CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Research Article*

DESIGN AND CHARACTERIZATION OF FLOATING MICROSPHERES OF FAMOTIDINE

Singireddy Anandam, Srilakshmi N, P Sobhita Rani*
Malla Reddy Pharmacy College, Maisammaguda, Dhulapally, Hyderabad-500100.

Abstract:

The present involves the preparation and evaluation of floating microspheres using Famotidine as a model drug for prolongation of the gastric retention time. The microspheres were prepared by the Ionotropic gelation method using different polymers i.e., HPMC K4M, HPMC K100M and Carbopol. The prepared microspheres were evaluated for particle size, buoyancy, entrapment efficiency. In Vitro drug release studies were performed and the drug release kinetics was evaluated using the linear regression method. Data obtained for floating microspheres of famotidine showed good buoyancy and prolonged drug release. The average particle size was in the range of 526µm to 644µm. % drug entrapment efficiency ranged from 62.35% to 97.24%. Diffusion was found to be the main release mechanism. Among all formulations F9 formulation was found to be satisfactory in terms of excellent micromeritic properties,% yield, drug entrapment efficiency, % buoyancy and In-vitro drug release in a sustained manner over an extended period of time for 12 hours. Thus the prepared microspheres proved to be a potential candidate as a microparticulate controlled release drug delivery device in this era.

Keywords: Famotidine, Floating Microspheres, Gastric Retention Time, Buoyancy, Entrapment Efficiency and In-vitro drug release.

Corresponding Author:
P Sobhita Rani,
Malla Reddy Pharmacy College,
Hyderabad,Telangana.
Email.id:sobhitarani@gmail.com.

QR code

Please cite this article in press as Sobhita Rani et al, ***Design and Characterization of Floating Microspheres of Famotidine****, Indo Am. J. Pharm. Sci, 2016; 3(3).*

INTRODUCTION:

Oral controlled drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action [1,2]. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in gastrointestinal tract is to control the gastric residence time (GRT) using gastro retentive dosage forms (GRDFs*)* that offer a new and better option for drug delivery [3]. Dosage forms that can be retained in stomach are called gastro retentive drug delivery systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time ensuring its optimal bioavailability. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs [4]. Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [5]. Based on the mechanism of buoyancy, two distinctly different technologies i.e. non-effervescent and effervescent systems have been utilized in the development of FDDS [6, 7, 8]:

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 needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments [9]. The main aim of the work was to formulate and evaluate floating microspheres of famotidine and to improve the bioavailability by using different polymers.

Famotidine, a competitive histamine H2-receptor antagonist is used to treat gastrointestinal disorders such as gastric or duodenal ulcer, gastroesophageal reflux disease, and pathological hypersecretory conditions. Famotidine inhibits many of the isoenzymes of the hepatic CYP450 enzyme system. Other actions of famotidine include an increase in gastric bacterial flora such as nitrate-reducing organisms [10].

Famotidine is widely used as the treatment of peptic ulcer disease and gastroesophageal reflux disease. Famotidine binds competitively to H2-receptors located on the basolateral membrane of the parietal cell, blocking histamine affects. This competitive inhibition results in reduced basal and nocturnal gastric acid secretion and a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole and pentagastrin [11].

MATERIALS AND METHODS:

Famotidine was purchased from Chandra labs, hyderabad., Sodium alginate, $NaHCO_3$, Ethanol were brought from Sisco Research Laboratories Pvt. Ltd., Carbopol 934-934, HPMC K4M , HPMC K100M were purchased from BARIS Pharmaceuticals Pvt. Ltd.

Preparation Of Standard Calibration Curve Of Famotidine:

10 mg of Famotidine was accurately weighed and dissolved in 10ml of methanol (Stock Solution – I) to get a concentration of 1000 µg/ml.

From the stock solution I,1ml of aliquots was taken and suitably diluted with 0.1N HCl (Stock Solution-II) to get concentrations of 100µg/ml.

From the stock solution-II,aliquots were taken and suitably diluted with 0.1N HCl (pH 1.2) to get concentrations in the range of 2 to 10µg/ml.The absorbance of these samples were analyzed by using UV-Visible Spectrophotometer at 265nm against reference solution 0.1N HCl (pH 1.2).

Fourier Transform Infrared Spectroscopy (FT-IR):

In order to check the integrity (Compatibility) of drug in the formulation,FT-IR spectra of the formulations along with the drug and other excipients were obtained and compared using Shimadzu FT-IR 8400 spectrophotometer. In the present study, Potassium bromide(KBr) pellet method was employed. The samples were thoroughly blended with dry powdered potassium bromide crystals. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded.The FT-IR spectra

of the formulations were compared with the FT-IR spectra of the pure drug and the polymers.

Preformulation Studies:

Micromeritic Studies:

The prepared microspheres are characterized by their micromeritic properties, such as microsphere size, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose [12].

Bulk Density:

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre sieved granules into a graduated cylinder via a large funnel and measure the volume and weight.

Bulk Density=Weight of granules/Bulk Volume of granules

Bulk density was expressed in g/cc.

Tapped Density:

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

Tapped Density=Weight of granules/Tapped Volume of granules

Carr's Index (CI):

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$CI = (TD-BD)/TD*100$$

Where TD = Tapped density

BD = Bulk density

Hausner's Ratio:

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio = Tapped density / Bulk density

Angle of Repose:

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder ion a conical heat on a level, flat surface and measure the included angle with the horizontal.

$$Tan\theta = h/r$$

Where, h= height of the heap

r= Radius of the heap

Preparation of Floating Microspheres of Famotidine

Ionotropic Gelation Method:

Batches of microspheres were prepared by ionotropic gelation method which involved reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the floating polymer were dispersed in purified water (10 ml) to form a homogeneous polymer mixture. The API, Famotidine (100 mg) were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (4% w/v) solution. The addition was done with continuous stirring at 200rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried. Table 1 shows the formulation of Biooadhesive Microspheres.

Table 1: Prepared formulation of Biooadhesive Microspheres (mg)

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	100	100	100	100	100	100	100	100	100
Sodium alginate	100	200	300	100	100	100	100	100	100
Carbopol 934	-	-	-	100	-	-	-	-	-
HPMC K4M	-	-	-	-	100	-	75	50	25
HPMC K100M	-	-	-	-	-	100	25	50	75
$NaHCO_3$	15	15	15	15	15	15	15	15	15
Ethanol	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml
Water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Evaluation of Microspheres:

In vitro Buoyancy studies:

The in vitro buoyancy was determined by floating lag time, and total floating time. The microspheres were placed in a 100ml beaker containing 0.1N HCl. The time required for the microspheres to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the microspheres constantly floats on the dissolution medium was noted as the Total Floating Time respectively (TFT) [13].

% Buoyancy = $Q_f / (Q_f + Q_s)$ X 100

Where Q_f and Q_s are the weight of the floating and settled microspheres respectively.

Swelling Index Studies:

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of microspheres was determined by placing the microspheres in the basket of dissolution apparatus using dissolution medium as 0.1N HCl at 37±0.5°C. After 0.5, 1, 2, 3, 4, 5, and 6h, each dissolution basket containing microspheres was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance (Schimdzu, AX 120). The experiment was performed in triplicate for each time point[14]. Swelling index was calculated by using the following formula

Swelling index = (Wet weight of microspheres – Dry weight of microspheres)/

Dry weight of microspheres.

Drug Entrapment Efficiency:

Microspheres equivalent to 100mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl (pH-1.2) repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using 0.1N HCl (pH-1.2). The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (UV 1700, Shimadzu, Japan) at 265 nm against appropriate blank [14,15]. The amount of drug loaded and entrapped in the microspheres was calculated by the following formulas:

(Drug entrapment efficiency (%) = Amount of drug actually present / Theoretical drug load expected × 100

Determination of Percentage Yield

The dried microspheres were weighed and percentage yield of the prepared Micro spheres were calculated by using the following formula [16].

$$\text{Percentage yield} = \frac{\text{Practical yield (mg)} \times 100}{\text{Theoretical yield}}$$

***In-vitro* Release Study:**

The drug release study was performed for microsphere containing quantity equivalent to 100mg of Famotidine by using USP dissolution apparatus Type I in 900 ml of 0.1N HCl dissolution media (pH-1.2) at 100 rpm and 37^{0}C temperature. 10 ml of sample was withdrawn at predetermined time interval for 12 hours and same volume of fresh medium was replaced to maintained sink condition. Withdrawn samples were assayed spectrophotometrically at 265 nm. Drug release was also performed for pure drug. The cumulative % drug release was calculated using standard calibration curve.

Details of dissolution testing:

- Apparatus: LAB INDIA DS8000
- Dissolution media: 0.1 N HCl (pH-1.2)
- Speed: 50 rpm
- Volume of medium: 900 ml
- Aliquots taken at each time interval: 5ml
- Temperature: 37±0.5°C
- Wavelength: 265nm**.**

Release Kinetics:

The matrix systems were reported to follow the Peppas release rate and the diffusion mechanism for the release of the drug. To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to,Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit model was selected [17,18].

Stability Studies:

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, and enables recommended storage conditions. Overall observations from different evaluation studies such as drug-polymer interactions, evaluation of prepared formulations and drug release studies were carried out. Based on the obtained

results best formulation was subjected for further stability study. The stability study was conducted as per ICH guidelines for the period of six months at various accelerated temperature and humidity conditions of 25°C/60%RH, 40°C/70%RH, 60°C/80%RH.The accelerated stability study of the best formulations was carried out as per the ICH guidelines. The selected formulation was analyzed for the drug entrapment efficiency and in vitro release study at different temperatures.

RESULTS AND DISCUSSION:

Preformulation Studies

Calibration curve of Famotidine in 0.1 N HCL:

Fig.1 shows the calibration curve with a regression value. The curve was found to be linear in the concentration range of 2-12µg/ml.

Compatibility Studies

Drug polymer compatibility studies were carried out using Fourier Transform Infr a Red spectroscopy to establish any possible interaction of Famotidine with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug. The results indicated that the characteristic absorption peaks due to pure Famotidine have appeared in the formulated microspheres, without any significant change in their position after successful encapsulation, indicating no chemical interaction between Famotidine and Polymer. The FT-IR spectra of pure drug and optimized formulation were shown in Figure 2 &3.

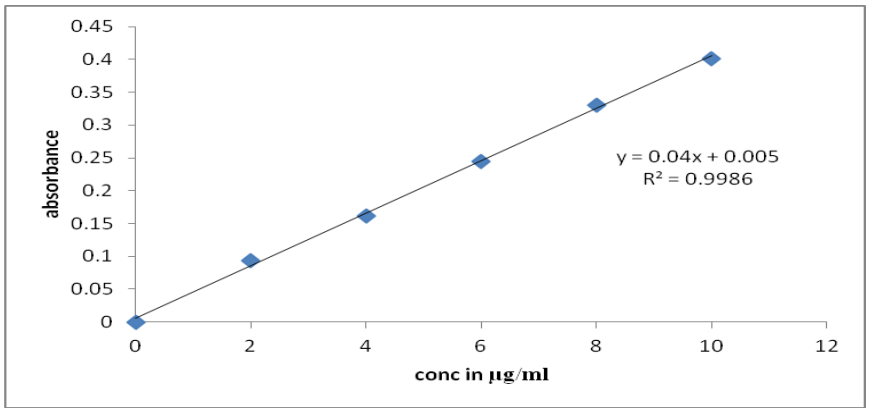

Fig.1: Standard Graph Of Famotidine in 0.1 N HCL

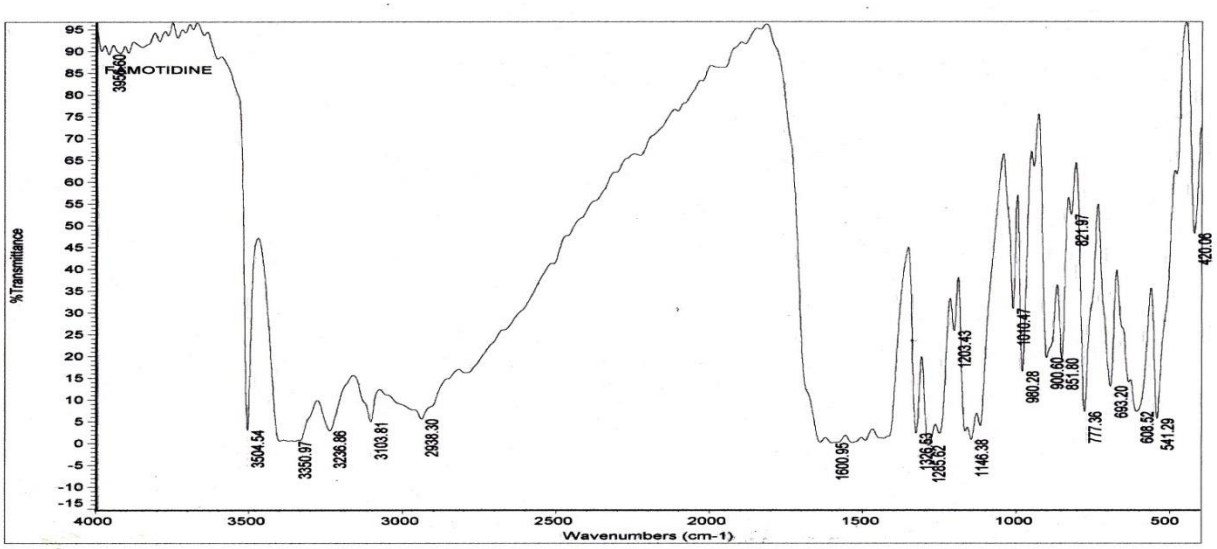

Fig 2: FT-IR Spectra of Pure Drug

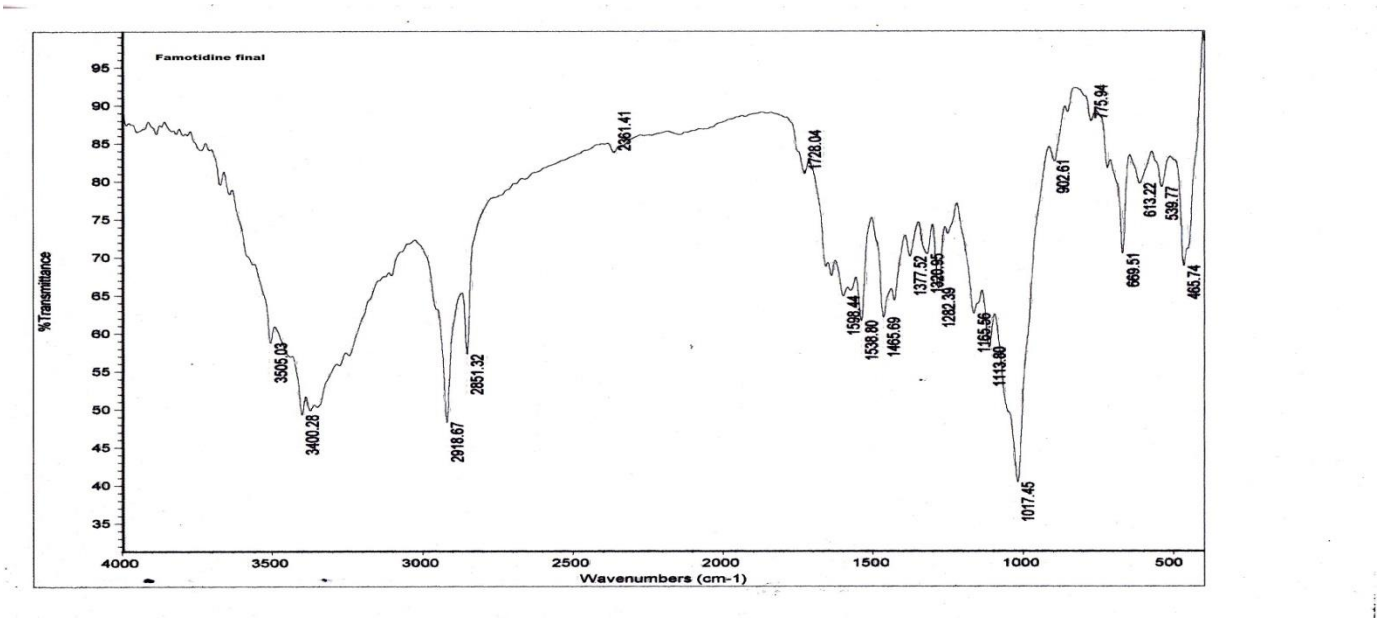

Fig 3: FT-IR Spectra of Optimized Formulation

Evaluation And Characterisation Of Microspheres:

Percentage Yield: It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug- polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The percentage yield of the prepared microspheres is recorded in Table 2.

Drug Entrapment Efficiency: Percentage Drug entrapment efficiency of Famotidine ranged from 60.4 to 97.6%. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microsphere is displayed in Table 2.

Table 2: Percentage Yield and Percentage Drug Entrapment Efficiency of the Prepared Microspheres

S.No.	Formulation code	% Yield	% Buoyancy	% Drug entrapment efficiency	%Swelling Index
1	**F1**	86.2	63	62.35	33.32
2	**F2**	89.24	67	86.04	35.66
3	**F3**	90.42	75	89.24	30.91
4	**F4**	91.21	79	86.24	32.33
5	**F5**	87.42	89	92.2	38.11
6	**F6**	79.25	85	94.4	38.18
7	**F7**	86.14	70	90.4	36.55
8	**F8**	87.2	76	92.1	37.32
9	**F9**	85.42	84	97.6	35.66

Mean Particle Size:

Mean particle size was determined by optical microscopy and the average particle size was calculated .The results were shown in table 3.

Table 3: Average particle size of Famotidine microspheres

S.No	Batches	Mean Particle Size(µm)
1	F_1	540 µm
2	F_2	602 µm
3	F_3	644 µm
4	F4	612 µm
5	F5	528 µm
6	F6	624 µm
7	F7	588 µm
8	F8	598 µm
9	F9	526 µm

***In-Vitro* Drug Release Studies :**

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type. I. The dissolution studies were conducted by using dissolution media, pH 1.2.

The results of the in-vitro dissolution studies of formulations F_1 to F_9 are shown in table no.16 The plots of Cumulative percentage drug release Vs Time. Figure shows the comparison of % CDR for formulations F_1 to F_3, figure for formulations F4 to F6 and figure for formulations F7 to F9. The results were shown in table 4 and Figure 4, 5 &6.

Table 4: Percentage Cummulative Drug Release For All Formulations

TIME(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	23	18	16	28.4	16.25	14.2	25.3	23.0	11.30
2	32	27.2	24	40.3	21.3	20.8	37.2	38.4	19.6
3	41.5	36	31	49.7	28.6	26.1	44.3	45.4	25.4
4	57.6	45	42	55.3	30.4	28.4	52.4	50.2	28.2
5	68.2	53	49	62.4	38.2	38.4	57.8	54.5	36.3
6	79.7	67	54	68.3	44.3	42.5	65.2	63.4	40.4
7	86.4	72	58.7	76.9	51.6	48.2	70.8	69.2	46.8
8	-	98	96.4	83.2	77.2	54.1	79.2	78.1	59.3
10	-	-	-	96.9	98.3	63.4	95.2	98.2	80.4
12	-	-	-	-	--	76.2	-	-	96.2

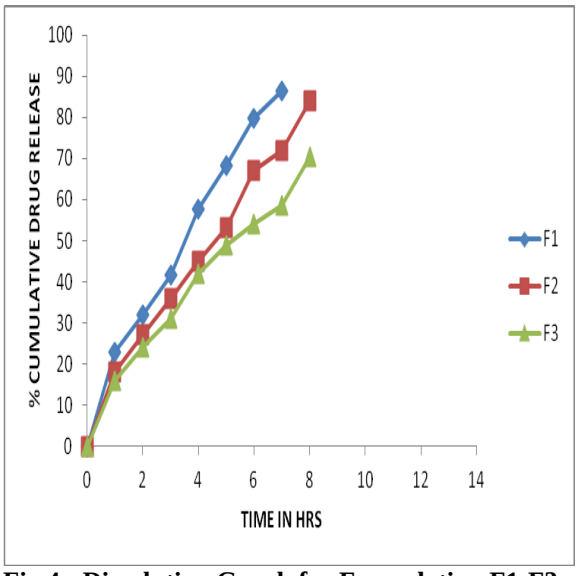

Fig 4 - Dissolution Graph for Formulation F1-F3

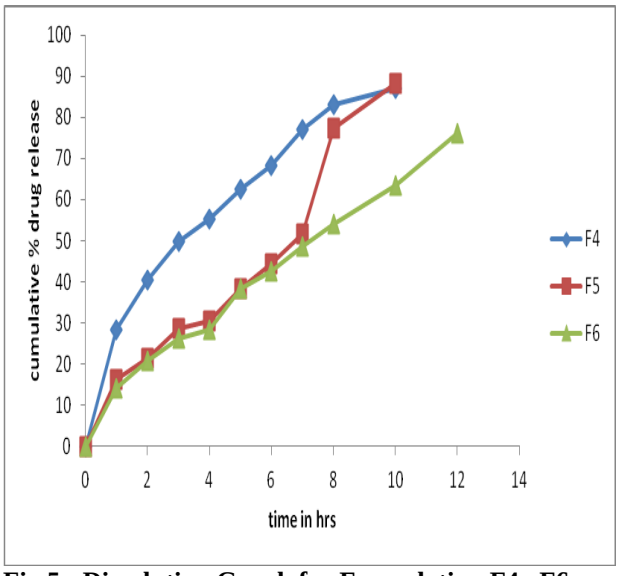

Fig 5: Dissolution Graph for Formulation F4 –F6

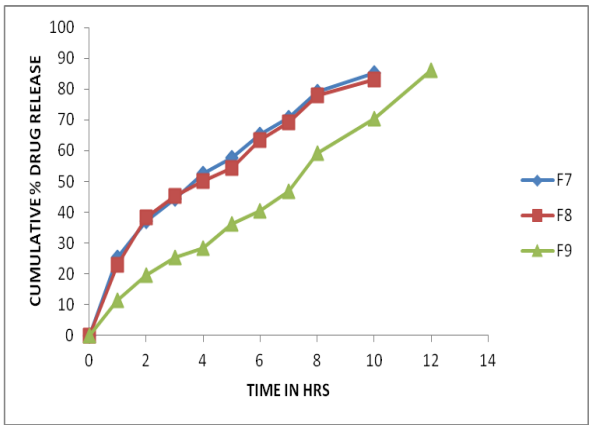

Fig 6: Dissolution Graph for Formulation F7 –F9

***In-Vitro* Drug Release Kinetics:**

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the in-vitro drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled in Table 5. The coefficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered. The kinetic data analysis of all the formulations reached higher coefficient of determination with the Zero order (R^2 = 0.985). From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

Stability Studies of Famotidine Optimized Formulation:

The optimized formulation of Famotidine (F9) were subjected to short-term stability testing by storing the microspheres at room temperature 25°C/60%RH. The results were shown in Table 6.

Results from stability studies indicate that the formulated microspheres are stable for a period of 3 months under room temperature i.e., 30˚C temp and 65±5% RH. There were no remarkable changes were observed during the period of storage.

The optimized formulation of Famotidine (F9) were subjected to accelerated stability testing by storing the microspheres at accelerated temperature 40°C/70%RH. The results were shown in Table 7.

Table- 5: R^2 Values for Release Kinetics

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	6.813043478	-0.11673207	24.39177782	2.107879725
Intercept	2.613043478	2.248971526	-12.314683	-0.20432997
Correlation	0.995475245	-0.78217290	0.954176529	0.915416958
R 2	0.990970963	0.611794458	0.910452849	0.837988207

Table-6: Stability Studies of Optimized Formulation at Room Temperature

Time	Colour	Drug entrapment efficiency ± St.D. at Room Temperature	Cumulative % drug release ± St.D.
First day	White	86.20± 0.91	86.20±0.55
30 days	White	85.84 ± 0.23	86.01±0.72
60 days	White	85. 06 ± 0.62	85.62±0.65
90 days	White	84. 92 ± 0.31	85.20±0.98

Table-7: Stability Studies of Optimized Formulation at Accelerated Temperature

Time	Colour	Drug entrapment efficiency ± St.D. at accelerated Temperature	Cumulative % drug release ± St.D.
First day	White	86.20± 0.91	86.20±0.55
30 days	White	85.72 ± 0.21	85.71±0.10
60 days	White	85. 01 ± 0.90	85.12±0.88
90 days	White	84. 66 ± 0.01	85.00±0.12

Results from stability studies indicate that the formulated microspheres are stable for a period of 3 months under accelerated temperature i.e., 40˚C temp and 70% RH. There were no remarkable changes were observed during the period of storage.

CONCLUSION:

The present study has been a satisfactory attempt to formulate floating microspheres of famotidine with a view of improving its oral bioavailability and giving a controlled release of the drug. From the experimental results it can be concluded that, FT-IR study shows no significant shifting of the peaks therefore it confirms the short term stability of the drug in the microspheres. Biocompatible polymers like can be HPMCK4M, HPMCK100M, and Carbopol used to formulate a floating Microspheres. Good percentage drug entrapment and practical yields were obtained with the polymers. The flow properties of all formulations were within the acceptable range and therefore they could be easily filled into capsules. The floating microspheres of drug with HPMCK4M, HPMCK100M, and Carbopol were buoyant. The prepared formulations were characterized for their percentage yield, micromeritics properties, morphology, buoyancy studies, drug entrapment, and drug release studies.

Percentage Drug entrapment efficiency ranges from 62.35 to 97.24% for microspheres. Almost all the formulations showed fairly acceptable values for all the parameters evaluated. The average particle size of floating microspheres was in the range of 526 µm-644 µm and improved drug entrapment efficiency could be depending upon the type and ratio of polymer used. The particle size increased significantly as the amount of polymer increased.The formulations showed good flow properties, suggesting that, in future they could be easily and successfully packed and developed into a capsule dosage form. Among all formulations F9 formulation with drug: polymer (1:2) was found to be satisfactory in terms of excellent micromeritic properties, percent yield(85.42%), drug entrapment efficiency (97.6%) , percent buoyancy (84%), and highest invitro drug release of 96.2% in sustained manner over a extended period of time for 12 hrs. Thus the prepared microspheres proved to be a potential candidate as a microparticulate controlled release drug delivery device in this era of patenting novel and controlled release formulations.

Cumulative percentage drug release significantly decreased with increase in polymer concentration. The overall curve fitting into various mathematical models was found to be on average. The formulations F9 best fitted into zero order and shows non fickian diffusion mechanism. Formulated microspheres were stable and compatible at the room and accelerated temperature and humidity in storage for 90days. From the stability studies it was found that there was no significant change in the drug entrapment, release characteristics of the microspheres. Thus, the formulated floating microspheres seem to be a potential candidate as an oral gastroretentive controlled drug delivery system in prolonging the drug retention stomach and increasing the bioavailability of drug.

REFERENCES:

1. Brahmankar D M., Jaiswal S B., Biopharmaceutics and Pharmacokinetics A Treatise, First Edition, Vallbh Prakashan, 1995, 337.
2. Chien YW, Concepts and System Design for Rate-controlled Drug Delivery, Chapter 1, Novel Drug Delivery System, 2nd Edition, Marcel Dekker, Inc, New York, 1992; l-42.
3. Chien YW; Rate-controlled Drug Delivery Systems; Indian J Pharm Sci, 1988; 63-65.
4. Sachine.E. Bhandke; Formulation and Development of Repaglinide Microparticles by Ionotropic Gelation Techniques; Indian J Pharm Edu Res, 2006.
5. Rouge N, Buri P, Doelker E; Drug absorption sites in the gastrointestinal tract and Dosage forms for site specific delivery; Int J Pharm,1996; 136: 117-139.

6. KD Tripathi.Essentials of Medical Pharmacology. 6th edition. Jaypee brother's Medical publishers P (LTD); 2008:244-66.
7. Zaware SR, Gaikwad PD, Bankar VH, Pawar SP. Floating drug delivery system: A Review.Int.J.Ph.Sci. 2010;2(3):834-47.
8. Swetha A, Javed Ali, Alka A, RK Khar, Sanjula B. Floating drug delivery Systems: A Review. AAPS PharmaSciTech. 2005;6(3):E372-90.
9. Dave BS, Amin AF, Patel MM. Gastroretentive Drug Delivery of Ranitidine Hydochloride: Formulation and In vitro Evaluation. AAPS Pharm Sci Tech 2004;5(2):1-6.
10. HG Brittain (Ed.), Profiles of drug substances, excipients and related methodology, Academic Press, Burlington (2009), pp. 115–151.
11. YI Muzib, Rekha Ch, Development and evaluation of mineral oil entrapped emulsion gel beads of famotidine, Int J Pharmacol Technol,2011; 3 (2) :83–900.
12. Streubel A, Siepmani J, Bodmeier R. floating microparticle based on low density foam powder. International Journal of Pharmaceutics. 2002; 241: 279-292.
13. Muthusamy,K.,Govindrazan,G.,Ravi,T.K.. Preparation and evaluation of lonsoprazole floating micro pellets, 2005;67(1):75-79.
14. Mostafavi A, Emami J, Varshosaz J, Davies NM, Rezazadeh M. Development of a prolonged-release gastroretentive formulation of ciprofloxacin hydrochloride: Pharmacokinetic characterization in healthy human volunteers. Int J Pharm 2011;409:128.
15. Shweta,A.,Javed,K.,Alka,A.,Roop,K.,Sanjula,B..F loating drug delivery system a review,AAPS pharmascitech ,2005; 6(3)E372-E390.
16. Rajashree M, Shiva Kumar Y, Bhushan RP, FV Manvi. Development and Evaluation of Floating Matrix Tablets of Riboflavin. Int.PharmTech Res. 2010;2(2):1339-45.
17. Lehr CM, Bowstra JA, Tukker JJ, Junginer HE. Intestinal transit of bioadhesive microspheres in an *in situ* loop in the rat. J Control Release. 1990;13:51–62.
18. Lehr CM, Bouwstra JA, Tukker JJ, Verhoef AC, de Boer AG, Junginger HE, et al. Oral bioadhesive drug delivery systems effects on G.I. transit and peptide absorption. Pharm Res. 1990;7:PDD 7226.