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Formulation And Evaluation Of Gastro-Retentive Drug Delivery System Of Anti-Ulcer Drugs (Floating Microspheres Of Famotidine)

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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 200µm. 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.

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

Drugs Unsuitable for Gastro retentive 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-aminosalicylic acid and corticosteroids, etc. classification of grdds: Dosage forms that can be hold within the stomach are called as Gastro retentive Dosage Forms(GRDF).

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 allows for 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 the stomach 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.

Super porous 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 considerably easy and logical approach in the development of GRDF.

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 oftime 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 drug to a specific site to achieve its pharmacological action.

Basic Gastrointestinal Tract Physiology:

The stomach is anatomically divided into 3 regions: fundus, body, and antrum (pylorus).

Fundus: proximal part.

Body: acts as a reservoir for undigested material,

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 thrown up 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.

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 isfurther divided into 4 stages.

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

Factors Controlling Gastric Retention Time of a Dosage Form:

A. Effervescent FDDS

1. Gas generating system
2. Volatile liquid containing system

B Non-Effervescent FDDS

3. Colloidal gel barrier system
4. Bi-layer floating tablets
5. Microporous compartment system
6. Floating Beads/ Alginate Beads
7. Micro balloons/ Hollow Microspheres

B. 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) andthe 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 liquidthat gasifies at the body temperature.

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 orbioadhesion 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 whichabsorbs the gastric fluid, creating an impermeable colloidal gel barrier on its surface and retaining a bulk density of less than 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 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.

Approaches to Design Floating Drug Delivery System:

For Single Unit Dosage Forms (Ex: Tablets):

A) Floating Lag Time: Time taken for the tablet to emerge onto the dissolution medium surface and is measured in seconds or minutes.

B) 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.

For Multiple Unit Dosage Forms :

Morphological and dimensional analysis, using electron microscopy (SEM) scanning. An optical microscope can also be used to determine the dimension.

A) In-vitro floating potential (Buoyancy level): A known quantity of microspheres is distributedover 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 (%) = W_f / (W_f +W_S) X 100

Where,

W_f and W_S 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:

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).

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:

Involve 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 anddoes not use water or organic solvents for granulation.

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:

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

$$= \frac{\rho t - \rho o}{\rho t} x100$$

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 Bulkdensity by the usage of following formula.

Hausner's Ratio= Tapped density / Bulk density

Table 1: 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 the maximum 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.

$$\text{Tan } \theta = (h/r) \theta = \tan^{-1} (h/r)$$

θ = angle of repose

h = height of the heap

r = radius of the heap

Table 2: 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

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. 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. in triplicate. The degree of

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

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; 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. 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 andsettled layers are separated, then dried in a dessicator and are weighed.

The buoyancy is calculated from the following formula.

2. 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.

Table 3: Formulation With HPMCK-4M

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

Table 4: Formulations with HPMC K-100M

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

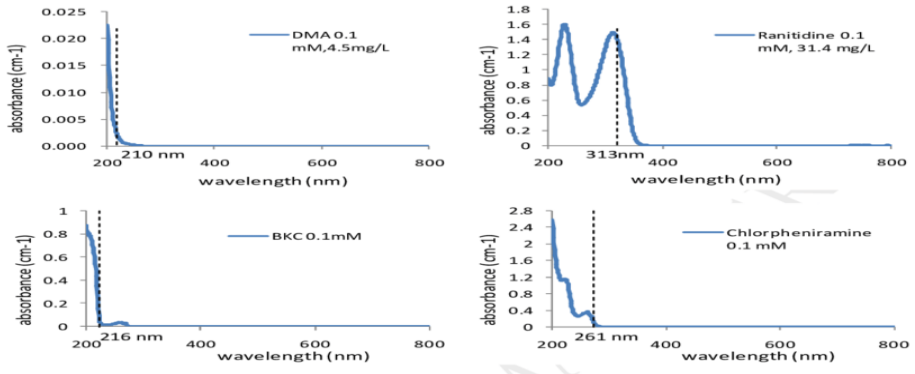
Table 5: Formulations with HPMC K-15M

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

3. 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 .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.

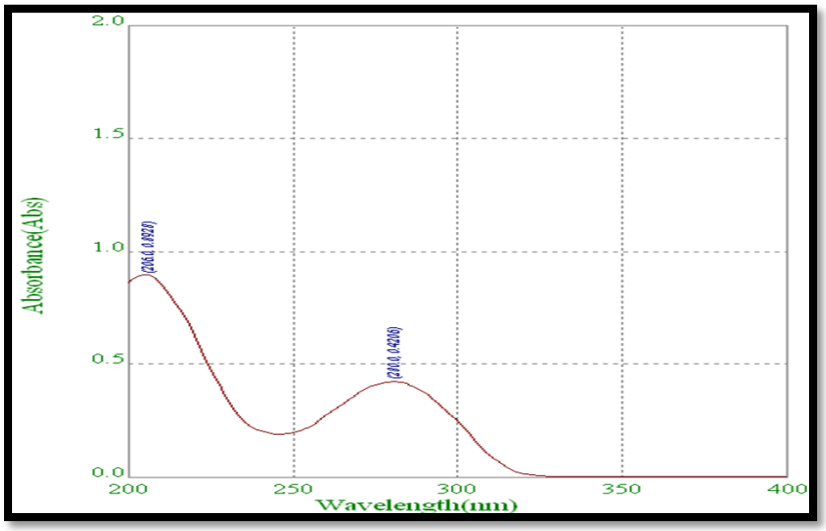


Fig.2: Standard curve of famotidin in 0.1 N HCl at 261 nm

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

Table 6: Standard curve of famotidine in 0.1 N HCl at 261 nm

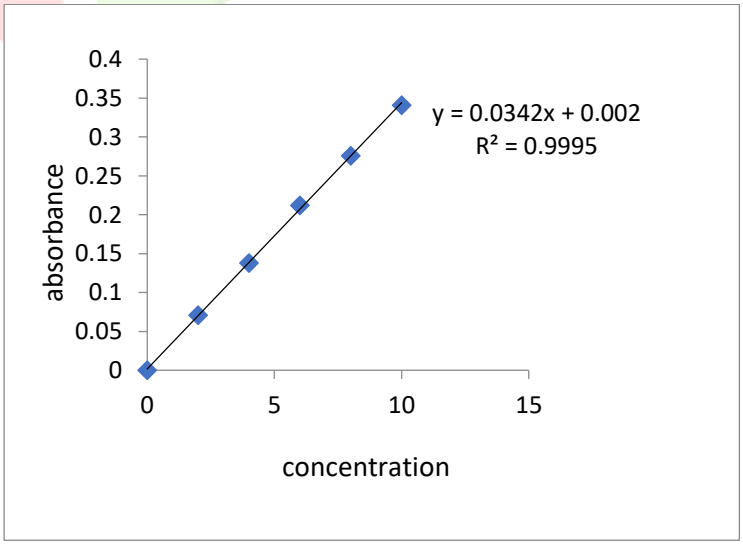


Fig.3: Standard curve of famotidine in 0.1 N HCl at 261 nm

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. 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).

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

Table 8: % 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

Table 9: Release order kinetics of optimized formulation Reference Standard:

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer- Peppas R^2	Peppas n 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

Fig 4: Schematic representation of microspheres prepared from Solvent Extraction Method.

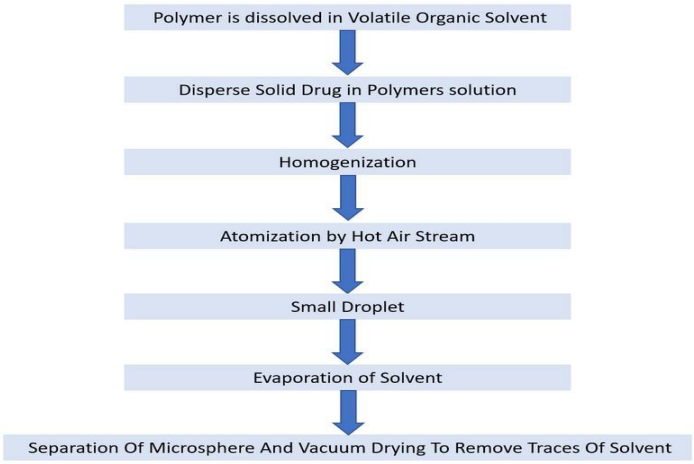


Fig 5: Floating microspheres

Fig. 6: Mathematical modeling of Marketed product

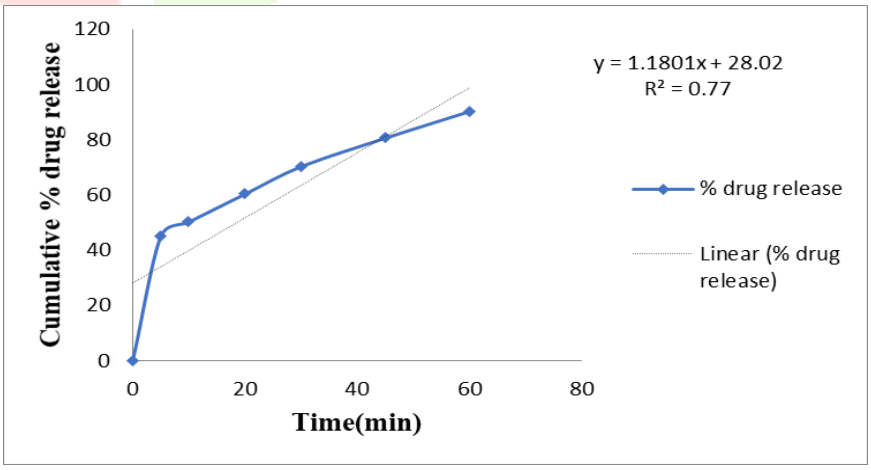


Fig. 7: Zero order plot for Marketed product:

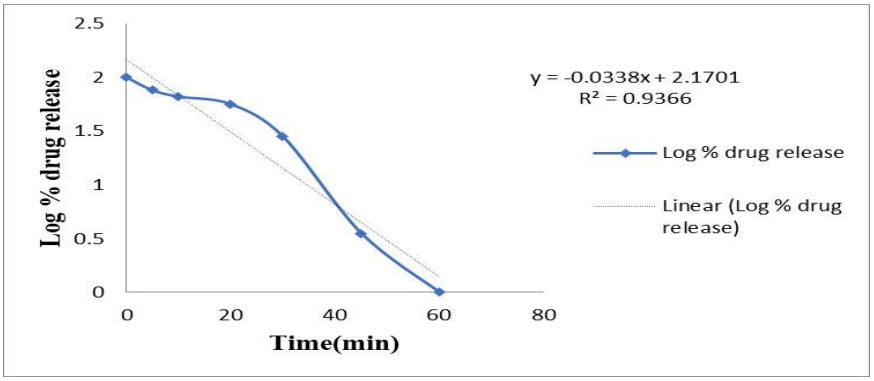


Fig. 8: First order plot for Marketed product

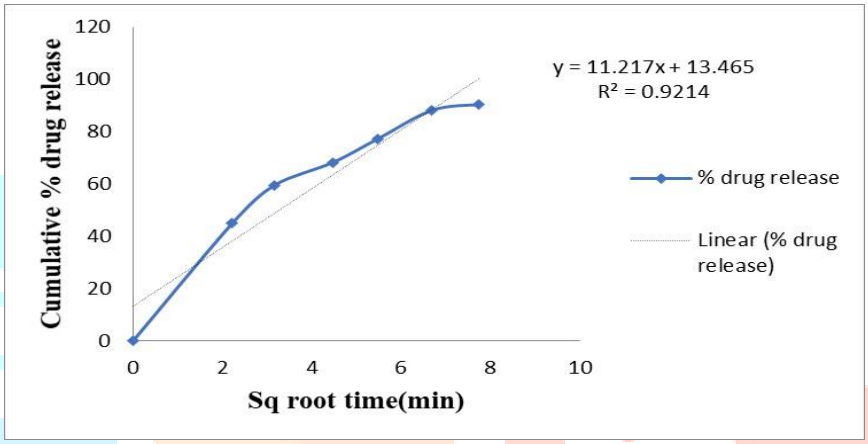


Fig. 9: Higuchi model for Marketed product

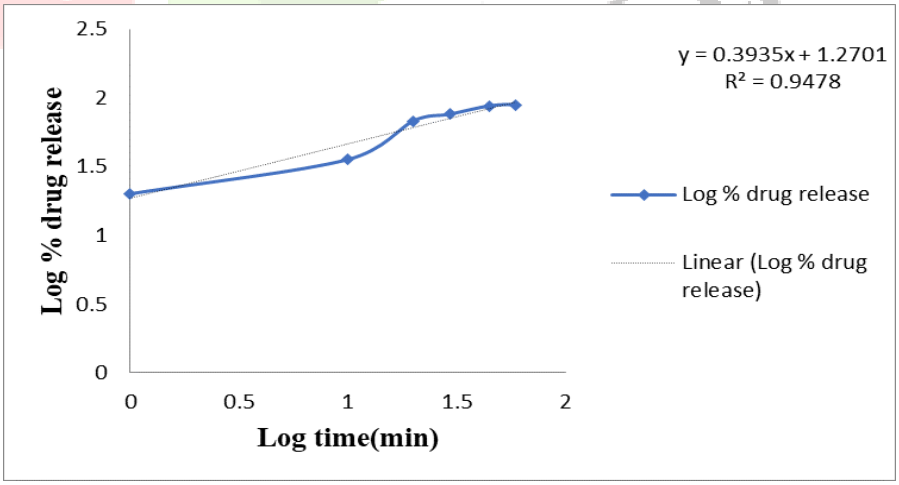


Table 10: Stability studies of optimized floating microspheres:

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
120 days	93.61 ± 0.265	90.87 ± 0.291	94.19 ± 0.253
180days	93.12 ± 0.321	90.12 ± 0.172	93.33 ± 0.184

4. Results and Discussion

The particle size, % buoyancy and micrometric 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 sizeof 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.

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References

1. Vyas Khar, Roop K khar. Microspheres. Chap 11, Targeted and controlled drug delivery. Published by CBS prakashan, 1st edition, 2002; 418.

2. A. A. Deshpande, C. T. Rhodes, N. H. Shah and A. W. Malick, Controlled-release drug delivery systems for prolonged gastric residence: an overview, Drug Dev. Ind. Pharm 1996; 531–539.

3. Raymond et.al, *Handbook of Pharmaceutical Excipients*. Published by Pharmaceutical Press, sixth edition, 2006; 262-267,333-337.

4. Muge klicarslan, Tamer Baykara. The effect of the drug/ polymer ratio on the properties of the verapamil HCl loaded microspheres. *Int.J.Pharmaceutics* 2003;256, 99-109.

5. James Swarbrick, James C.Boylan. *Encyclopedia of Pharmaceutical technology*, New York (NY), Marcel Dekker,1995;12:35-40.

6. L. Whitehead, J. T. Fell, J. H. Collett, H. L. Sharma and A. M. Smith, Floating dosage forms: an in vivo study demonstrating prolonged gastric retention, *J. Control. Rel.* 55 1998; 3–12.

7. R. Talukder and R. Fassihi, Gastro retentive delivery systems: a mini review, *Drug Dev. Ind. Pharm* 2002;30;1019-1028

8. N. Rouge, J. C. Leroux, E. T. Cole, E. Doelker and P. Buri, Prevention of the sticking tendency of floating minitablets filled into hard gelatin capsules, *Eur. J. Biopharm;* 1997; 43:165–171.

9. *WWW.CRBestbuydrug.com*

10. Varaporn, Floating properties and release characteristics of hallow microsphere of Acyclovir, *Drug delivery*, 2008;15(5): 331-341.

11. E dini et.at, Synthesis and Characterization of cross – linked chitosan microspheres for drug delivery application. *Journal of Microencapsulation* 2003; 20(3): 375-385.

12. Anand kumar shrivastava Floating microsphere formulation characterization of Cemitidine *acta pharm* 2005;55;277-285.

13. T.Comoglue.Preparation and development and in vitro evaluation of Pentaprazole loaded microsphere,*Drug delivery* 2008;15(5); 295-302.

14. Hui Yun Zhou Cellulose acetate/Chittosan multi microsphere of ranitidine in vitro release *Drug Release* 2006;13;261-267.

15. A.K.Jain, Buoyant microsphere of famotidine an approach dosage form for gastric dosage form *J.young pharm* 2009;1;20-23.

16. Senthilkumar KS, Jaykar B, Kavimani S. Formulation, characterization and invitro evaluation of floating microsphere containing rabeprazole sodium.*IJPTS*, 2010; 1 (6): 274-282.

17. Punitha K, Khadhir S, Ravichandiran V, Umadevi SK, Vaijayanthi V, Padmapriya S, Suresh KS. Intragastric floating drug delivery system of ranitidine hydrochloride.*International journal pharm sci*, 2010; 2 (4): 105-108.

18. Yogesh SG, Durgacharan AB, Akhil PM. Formulation and evaluation of intragastric floating drug delivery system of diltiazem hydrochloride.*Asian Journal of Pharmaceutics*. 2008:31; 228-231.

19. John TF, Lynne W, John HC. Amoxycillin release from a floating dosage form based on alginate. *International Journal of Pharmaceutics*. 2000;210;45-49.

20. Frances S, John TF, John HC, Luigi GM. Floating dosage forms to prolong gastro-retention—the characterization of calcium alginate beads.*International journal of Pharmaceutics*. 2008; 4: 301-305.

21. Atmaram PP, Shardha SB. Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery.*European Journal of pharmaceutics and biopharmaceutics*.2007;65: 85–93.

22. Asha P, Subhabrata R, Ram ST. Invitro evaluation and optimization of controlled release floating drug delivery system of metformin hydrochloride.*DARU Journal of pharm.sci*. 2006; 14(2): 57-64.

23. Rajeev G, Gupta GD. Gastro retentive floating microspheres of silymarin: preparation and in-vitro evaluation. Available from:URL: http://www.bioline.org.br/request?pr0008.

24. Shoufeng L, Yie WC, Senshang L, Bruce PD, Haresh LM. The effect of formulation variables on floating property of gastric floating drug delivery system.*Drug Development and international pharmacy*. 2002; 28 (7): 783–793.