulation and require frequent dosing. To avoid these problems, the oral controlled release formulations have been developed in attempt to release the drug slowly into the gastrointestinal tract and maintain the constant drug concentration[1].

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery system. This drug delivery systems have a bulk density less than that of gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.[2] The gastroretentive drug delivery system (GRDDS) is of special interest in improving the bioavailability of drugs that are poorly soluble, unstable at higher intestinal p^H or colonic environment and having absorption window in stomach.[3]

Drug Suitable for Gastro retentive Drug Delivery System:

- The Drugs which are locally active in the stomach like Antacids, Misoprostol, etc.
- Drugs showing narrow absorption window in Gastro intestinal tract e.g. Riboflavin,Furosemide, etc.
- Drugs showing instability in the colonic environment e.g. Ranitidine HCl, Captopril, etc.
- Drugs which are effective against normal colonic microbes e.g. antibiotics against Helicobacter pylori.

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- Drugs which have low solubility at high pH values e.g. Chlordiazepoxide, Diazepam, etc.

Drugs Unsuitable for Gastroretentive Drug Delivery System:[7]

- Drugs which have very limited solubility in the acid medium e.g. Phenytoin, etc.
- Drugs enduring instability in the gastric environmental conditions e.g. Erythromycin, etc.
- The Drugs which are mainly employed for their selective release in the colon e.g. 5-amino salicylic acid and corticosteroids, etc.

CLASSIFICATION OF GRDDS: [8-12]

Dosage forms that can be hold within the stomach are called as Gastro retentive Dosage Forms(GRDF).

Figure 1: Types of Gastro retentive Dosage Form.[12]

High Density System:

These GRDF type have a density of -3g / cm3, and are retained in the stomach rugae. These systems can be maintained in the lower part of the stomach above a maximum threshold density of 2.4-2.8g / cm3. The major limitation of it is that they are technically difficult to manufacture with a large amount of drug product.

Swelling and Expandable System:

The expandable GRDF is typically based on three configurations, a small configuration that allowsfor easy oral intake; an expanded form that is accomplished in the stomach and thus preventing its passage through the pyloric sphincter and finally another small form that is achieved in thestomach when retention is no longer necessary. Swelling usually occurs due to osmosis and the unfolding is because of mechanical shape memory.

Mucoadhesive or Bio adhesive System:

These systems allow the incorporation with the bioadhesive agents that allow the system to adhere to the walls of the stomach, thus avoiding gastric emptying. Bio/Mucoadhesive systems binds to the surface of the gastric epithelial cell, or mucin, and extend the GRT by increasing the intimacy and contact duration between the dosage type and the biological membrane.

Superporous Hydrogel:

These are the swellable systems with an average pore size of > 100µm, within a minute they swell to equilibrium due to a rapid absorption of water through capillary wetting through multiple interconnected open pores. They swell to a large size and expect to provide enough mechanical strength to endure the pressure by the gastric contraction.

Magnetic System:

The magnetic dosage types contain an extra-corporal magnet and a small internal magnet that controls the gastrointestinal transit of the dosage form.

From the formulation and technological point of view Floating Drug Delivery System (FDDS) is

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considerably easy and logical approach in the development of GRDF.[8,9,11]

Table 1: Comparison between Conventional drug delivery systems and GRDD

Sr.No.		Conventional DDs	GRDDs
1.	Toxicity	High risk of Toxicity	Low risk of toxicity
2.	Patient compliance	Less	Improves patient compliance
3.	Drug with narrow absorption window in Small intestine	Not suitable	Suitable
4.	Drug acting locally in the stomach	Not much advantageous	Very much advantageous
5.	Drugs having Rapid absorption through GIT	Not much advantageous	Very much advantageous
6.	Drug which degrades inthe colon	Not much advantageous	Very much Advantageous
7.	Drugs which are poorly soluble at an alkaline pH	Not much advantageous	Very much advantageous
8.	Dose dumping dumping	High risk of dose dumping	No risk of dose dumping

FLOATING DRUG DELIVERY SYSTEM:

FDDS or Hydro-dynamically balanced systems (HBS) are low-density systems having sufficient tendency to float over the gastric contents and remain in the stomach for an extended period of time that releases the drug component at the desired rate, while floating over the gastric contents it contributes to increased gastro-retention time and reduced fluctuation.

Floating microspheres (Hollow Microspheres) are gastroretentive drug delivery systems based on non effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core, free flowing powders consisting of proteins or synthetic polymers, ideally having a size in the range 1-1000 micrometer. When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content is needed to allow proper achievement of buoyancy[4].

Peptic ulcer is a break in the inner lining of the esophagus, stomach, or duodenum. A peptic ulcer of the stomach is called a gastric ulcer. Acetylcholine and histamine is responsible for development of peptic ulcer leads to decrease in pH[5].

Drugs used in treatment of peptic ulcers are mainly classified into three categories:

1. Antacids
2. Anticholinergics
3. H_2 receptor antagonists[6].

The Aim of the present study is to formulate and evaluate Famotidine floating microspheres in a cost effective and simple technique.Famotidine is H2 receptor antagonist which is used for ulcers thus by formulating it in the form of floting microspheres it will not only shown targeted action but also shows sustainability and reduced dosing interval.Thus by formulating it as a floating microsphers the targeted action can be achieved,absorption of the drug can be monitored and increased thus showing effective absorption and better bioavailability, Thus showing effective action.

- a gastro-retentive drug delivery system which controls the pharmacokinetic release rate of a drugto a specific site to achieve its pharmacological action.

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Basic Gastrointestinal Tract Physiology: [11]
The stomach is anatomically divided into 3 regions: fundus, body, and antrum (pylorus).
Fundus: proximal part.
Body: acts as a reservoir for undigested material,
Pylorus: it is a site for mixing of contents and act as a pump for gastric emptying by propelling actions.

Stomach Physiology:
The stomach is an expanded digestive tube section present between the oesophagus and small intestine. The stomach is contracted in the empty state, and the mucosa and sub mucosa are thrownup into distinct folds called rugae.
Below are identified the four major types of secretary epithelial cells which cover the surface of the stomach and extend into gastric pits and glands.
Mucous cells: secrete alkaline fluid.
Parietal cells: secretes a acid that is hydrochloric acid.
Chief cells: secrete pepsin, a proteolytic enzyme.
G cells: secrete the hormone gastrin.

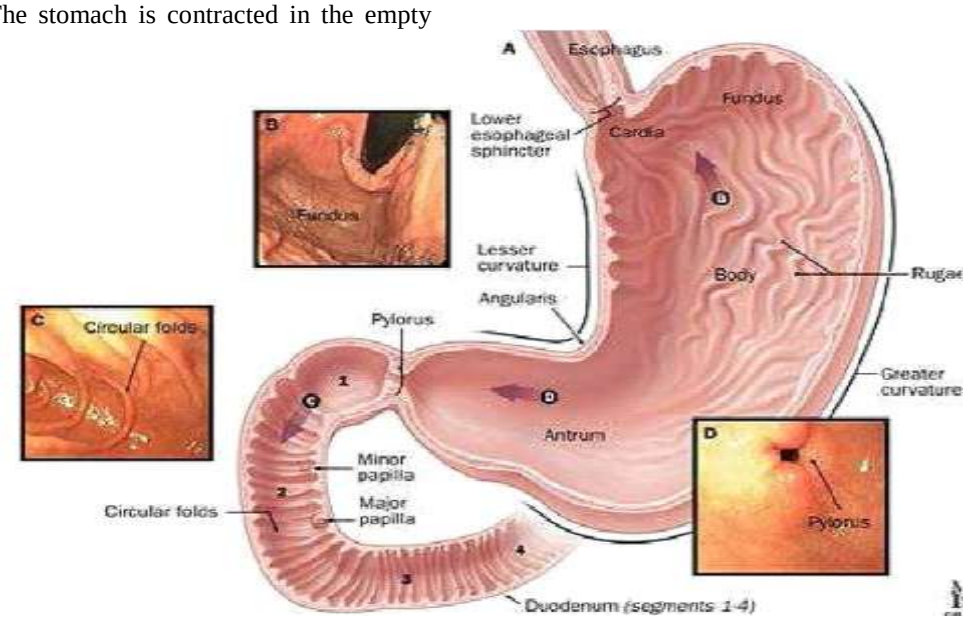

Figure 2: Physiology of stomach

Gastric empty rate:
Gastric emptying happens during both fasting and fed conditions. An inter-digestive sequence of electrical events take place during the fasting process, which pass every 2 to 3 hours in both the stomach and intestines.
It is called the inter-digestive mylo-electric cycle or myloelectric migratory cycle (MMC), which is further divided into 4 stages.

- **Phase I (Basal phase):** it lasts from 40 to 60 minutes with rare contractions.
- **Phase II (Preburst phase):** lasts for 40 to 60 minutes with intermittent action potential and contractions.
- **Phase III (burst phase):** lasts for 4 to 6 minutes, which includes intense and regular contractions for short period of time.
- **Phase IV:** lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutivecycles.[11]

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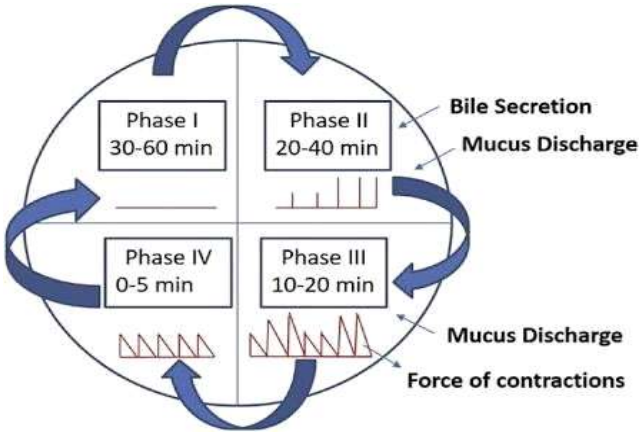

Figure 3: Motility Pattern in GIT.

Factors Controlling Gastric Retention Time of a Dosage Form: [13]

- Nature of the meal
- Fed or Unfed State
- Age
- Frequency of feed
- Concomitant drug administration
- Density
- Size and Shape
- Caloric Content

- **Effervescent FDDS**
- Gas generating system
- Volatile liquid containing system
- **Non-Effervescent FDDS**
- Colloidal gel barrier system
- Bi-layer floating tablets
- Microporous compartment system
- Floating Beads/ Alginate Beads
- Micro balloons/ Hollow Microspheres
- **Raft forming systemEffervescent FDDS**

This system makes use of a floating chamber filled with water, vacuum, air, or inert gas. CO2 which is formed as a result of an effervescent reaction between the organic acid (citric acid) and the carbonate / bicarbonate salts can be introduced into the floating chamber. Such a system uses matrix prepared with swellable polymers such as chitosan-like polysaccharides, effervescent materials such as citric acid, sodium bicarbonate, and tartaric acid, or chambers containing a liquid that gasifies at the body temperature.

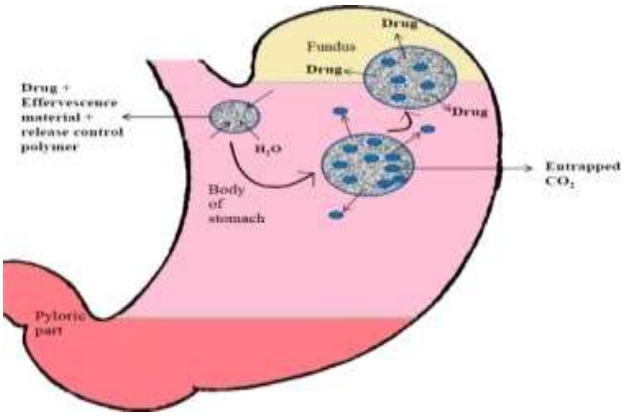

Figure 4: GRDDS based on effervescence.[10]

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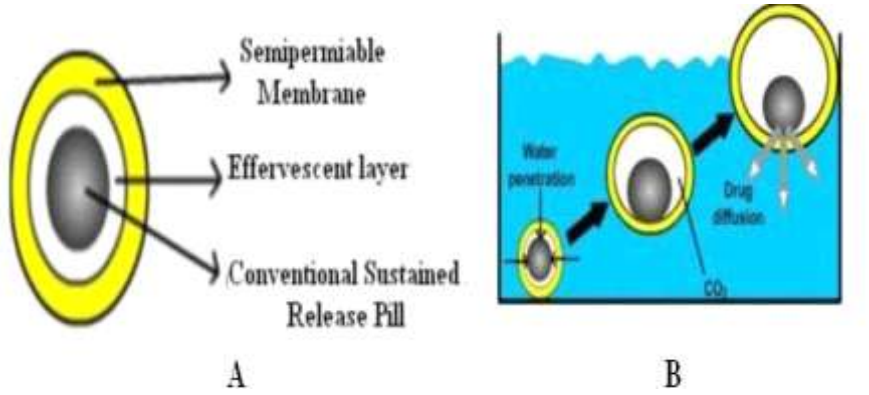

Figure 5: Multiple-unit oral drug delivery system.[14]**Gas generation system**:

This buoyant delivery system uses effervescence reaction between citric acid / tartaric acid and carbonate / bicarbonate salts to release CO2 which further reduces its specific gravity and makes it float over chime.

Volatile liquid storage system:

These contain an inflatable chamber consisting of a liquid, e.g. cyclopentane, ether, which gasifies at body temperature to induce inflation of the chamber in the stomach. The system consists of two chambers the first chamber consisting of the drug, and the volatile liquid in the second chamber.

Non-Effervescent FDDS

In GI tract, the non-effervescent FDDS is based on the mechanism of polymer swelling or bioadhesion to the mucosal layer. The excipients most frequently used in non-effervescent FDDS are:

- Hydrophilic gums,
- Gel forming or highly swellable cellulose type hydrocolloids
- Polysaccharides and matrix forming materials such as polymethacrylate, polycarbonate, polystyrene, polyacrylate, as well as bioadhesive polymers such as Carbopol and Chitosan.

Colloidal gel barrier systems / Single layer floating tablets:

Such systems contain a high degree of one or more gel forming, cellulose type hydrocolloids, polysaccharides, and polymers forming matrix, which are extremely swellable.

Bi-layer floating tablets:

A bi-layer tablet comprises of two layers with first layer is the immediate release layer, which releases the initial dose from the system while the other is the sustained release layer which absorbs the gastric fluid, creating an impermeable colloidal gel barrier on its surface and retaining a bulk density of less than 1.

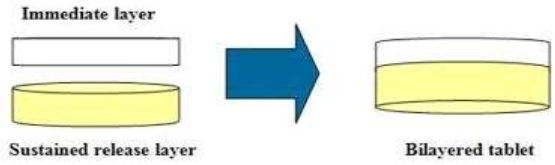

Figure 6: Bilayer tablet.[1]

Microporous compartment systems:

This technology is based on a drug reservoir being encapsulated within a micro porous compartment with apertures along its top and bottom walls.

Multi particulate system: Floating beads / Alginate beads:

Multi-particulate drug delivery systems are often oral dosage types consisting of a multiplicity of small discrete units.

Micro balloons/Hollow microspheres:

Hollow microspheres, also known as micro balloons when immersed in aqueous media they were found to float in vitro for 12 hrs.

Raft Forming System

For the delivery of antacid and other medications for gastro-infection and gastro intestinal disorders, a Raft forming systems are mostly considered. Upon contact with gastric fluid the gel forming solution swells and creates a

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viscous compact gel containing an entrapped CO2 bubbles forming raft layer on top of gastric fluid that gradually releases the drug substance into the stomach.

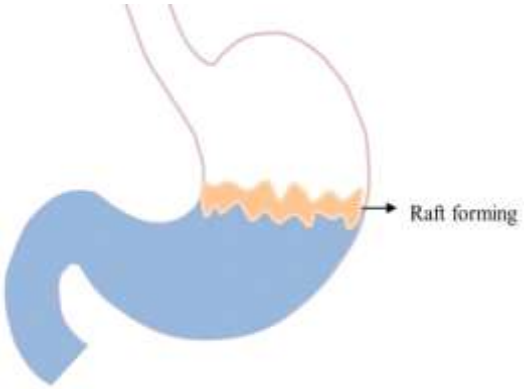

Figure 7: GRDDS based on Raft Forming System.[16]

Approaches to Design Floating Drug Delivery System: [11]

For Single Unit Dosage Forms (Ex: Tablets):

- Floating Lag Time: Time taken for the tablet to emerge onto the dissolution medium surface and is measured in seconds or minutes.
- In-vitro drug release and floating duration: This is calculated by the use of USP II devices (paddle) stirring in simulated gastric fluid (pH 1.2 without pepsin) at a speed of 50 or 100 rpm at 37±0.20C.the samples are then frequently collected and analyzed for the drug content.

The time (hrs) during which the tablets remain buoyant on the dissolution medium surface is the floating duration and is observed visually.

(C) In-vivo Gastro-Retention Assessment: This is done by X-ray or gamma-scintigraphic testing of the dosage form transition in GIT. The tablets are also tested for hardness, variation in the weight etc.

Hydrodynamically Balanced System:

The delivery system are designed to extend the stay of medication types in the gastro intestinal tract, and to help enhance absorption. HBS system produces drugs which have a greater solubility in acidic conditions and also have a particular absorption site in the upper part of the small intestine. For the drug to retain in stomach for an extended period of time the dosage form should have the bulk density of less than '1' and release the drug constantly from the dosage form.

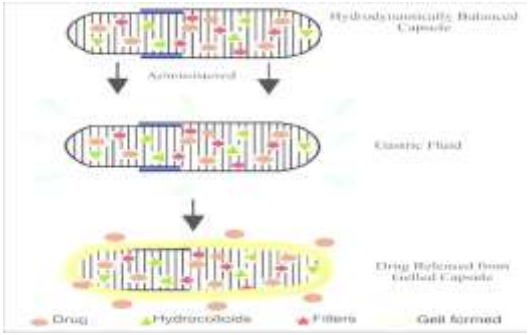

Figure 8: Working principle of Hydrodynamically Balanced System.[17]

For Multiple Unit Dosage Forms (Ex: Microspheres):

- Morphological and dimensional analysis, using electron microscopy (SEM) scanning. An optical microscope can also be used to determine the dimension.
- In-vitro floating potential (Buoyancy level): A known quantity of microspheres is distributed over the surface of a USP (Type II) dissolution system filled with 900ml 0.1 N HCl containing
- level v / v Tween 80 and agitated at 100 rpm for 12 h. After 12 hours, the floating layer and settled layers are separated, then dried in a dessicator and are weighed.

The buoyancy is calculated from the following formula.

Buoyancy (%) = Wf / (Wf +Ws) X 100

Where,

Wf and Ws are the weights of floating and settled microspheres, respectively.

Drug-excipient (DE) interactions: This is usually done by using FTIR. The appearance of a new peak, and/or disappearance of original drug or excipient peak indicates the Drug-excipent interaction.

Methods of Developing Floating Drug Delivery System:[18-21]

- **Direct compression technique**:

It means compressing tablets directly from powder content without altering the substance's physical structure itself. Dicalcium trihydrate phosphate, tricalcium phosphate, etc. are the most widely used carriers.

- **Effervescent Technique**:

An effervescent reaction between organic acid (citric acid) and bicarbonate salts will fill the floating chamber of the drug delivery system with inert gas (CO2).

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- **Wet granulation technique**:

Involves wet powder massaging, milling or drying. Wet granulation shapes the granules by binding the powders together with an adhesive rather than compacting them.

- **Ionotropic Gelation Technique**:

Gelation of anionic polysaccharide sodium alginate, the primary polymer of natural origin, was accomplished with opposite charged calcium ions (counter-ions) with the objective of forming instantaneous micro particles.

- **Solvent evaporation technique**:

Continuous phase ability is inadequate to remove the entire amount of liquid dispersal solvent. Solvent evaporates from the dispersal surface to receive hardened microspheres.

- **Spray Drying Technique**:

Involves dispersing the core layer into the liquefied coating content and spraying the core coating mixture into the environment so that the coating is solidified by rapidly evaporating in which the coating material is solubilized.

- **Melt Solidification Technique**:

This method involves emulsifying the molten mass in the aqueous phase followed by cooling it to solidify. Lipids, waxes, polyethylene glycol, etc. are the carriers used for this technique.

- **Melt Granulation Technique**:

This is the method that agglomerates the pharmaceutical powders using a meltable binder and does not use water or organic solvents for granulation.

Excipients Incorporated in Different Floating Dosage Form: [22]

- **Effervescent Agents:** E.g. citric acid, tartaric acid, sodium bicarbonate, Di-SGC (Disodium glycine carbonate), CG (Citroglycine).
- **Release rate Retardants:** Some substances such as, Talc, Dicalcium phosphate, Magnesium stearate are used for retarding the release rate.
- **Inert Fatty Materials:** E.g. Long chain fatty alcohols, Beeswax, Fatty acids, Gelucires 39/01 and 43/01.
- **Release rate Accelerants:** E.g. Mannitol, lactose, etc.
- **Hydrocolloids:** E.g. Acacia, β-cyclodextrin , Gelatin, Alginates, Pectin, HPMC, carbopoletc.
- **Buoyancy increasing Agents:** E.g. Ethyl Cellulose and Polypropylene Foam Powder (Accurel MP 1000).

Advantages of Floating Drug Delivery System:[23]

- FDDS can remain in the stomach for several hours and thereby prolonging the gastric retention time of various drugs.
- Advantageous for drugs which are meant for local action in the stomach

E.g. Antacids.

- Formulation of FDDS are useful in intestinal movement and in diarrhoea to hold the drug in floating state in the stomach in order to get comparatively better response.
- By decreasing the dosing frequency FDDS improves patient compliance.
- Treatment of gastrointestinal disorders such as gastroesophageal reflux.
- Despite of first pass effect the bioavailability since the plasma drug concentration areavoided.
- HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs since these drugs are acidic and causes irritation on the stomach wall
- Advantageous for drugs which are absorbed through the stomach E.g. Ferrous salts,Antacids.
- Delivery of the drug to the specific site.

Disadvantages of Floating Drug Delivery System:[23]

- The drug substances which are unstable in the acidic environment of the stomach are not suitable candidates for integration into the systems.
- In these systems the presence of food is usually required to prolong their gastric emptying.
- It is not suitable for drugs which are having stability or solubility problem in GIT.
- The drugs which undergo first pass effect and the drugs which are significantly absorbed throughout gastrointestinal tract are only desirable candidate.
- The tendency to float depends on the hydration state of the dosage form. Intermittent wateradministration is useful in order to keep these tablets floating.

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Evaluation of Floating Drug Delivery System:

Bulk Density:

It is the ratio of total mass of powder (m) to the bulk volume (Vo) of powder.

Db=m/Vo

Tapped Density:

It is the ratio of total mass of powder (m) to the tapped volume (Vi) of powder.

Dt = m/Vi

Compressibility Index:

$= \frac{\rho t - \rho o}{\rho t} x100$ The flowability of powder can be evaluated via evaluating the bulk density (ρo) and tapped density(ρt) of powder and the rate at which it packed down. Compressibility index calculated by means of

Where,

ρo = Bulk density g/ml,

ρt = Tapped density g/ml.

Hausner's Ratio: It is evaluated by means of taking Tapped density and it divided by Bulk density by the usage of following formula.

Hausner's Ratio= Tapped density / Bulk density

Table 2: Specification for Carr's index and Hausner's ratio.[29]

Sl. No.	Flow ability	Carr's index (%)	Hausner's ratio
1	Excellent	0-10	1.00-1.11
2	Good	10-15	1.12-1.18
3	Fair	16-20	1.19-1.25
4	Possible	21-25	1.26-1.34
6	Poor	26-31	1.35-1.45

Angle of Repose:

The frictional forces in a loose powder or granules can be measured via angle of repose. This is themaximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules are allowed to flow through the funnel fixed to a stand at fixed height (h).

The angle of repose, then calculated by measuring the height and radius of the heap of granules formed.

Tan θ = (h/r)θ= $\tan^{-1}$ (h/r)

θ = angle of repose

h = height of the heap

r = radius of the heap

Table 3: The relationship between Angle of repose and powder flow.

Angle of repose	Powder flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Tablet Dimensions:

Thickness and diameter were measured using a calibrated Vernier Caliper. Three tablets of eachformulation have been picked randomly and thickness were measured separately.

Hardness:

Hardness shows the capability of a tablet to face up to mechanical shocks while handling. The hardness of the tablets was evaluated using Monsanto hardness tester. It was expressed in kg/cm2. Three tablets have been randomly picked and hardness of the tablets was decided.

Friability test:

The friability of tablets was evaluated by using Roche Friabilator. It was expressed in percent (%). Ten tablets had been to start with weighed (W) and transferred into friabilator. The friabilator wereoperated at 25 rpm for 4 minutes or run as much as 100 revolutions. The tablets have been weighedagain (Wo). The % friability was then calculated by using formula–

%F = 100 (1-Wo/W)

% Friability of tablets less than 1% was considered desirable.

Tablet Density:

Tablet density was an excellent parameter for floating tablets. The tablet could floats most effective when its density turned into much less than that of gastric fluid (1.004). The density was determined by the usage of following formula.

V = ᴨr^{2}hd = m/v

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Where,
v = volume of tablet (cc)r =radius of tablet (cm)
h = crown thickness of tablet (g/cc) m = mass of tablet

Weight Variation Test:

Ten tablets were selected randomly from each batch and weighed separately to test for weight variation. A little variation was allowed in the weight of a tablet through U.S. Pharmacopoeia.

Table 4: Percentage deviation in weight variation.

Average weight of a tablet	Percent deviation
130 mg or less	10
>130mg and <324mg	7.5
324mg or more	5

Determination of Buoyancy lag time:

The buoyancy lag is the time required for tablet to come out towards surface & float. The buoyancy of tablets was studied at 37±0.5ºc in 900ml of simulated gastric fluid. The buoyancy lag time was determined by the usage of stop watch and overall floating time was observed visually.

Floating time:

Floating time was measured by the use of USP dissolution apparatus-II at 50 rpm using 900ml of 0.1N HCl and temperature was set at 37±0.5ºC, throughout the study. The duration of floating (floating time) is the time the tablet floats within the dissolution medium (including floating lag time, which is the time required for the tablet to rise to the surface) is measured by visual observation.

Swelling Index:

Swelling study was carried out for the floating sustained release layer tablets. The accurately weighed tablets were placed in USP dissolution apparatus II containing 900ml of 0.1N HCL.

$$\text{Swelling index} = \frac{(W_g - W_o)}{W_o} \times 100$$

maintained at 37±2ºC and allowed to swell up to constant weight. The tablets had been removed, blotted with filter paper, and changes in weight were determined. The experiments were performed in triplicate. The degree of swelling (Swelling index) was then determined from the formula.

Where,
Wo is the initial weight of tablet and Wg is the weight of tablet at equilibrium swelling in the medium.

Drug Content:

Five tablets were chosen randomly from a batch, weighed and powdered in a mortar. An accurately weighed quantity of powdered tablets equivalent to 100 mg was taken in a standard flask and the volume was filled up to the mark with 0.1 N HCl and the solution was filtered through a 0.45 um membrane paper. Analysis was done by the usage of spectrophotometric method.

In-vitro dissolution studies:

The release rate of floating tablets was determined by the usage of USP dissolution testing apparatus II (Paddle type). The dissolution test was carried out using 900 ml 0.1N HCL, at 37 ± 0.5°C. A sample (5ml) of the solution was taken from the dissolution apparatus at every hour for 12 h, and the samples were replaced with fresh dissolution medium. The samples were passed via Whatman's filter paper and the absorbance of these solutions was measured.

Application of Floating Drug Delivery System: 28

Enhanced Bioavailability:

The bioavailability of famotidine CR-GRDF is substantially increased compared with the administration of non GRDF CR polymeric formulations.

Sustained delivery of drugs:

Oral CR formulations experienced problems in the GIT like gastric residence time. HBS systems that can stay in the stomach for prolonged period of time and having a bulk density of less than 1 and can float on the gastric contents can usually overcome these problems.

Site specific drug delivery systems:

The controlled, gradual drug delivery to the stomach provides appropriate local therapeutic rates and reduces the systemic exposure of the drug. The dosing frequency can be decreased by extended gastric availability from a site driven drug delivery system. E.g. Furosemide and Riboflavin.

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Improvement of Absorption:

Drugs with low bioavailability due to site specific absorption from the upper part of the GIT are possible candidates to be developed as floating drug delivery systems, by optimizing their absorption.

Minimized adverse reaction at the colon:

Retention of the drug in the stomach in HBS minimizes the amount of drug entering the colon. Unwanted drug activity in the colon region can thus be avoided.

Reduced drug concentration fluctuation:

Continuous input of the drug following CR-GRDF administration creates concentrations of the blood drug within a narrower range compared with types of immediate release dosage forms.

Table 5: List of Drugs formulated as single and multiple unit forms of Floating DrugDelivery System.[29]

Tablets	Ciprofloxacin, Chlorpheniramine maleate, Theophylline, Furosemide, Captopril, Acetylsalicylic acid, Sotalol, Nimodipine, Amoxycillintrihydrate, Verapamil HCl, Isosorbidedinitrate, Isosorbide mononitrate, Prednisolone, Acetaminophen, Ampicillin, Cinnarazine, Riboflavin 5 Phosphate, Diltiazem, Flurouracil, Piretanide.
Capsules	L Dopa, Benserazide, Urodeoxycholic acid, Chlordiazepoxide HCl, Furosemide, Nicardipine, Misoprostol, Diazepam, Propranolol.
Microspheres	Aspirin, Griseofulvin, Verapamil, p-Niroaniline, Ketoprofen, Terfenadine, Tranilast, Ibuprofen.
Granules	Diclofenac sodium, Prednisolone, Indomethacin
Films	Drug Delivery Device, Cinnarizine.
Powders	Several basic drugs.

Table 6: The Marketed Products of Floating Drug Delivery System.[13]

Brand Name	Delivery System	Drug	Company
Valrelease®	Floating Capsule	Diazepam	Hoffmann-LaRoche
Modopar® HBS (Prolopa® HBS)	Floating, CR capsule	Benserazide and L –Dopa	Roche Products, USA
Liquid Gaviscon®	Effervescent floating liquid alginate preparations	Aluminium hydroxide, MgCarbonate	Glaxo Smithkline,India
Topalkan®	Floating liquid alginate Preparations	Al – Mg antacid	Pierre Fabre Drug, France
Conviron®	Colloidal gel formingFDDS	Ferrous sulphate	Ranbaxy, India
Cytotech®	Bilayer floating capsule	Misoprostol	Pharmacia, USA
Cifran OD®	Gas-generating floating form	Ciprofloxacin	Ranbaxy, India

AIM AND OBJECTIVE:

- The main aim of study is to prepare the floating microspheres which will help in releasing the proton pump inhibitor drugs in stomach. So that they can be absorbed in stomach for a longer period of time and show better bioavailability.
- The Proton pump inhibitor drugs are used in the treatment when there is more acid secretion in the stomach. These drugs will bind to the H+/K+ ATPase present in the parietal cells in stomach. So to show their maximum action these drugs should remain in the stomach, which is possible by preparing the Floating Microspheres of Proton pump inhibitor drugs.
- The proton pump inhibitors are well absorbed in the stomach at pH 5 than in intestine. The floating microspheres are helpful in increasing the absorption of these drugs.

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- The floating microspheres have the following advantages over the floating tablet; it is

having less intersubject variation than the floating tablets.

b) The floating microspheres will reduce the fluctuation of the drug.

c) The floating microspheres will reduce the adverse effect of acidic drugs causing

gastric irritation by controlled release of these drugs.

The floating microspheres of Proton Pump Inhibitor drug famotidine will be prepared by the methods like solvent evaporation. The polymer ethyl cellulose, hydroxy propyl ethyl cellulose, acrycoat S100, celulose acetate, methyl cellulose will be used in the Study.

II. MATERIALS AND METHODS

- Formulation of famotidine Floating Microspheres were prepared by using various excipients includes sodium alginate as microsphere core forming agent, HPMC K4M, HPMC K15M and HPMC K100M as rate controlling agent, calcium carbonate as gas generating agent, and calcium chloride as cross-linking agent.
- Floating microspheres Preparation Famotidine Microspheres were formulated by ionotropic gelation technique mentioned in Table 1. Initially, 2% sodium alginate solution was prepared by dissolving in distilled water and stirred thoroughly by magnetically. On complete solution, accurately weighed quantity of drug followed by HPMC K4M, HPMC K15M, HPMC K100M and calcium carbonate of different weights were added to the above dispersion.
- Then the above dispersion was stirred at 500 rpm, maintained room temperature. The mixture was sonicated for 30 min to eliminate air bubbles that may have been formed during the stirring process. The homogenous dispersion was extruded using a 20G needle fitted with a 10 ml syringe into 100 ml of 1% of calcium chloride solution, being stirred at 100 rpm for 10 min into the gelation medium. Then microspheres were collected, washed with distilled water and oven dried at 60°C.

Formulation With HPMCK-4M

Formulation code	Famotidine (mg)	Sodium alginate (%)	HPMCK 4M (mg)	Calcium Carbonate (mg)	Calcium Chloride (%)
F1	150	2	300	50	1
F2	150	2	250	100	1
F3	150	2	200	150	1
F4	150	2	150	200	1
F5	150	2	100	250	1
F6	150	2	50	300	1

Formulations with HPMC K-100M

Formulation code	Famotidine (mg)	Sodium alginate (%)	HPMC K100M (mg)	Calcium Carbonate (mg)	Calcium Chloride (%)
F7	150	2	300	50	1
F8	150	2	250	100	1
F9	150	2	200	150	1
F10	150	2	150	200	1
F11	150	2	100	250	1
F12	150	2	50	300	1

Formulation code	Famotidine (mg)	Sodium alginate (%)	HPMC K15M (mg)	Calcium Carbonate (mg)	Calcium Chloride (%)
F13	150	2	300	50	1

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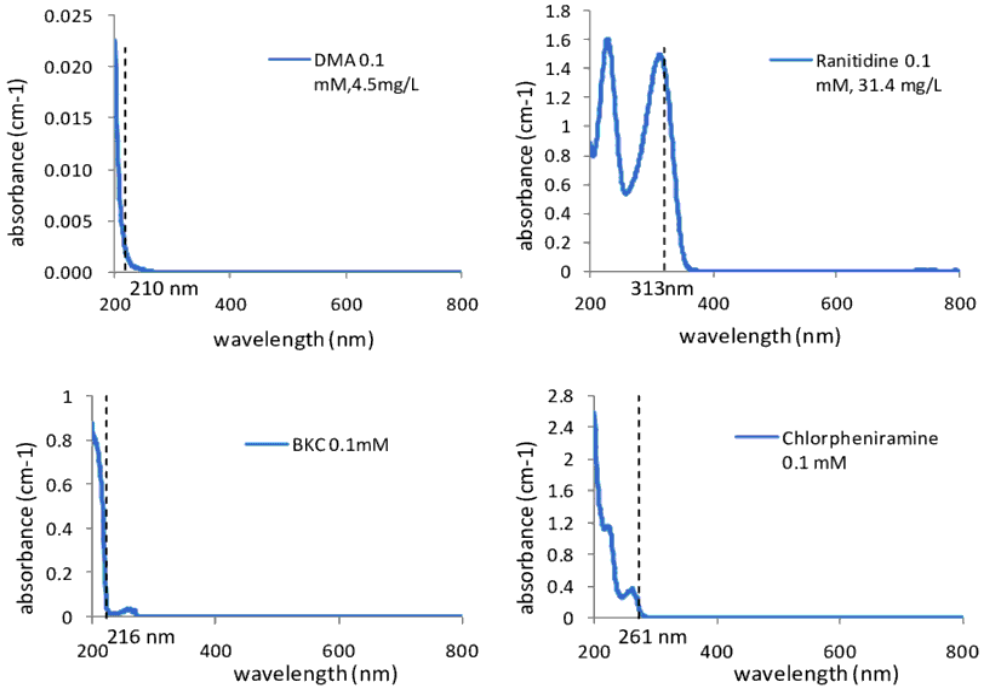
F14	**150**	**2**	**250**	**100**	**1**
F15	**150**	**2**	**200**	**150**	**1**
F16	**150**	**2**	**150**	**200**	**1**
F17	**150**	**2**	**100**	**250**	**1**
F18	**150**	**2**	**50**	**300**	**1**

Formulations with HPMC K-15M

Analytical Methods

Suitable analytical method was developed for famotidine using UV spectroscopy and analytical wavelength of λ_{max} 263nm were identified in 0.1 N hydrochloric acid solution. Calibration curve were constructed in this media. The methods have shown good reproducibility. Beer Lambert‟s law was obeyed in the range of 2 to 10 µg/ml for 0.1 N HCl solutions.

Figure 9.1: UV spectrum of famotidine



Equilibrium solubility study of pure drug:

Equilibrium solubility of pure drug was determined in various solvents, such as 0.1 N HCl, phosphate buffer pH 7.4 and in distilled water by using UV spectrophotometer represented in table 4. Pure drug was found to be practically insoluble in distilled water as the solubility was found to be 10 µg/ml at equilibrium state. In 0.1 N HCl drug solubility was found to be 261 µg/ml, which indicates that drug is highly soluble in acidic medium.

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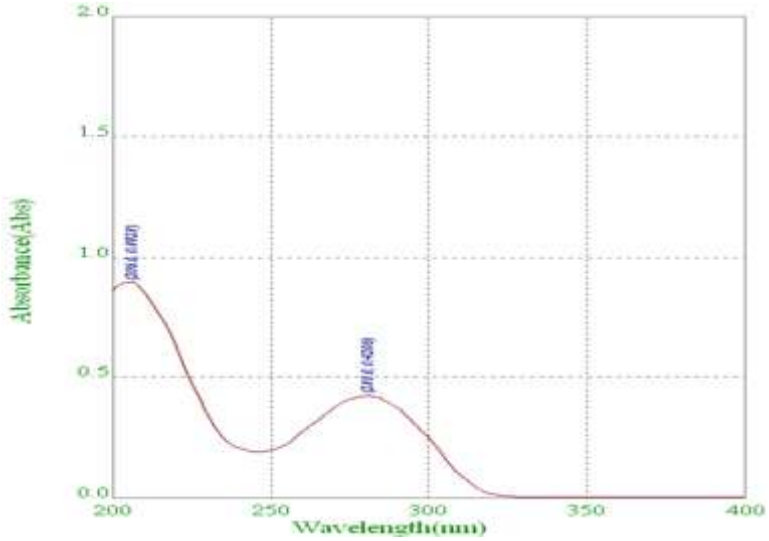

Fig.10: Standard curve of famotidin in 0.1 N HCl at 261 nm

concentration	absorbance
2	0
4	0.071
6	0.138
8	0.212
10	0.276

Table-1: : Standard curve of famotidine in 0.1 N HCl at 261 nm

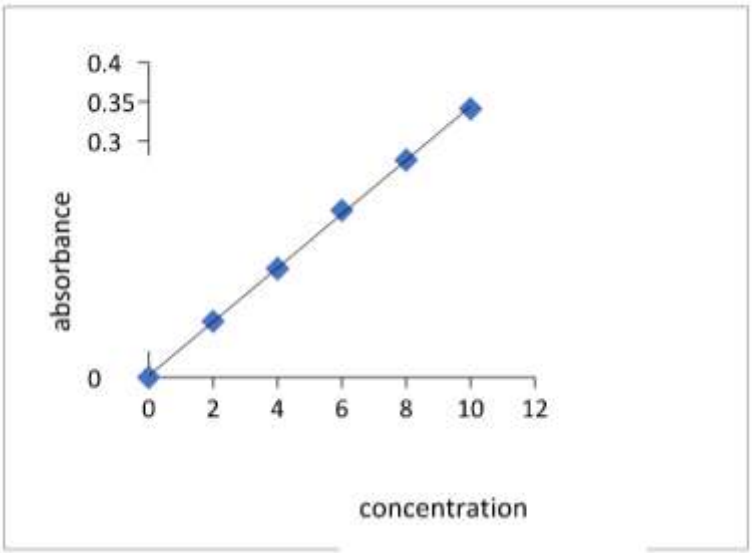

Fig.11: Standard curve of famotidine in 0.1 N HCl at 261 nm

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Table- 2: Formulation trials of Famotidine Floating microspheres:

Formulation code	Particle Size (µm)	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	Carr's Index (%)	Buoyancy % (%)
F1	55.4±0.04	0.59	**0.58**	27°.93	14.56	50.13
F2	60.12± 0.08	**0.66**	**0.59**	23°.91	9.34	64.42
F3	65.29± 0.13	**0.74**	**0.62**	29°.67	8.34	78.86
F4	73.43± 0.04	**0.76**	**0.73**	30°.54	13.36	69.53
F5	62.35±0.04	**0.59**	**0.57**	27°.94	8.12	69.24
F6	79.67±0.09	**0.89**	**0.83**	30°.15	9.23	91.24
F7	77.22±0.02	**0.67**	**0.72**	30°.15	13.95	67.12
F8	75.45±0.09	**0.79**	**0.67**	25°.54	10.32	90.17
F9	55.23±0.14	**0.68**	**0.51**	22°.91	11.04	65.08
F10	63.22±0.11	**0.67**	**0.79**	23°.70	12.34	52.05
F11	83.34±0.10	0.68	0.68	30°.24	12.34	66.74
F12	78.45±0.21	0.67	0.67	22°.91	10.98	87.29
F13	65.32±0.09	0.82	0.82	25°.54	13.95	70.18
F14	55.23± 0.14	0.56	0.63	22°.91	10.32	70.18
F15	73.22± 0.11	0.72	0.77	21.70	8.08	75.30
F16	81.34± 0.10	0.68	0.65	30°.24	7.67	80.47
F17	50.67±0.13	0.47	0.51	20°.74	7.67	94.23
F18	74.35 ± 0.32	0.80	0.72	29°.67	11.43	85.16

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Drug-excipient compatibility studies Fourier Transform Infrared Spectroscopy (FTIR):

The FTIR technique can be used to recognize the functional groups in the pure drug and drug-excipient compatibility. Pure Famotidine FTIR spectra and optimized formulation were recorded by using FTIR (SHIMADZU). Weighed quantity of KBr and excipients were taken in the ratio 100: 1 and mixed by mortar. The samples were made into pellet by the application of pressure. Then the FTIR spectra were recorded between 4000 - 400 cm−1. SEM studies Surface nature of microspheres includes size and shape was examined with the help of Scanning Electron Microscope (HITACHI, S-3700N).

The microspheres were dried completely prior to analysis and SEM was carried out at various magnifications.

Stability studies Optimized formulation was subjected to stability testing at 40°C ± 2°C/75% RH ± 5% RH for 6 months using stability chamber (Thermo Lab, Mumbai). Samples were withdrawn at predetermined intervals 0, 30, 60, 120 and 180 days period according to ICH guidelines. Various in vitro parameters like % yield, entrapment efficiency and in vitro release studies were determined.

Pre-formulation studies:

Formulation code	Particle Size (µm)	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	Carr's Index (%)	Buoyancy% (%)
F1	55.4±0.04	0.59	**0.58**	27˚.93	14.56	50.13
F2	60.12± 0.08	**0.66**	**0.59**	23˚.91	9.34	64.42
F3	65.29± 0.13	**0.74**	**0.62**	29˚.67	8.34	78.86
F4	73.43± 0.04	**0.76**	**0.73**	30˚.54	13.36	69.53
F5	62.35±0.04	**0.59**	**0.57**	27˚.94	8.12	69.24
F6	79.67±0.09	**0.89**	**0.83**	30˚.15	9.23	91.24
F7	77.22±0.02	**0.67**	**0.72**	30˚.15	13.95	67.12
F8	75.45±0.09	**0.79**	**0.67**	25˚.54	10.32	90.17
F9	55.23±0.14	**0.68**	**0.51**	22˚.91	11.04	65.08
F10	63.22±0.11	**0.67**	**0.79**	23˚.70	12.34	52.05
F11	83.34±0.10	0.68	0.68	30˚.24	12.34	66.74
F12	78.45±0.21	0.67	0.67	22˚.91	10.98	87.29
F13	65.32±0.09	0.82	0.82	25˚.54	13.95	70.18
F14	55.23± 0.14	0.56	0.63	22˚.91	10.32	70.18
F15	73.22± 0.11	0.72	0.77	21.70	8.08	75.30
F16	81.34± 0.10	0.68	0.65	30˚.24	7.67	80.47
F17	50.67±0.13	0.47	0.51	20˚.74	7.67	94.23
F18	74.35 ± 0.32	0.80	0.72	29˚.67	11.43	85.16

Table-3: Bulk density (g/ml) Tapped density (g/ml) Angle of repose Carr's Index (%) Buoyancy

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Table 3: % yield, % swelling index, and entrapment efficiency of famotidine Floating microspheres formulations

Formulation Code	Percentage Yield (%)	Swelling index (%)	Entrapment Efficiency (%)
F1	90.35 ± 0.12	82.24 ± 0.24	70.23 ± 0.31
F2	84.35 ± 0.35	78.24 ± 0.16	89.14 ± 0.22
F3	77.95 ± 0.27	80.15 ± 0.31	87.63 ± 0.17
F4	92.45 ± 0.21	70.51 ± 0.28	83.45 ± 0.34
F5	68.75 ± 0.32	87.31 ± 0.25	78.29 ± 0.12
F6	83.92 ± 0.28	80.19 ± 0.17	67.83 ± 0.35
F7	65.45 ± 0.19	65.45 ± 0.19	76.17 ± 0.23
F8	73.16 ± 0.30	74.35 ± 0.17	74.35 ± 0.17
F9	82.93 ± 0.36	65.27 ± 0.21	88.65 ± 0.36
F10	85.31 ± 0.24	78.13 ± 0.15	78.35 ± 0.33
F11	69.27 ± 0.19	75.52 ± 0.28	86.98 ± 0.29
F12	89.11 ± 0.33	89.11 ± 0.33	91.23 ± 0.12
F13	62.75 ± 0.25	73.92 ± 0.12	78.25 ± 0.33
F14	82.34 ± 0.31	88.92 ± 0.26	75.16 ± 0.14
F15	76.95 ± 0.11	81.62 ± 0.31	70.19 ± 0.26
F16	85.45 ± 0.24	77.24 ± 0.32	68.10 ± 0.15
F17	95.47 ± 0.36	92.13 ± 0.17	62 ± 0.29
F18	80.42 ± 0.29	19 ± 0.30	84.73 ± 0.13

Release order kinetics of optimized formulation Reference Standard:

Formulation code	**Zero order R2**	**First order R2**	**Higuchi R2**	**Korsmeyer-Peppas R2**	**Peppasn value**
F1	**0.905**	**0.668**	**0.911**	**0.922**	**0.555**
F2	**0.911**	**0.711**	**0.914**	**0.933**	**0.636**
F3	**0.965**	**0.815**	**0.922**	**0.944**	**0.587**
F4	**0.925**	**0.718**	**0.922**	**0.924**	**0.688**
F5	**0.954**	**0.804**	**0.931**	**0.941**	**0.647**
F6	**0.907**	**0.709**	**0.918**	**0.933**	**0.599**
F7	**0.913**	**0.804**	**0.949**	**0.916**	**0.596**
F8	**0.939**	**0.721**	**0.922**	**0.951**	**0.666**
F9	**0.957**	**0.807**	**0.949**	**0.55**	**0.647**
F10	**0.981**	**0.819**	**0.933**	**0.922**	**0.720**
F11	**0.977**	**0.824**	**0.952**	**0.970**	**0.567**
F12	**0.984**	**0.785**	**0.944**	**0.958**	**0.679**
F13	**0.957**	**0.824**	**0.919**	**0.949**	**0.622**
F14	**0.944**	**0.829**	**0.958**	**0.971**	**0.597**
F15	**0.954**	**0.819**	**0.911**	**0.947**	**0.711**
F16	**0.980**	**0.824**	**0.957**	**0.967**	**0.714**
F17	**0.989**	**0.839**	**0.964**	**0.976**	**0.720**
F18	**0.944**	**0.816**	**0.954**	**0.967**	**0.711**
Marketed product	**0.77**	**0.936**	**0.921**	**0.948**	**0.393**

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Mathematical modeling of Marketed product

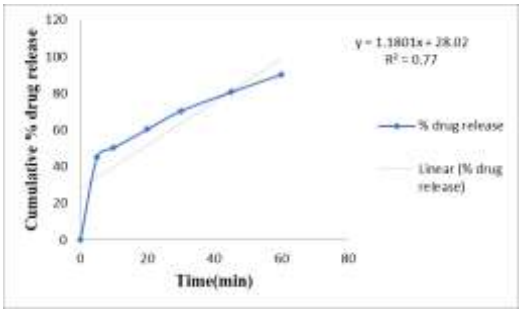


Fig. 8: Zero order plot for Marketed product:

Fig. 9: First order plot for Marketed product

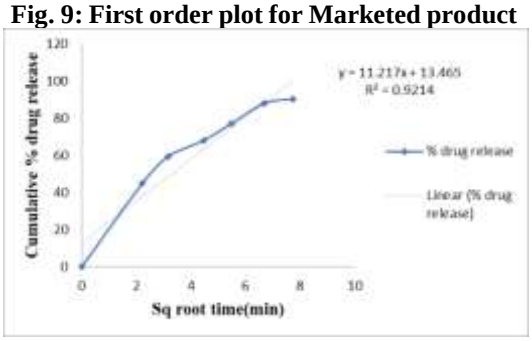
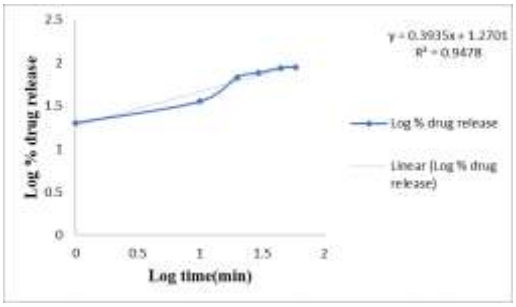


Fig. 10: Higuchi model for Marketed product



Stability studies of optimized floating microspheres:

Retest Time for Optimized formulation	**% yield**	**Entrapment efficiency (%)**	**In vitro drug release profile (%)**
0 day	95.47 ± 0.36	92.13 ± 0.17	96.54 ± 0.72
30 days	94.75 ± 0.242	91.91 ± 0.186	96.25 ± 0.293
60 days	94.28 ± 0.173	91.26 ± 0.153	95.33 ± 0.184

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120 days	93.61 ± 0.265	90.87 ± 0.291	94.19 ± 0.253
180days	93.12 ± 0.321	90.12 ± 0.172	93.65 ± 0.341

III. RESULTS AND DISCUSSION:

The particle size, % buoyancy and micromeritic properties of the microspheres were determined in the form of bulk density, tapped density, angle of repose and carr's index results mentioned in Table 2. The size of prepared microspheres ranged in from 50.67 ± 0.13 to 83.34 ± 0.10µm, comparatively, lower particle size was observed in HPMC K100M as rate retarding polymer. The bulk density and tapped density of were ranged from 0.47 to 0.89 g/ml and 0.51 to 0.83 g/ml, respectively. The angle of repose values was in the range of 20˚.74 - 30˚.54, which shows excellent to good flow properties, while the carr's index for all formulations was in the range of 7.67% - 14.56%, which indicated excellent to good flow properties. This suggests that the microspheres can be easily handled during processing. The % buoyancies of the microspheres were found highest (94.23) in F17 this may be due to slow penetration of the dissolution medium in the microspheres, as HPMC K100M is better water swellable polymer than HPMC K4M and HPMC K15M.

In vitro drug release studies:

The drug release from the floating microspheres of Famotidine was controlled over a period of 12h and graphical representation of all the formulations were shown in Figures 1, 2 & 3. The Cumulative % drug release of optimized formulation F17 was found to be 96.54 ± 0.72% at the end of 12 h where as marketed product noted 94.53 ± 0.26% within 12 h.

SEM studies of Famotidine microspheres:

The microspheres surface was rough and spherical in shape as seen in Figure 14. The surface of the Famotidine microspheres was rough due to higher concentration of drug consistently discreted at the molecular level in the matrices.

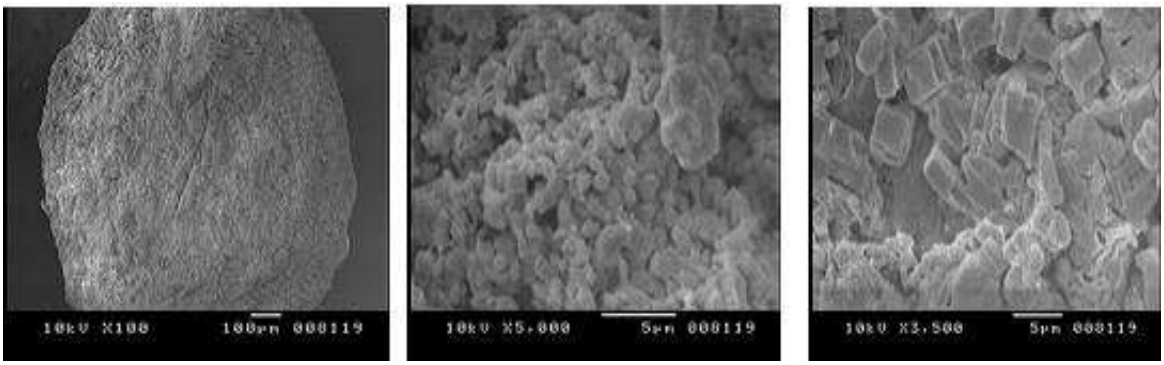

Fig. 14: Scanning electron micrographs of optimized floating microspheres

Stability studies:

Stability studies of optimized Famotidine microspheres as per ICH guidelines was carried out for 6months at 40°C ± 2°C/75% RH ± 5% RH showed in the Table 5. At predetermined time intervals samples were withdrawn and subjected to % yield, entrapment efficiency and in vitro drug release analysis. Significant change was not observed in results before and after stability studies.

Indicating the optimized formulation (F17) was stable. Famotidine loaded floating microspheres were prepared by ionotropic gelation method. From the results it concluded that formulation F17 was found to be satisfactory results in terms of excellent Micromeretic properties, particle size (50.67 ± 0.13µm), yield of microsphere (95.47 ± 0.36%), Entrapment efficiency

(93.67 ± 0.29%), % buoyancy (94.23%), swelling index(92.13 ± 0.17%) and highest in vitro drug release of 98.23

± 5.49% in a sustained manner with constant fashion over extended period for 12 h compared with marketed product 95.87 ± 0.31 in 12 h. The drug and excipients were compatible studied by using FTIR. Drug release from Famotidine microspheres followed Zero order and Higuchi model. It was suggested that mechanism of drug release from microspheres was diffusion controlled. The prepared microspheres were spherical in shape studied by SEM studies. The

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optimized formulation F17 was stable. Hence the formulated and prepared floating Famotidine microspheres may establish to be potential candidate for safe and effective sustained drug delivery and improve the bioavailability.

Drug excipient compatibility studies

FTIR spectroscopy of Famotidine microspheres

The FTIR spectrum of pure drug (Figure 13) showed characteristic sharp peaks at 3421 cm^{-1} (C-N stretch), 2951 cm-1 (C-H stretch), 1436 cm-1 (C=H deformation inNCH, CH), 1500 cm-1 (CH & OCH groups), 1587 cm-1

(Conjugated with NO), 1419 cm^{-1} for CH2 bond. There were no new significantbonds observed in the pure

FTIR spectroscopy of Famotidine microspheres

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(Conjugated with NO), 1419 cm^{-1} for CH2 bond. There were no new significant bonds observed in the pure drug (Figure 12) and optimized formulation (Figure 13), which indicates that no interaction observed between the drug and excipients.

FTIR GRAPHS:

The FTIR technique can be used to recognize the functional groups in the pure drug and drug-excipient compatibility. Pure Famotidine FTIR spectra and optimized formulation were recorded by using FTIR (SHIMADZU). Weighed quantity of KBr and excipients were taken in the ratio 100: 1 and mixed by mortar. The samples were made into pellet by the application of pressure. Then the FTIR spectra were recorded between 4000 - 400 cm^{-1}

Fig-12: FTIR spectrum of pure drug Famotidine.

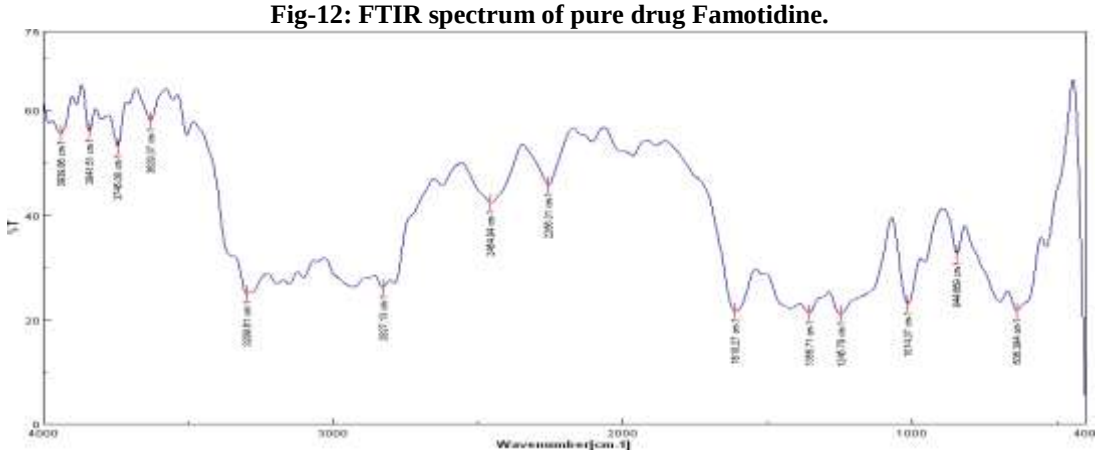
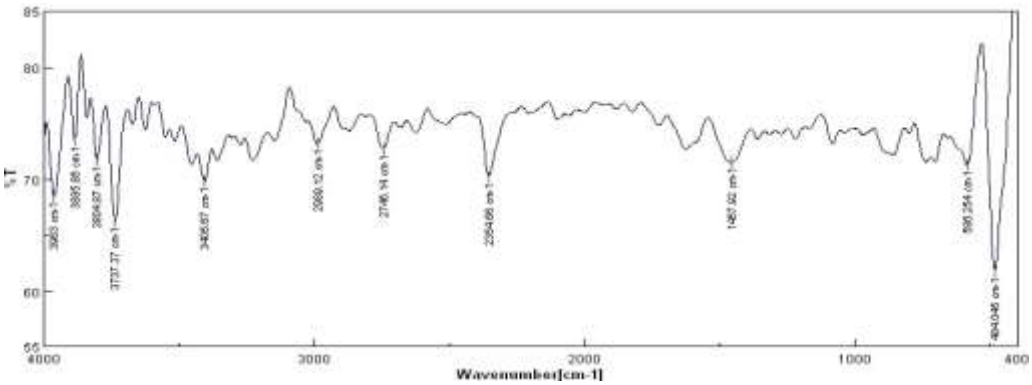


Fig13: FTIR Spectrum of Floating Famotidine microspheres:



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The FTIR spectrum of pure drug (Figure-12) showed characteristic sharp peaks at 3421 cm-1 (C-N stretch), 2951 cm-1 (C-H stretch), 1436 cm-1 (C=H deformation in NCH, CH), 1500 cm-1 (CH & OCH groups), 1587 cm-1

(Conjugated with NO), 1419 cm^{-1} for CH2 bond. There were no new significant bonds observed

in the pure drug (Figure-13) and optimized formulation (Figure 13), which indicates that no interaction observed between the drug and excipients.

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