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Research Article

Development and Evaluation of Floating Micropsheres of Famotidine using Different Polymers

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ABSTRACT

Earlier patients have been using conventional dosage form like tablet, capsule to treat the acute and chronic disease but these conventional dosage from have to be taken several times in a day for maintaining the plasma peak level concentration. Hence to overcome these problems. controlled release drug delivery system were developed. Microsphere release the drug in controlled rate and overcome the problem of conventional drug delivery system. In this preformulation of famotidine has been alone. Famotidine drug also identified by IR and UV Spectroscopy different famotidine different formulation floating microsphere were prepared and the identification of famotidine drug was confirmed by characteristics bond delivery system. The standard curve of drug was prepared SGF at 292nm. Floating microsphere of famotidine was prepared by CAP and Ethyl cellulose. The presence of pthalose group in CAP might impart more lipophilicity. In vitro study of floating microsphere was done in dissolution medium for more than 12h formulation F9 consisting ethyl cellulose and CAP (3:1) exhibited highest floating of 93% respectively floatability.

Keywords: Famotidine ,Ethyl cellulose, Hydroxyl Propyl methyl cellulose.

INTRODUCTION

Earlier patients have been using conventional dosage forms like Tablet, Capsule treat the acute and chronic diseases, but these conventional dosage forms have to be taken several times in a day for maintaining the peak plasma level concentration. Hence to overcome these problems controlled release drug delivery system were developed. Controlled drug delivery system (Microspheres) releases the drug controlled rate and overcome the problems of conventional drug delivery system and enhances the therapeutic efficacy of a given drug. The main purpose of Controlled drug delivery system is to ensure optimum plasma drug concentration, patient compliance Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature and ideally having a particle size less than 200µm. This is the important approach in delivering therapeutic substance to the target site in sustained and controlled release fashion.

Certain type of drugs can benefit from using gastric retentive devices.

These include:

• Drugs acting locally in the stomach.
• Drugs that are primarily absorbed in the stomach.
• Drugs those are poorly soluble at an alkaline pH.
• Drugs with a narrow window of absorption.
• Drugs absorbed rapidly from the GI tract.
• Drugs that degrade in the colon.

GASTRIC EMPTYING

- The passage from stomach to the small intestine, called gastric emptying is a first order process. The process of gastric emptying occurs both during fasting as well as fed states. However, the pattern of motility differs markedly in the two states. During the fasting state an interdigestive series of electrical events take place, which cycles both through the stomachand small intestine every 2-3 hours This is called the Interdigestive Myloelectric Cycle or Migrating Myloelectric cycle (MMC), which is further divided into following 4 phase
- **Phase I** (Basal phase) lasts from 40-60 minutes with rare contractions.
- **Phase II** (Prebrust phase) of similar duration consists of intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- **Phase III** (Brust phase) is a short period of intense, large regular contraction lasting from 4-6 min. It is phase, which gives the cycle referred as 'housekeeper wave', since it serves to sweep undigested materials out of the stomach and down the small intestine. As phase III of one cycle reaches the end of small intestine, phase I of the next cycle begins in the duodenum.
- **Phase IV** is a brief transitional phase that occurs between phase III and phase I two consecutive cycles.

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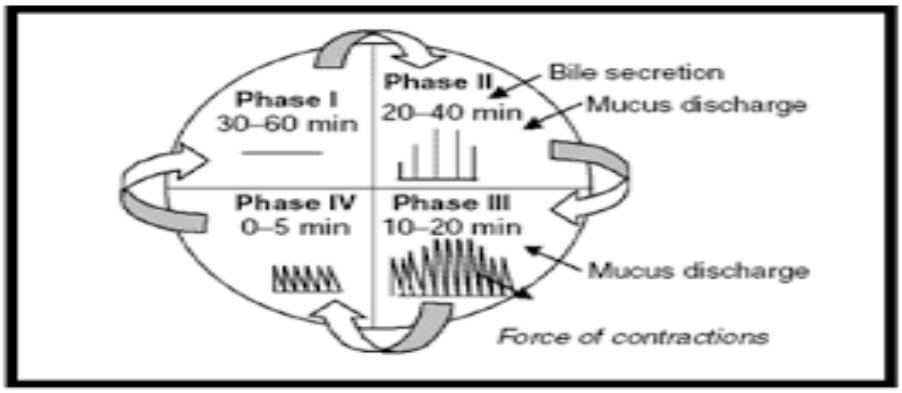


The typical GIT motility patterns in the fasting state.

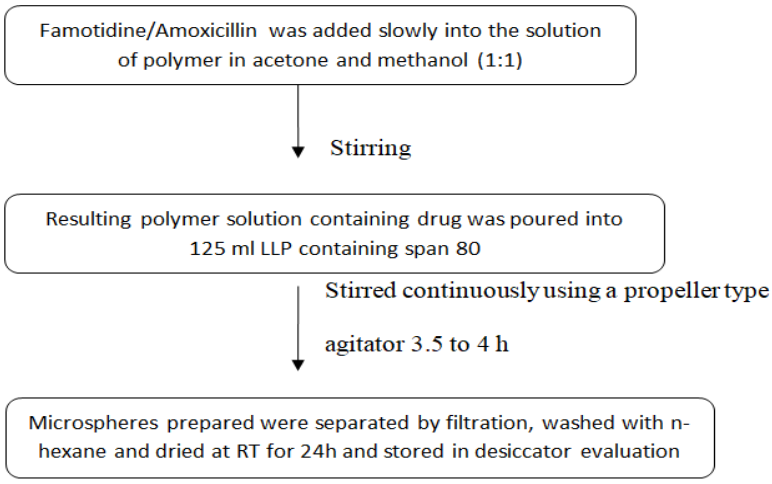
MATERILS AND METHOD:

MATERIALS-The sample of famotidine was gifted from M/s Cadila Pharmaceutical, Ahmedabed (India). It was subjected to preformulation studies. Cellulose acetate pthalate source from sigma Aldrich Laborchemikalien GMBH Bombay. Ethyl cellulose from Himedia Labortories, Mumbai. ,Hydroxyl propyl methyl cellulose, was purchased from G.S Chemical Testing Laboratories, New Delhi. Ethanol and polyvinyl acetate source analytical grade.

METHODS:

Formulation of Floating Microspheres[1]

The drug and polymers in different proportions (Table 5.3) were weighed and co-dissolved at room temperature into a mixture of acetone: methanol (1:1 %v/v) with vigorous agitation, with the help of magnetic stirrer, to form a uniform drug–polymer dispersion. This was slowly poured into the dispersion medium consisting of light liquid paraffin (LLP) (125 ml) containing 0.5% Span 80 (previously melted). The system was stirred using an overhead propeller agitator at 500 rpm and room temperature over a period of 3.5–4 h, to ensure complete evaporation of the solvent. The liquid paraffin was decanted and the micro particles were separated by filtration through a Whatman filter paper, washed thrice with 50 ml portion of n-hexane, air dried for 24 h and stored in dessicator until further evaluation.



Schematic of preparation of floating microspheres

EVALUATION OF FLOATING MICROSPHERES

1.Yield of microspheres

The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

% Yield = (actual weight of product / total weight of excipients and drug) × 100

2.Particle size analysis

The particle size and size distributions of floating microspheres were evaluated by optical microscopy. The microscope eyepiece was fitted with ocular micrometer and least count was determined with the help of stage micrometer (Erma, Japan). The microsphere suspended in 2% tween 80 and was mounted on a slide with the help of a cover slip and placed on the mechanical stage of microscope. The size of particles was measured along an arbitrarily chosen fixed line with the help of calibrated ocular micrometer.

3.Percentage drug entrapment efficiency (%DEE)

Microspheres equivalent to dose of the drug (famotidine and amoxicillin) were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of SGF (pH 1.2) repeatedly. The extract was transferred to a 50 ml volumetric flask and the volume was made up using SGF (pH 1.2). The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (Systronics 2202, India) at 292 nm (famotidine) and 277 nm (amoxicillin) against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula % Drug Entrapment Efficiency = (amount of drug actually present / theoretical drug load expected) × 100

4. *In-vitro* evaluation of floating ability (% Buoyancy)

An *in vitro* floating study was carried out using simulated gastric fluid USP containing 0.02 % tween 80 as a dispersing medium. Microspheres were spread over the surface of 500 ml of dispersing medium at 37 ± 0.5°C. A paddle rotating at 100 rpm agitated the medium. Each fraction of microspheres floating on the surface and those settled down were collected at a predetermined time point (12 h). The collected samples were weighed after drying. % Buoyancy = (weight of floating microspheres/ initial weight of floating microspheres) ×

5. *in-vitro* drug release studies

In vitro drug release studies were carried out in USP type II dissolution test apparatus. Weighed amount of microspheres equivalent to dose (mg) of the pure drug (famotidine) was filled into a capsule and placed in the basket of dissolution apparatus. Microspheres containing drug were placed in 900 ml of dissolution medium SGF (pH 1.2) with 0.02 % tween 80 and stirring rate was 100 rpm. The temperature maintained at 37 ± 0.5°C in dissolution test apparatus. Ten ml of the aliquot was withdrawn at predetermined intervals and filtered. The required dilutions were made with SGF (pH 1.2) and the solution was analyzed by spectrophotometrically (Systronics 2202, India) at 292 nm for famotidine against suitable blank. Equal volume of the dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition.The dissolution study was repeated using PBS (pH 7.4) Three trials were carried out for all formulations. From this percentage drug release was calculated and plotted against function of time to study the pattern of drug release.

6. Surface topography (SEM)

The surface morphology of the microspheres was examined by scanning electron microscopy (SEM). The surface of formulations F4 were studied by SEM.

The samples for SEM were prepared by lightly sprinkling the powder on a double adhesive tape stuck to an aluminum stab. The stubs were then coated with gold to a thickness of about 300 A^0 under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned using a scanning electron microscope (SEM, Leo Co., Ltd., type LEO-435VP) and photomicrographs were taken.

Table 1: Floating microspheres of famotidine

Formulation code	Mean particle size (µm)	% Yield	Drug Entrapment Effiecny (%)
F1	67	69	59
F2	92	79	81
F3	148	81	86
F4	54	72	64
F5	88	83	78
F6	129	89	87
F7	76	67	51
F8	103	76	73
F9	142	84	79

RESULT AND DISCUSSION

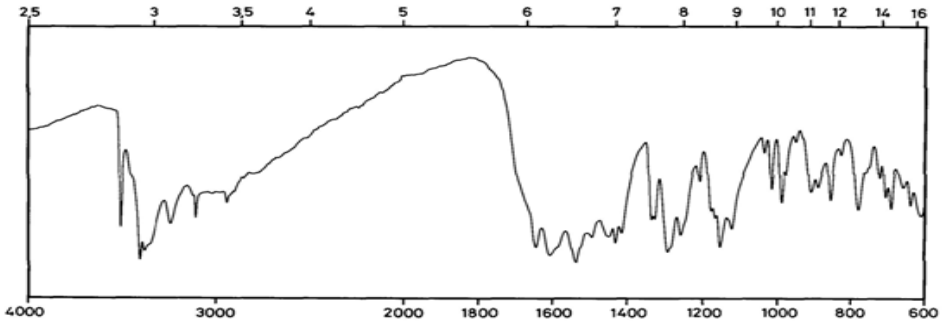


Figure 1 : IR spectrum of famotidine (Standard)

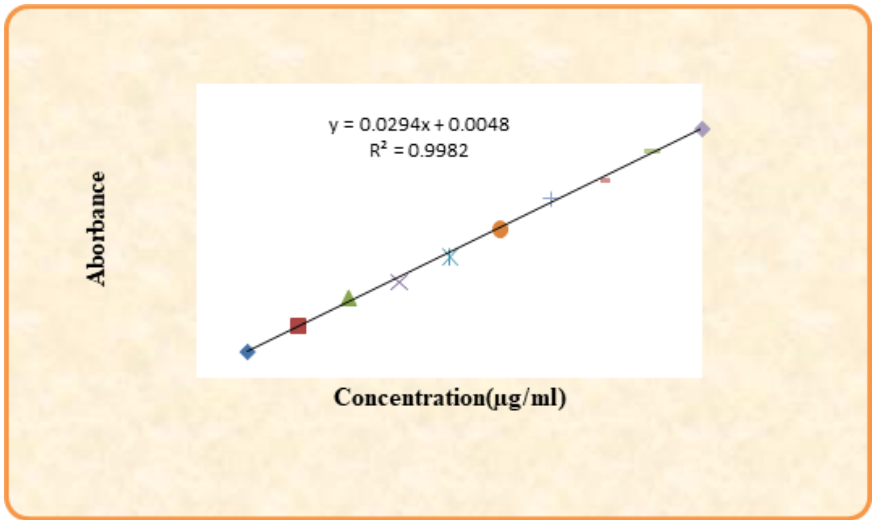


Figure 2: Standard curve of famotidine in SGF (pH 1.2)

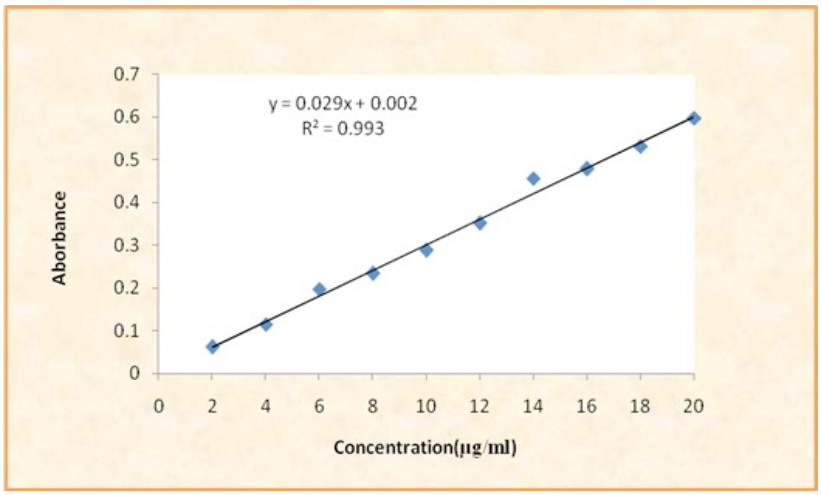


Figure 3: Standard curve of famotidine in PBS (pH7.4)

Table 2: Characteristic IR absorption bands of famotidine (wave number cm^{-1})

S.No	Frequency cm^{-1}	Vibration mode
1	3406	N-H stretching asymmetry
2	3241	N-H stretching symmetry
3	3104	C-H stretching
4	2236	C=C stretching
5	1546	C=N ring skeleton
6	1140	O=S=O stretching symmetry

Table 3: Standard curve of famotidine in PBS (pH 7.4) at λ 292nm

S. No	Concentration (µg/ml)	Absorbance	Statistical parameters
1	0	0	Correlation coefficient:(r^2)=0.993 Slope (m) = 0.029 Intercept (c)= 0.002 y = 0.029x + 0.002
2	2	0.0617	
3	4	0.1155	
4	6	0.1787	
5	8	0.2342	
6	10	0.2884	
7	12	0.3517	
8	14	0.4363	
9	16	0.4784	
10	18	0.5318	
11	20	0.5979	

Table 4:Standard curve of famotidine in SGF (pH 1.2) at λ 292nm

S. No	Concentration (µg/ml)	Absorbance	Statistical parameters
1	0	0	Correlation coefficient:(r^2) = 0.998 Slope (m) = 0.029 Intercept (c)= 0.004 y = 0.029x + 0.004
2	2	0.0639	
3	4	0.1255	
4	6	0.1922	
5	8	0.2292	
6	10	0.2894	
7	12	0.3547	
8	14	0.4263	
9	16	0.4694	
10	18	0.5408	
11	20	0.5926	

Table 5: Solubility profile of famotidine in different solvents

S. No.	Solvent (S)	Solubility indicator
1	Distilled water	Insoluble
2	Glacial acetic acid	+++
3	Ethanol (95%)	Insoluble
4	Methanol	+
5	Ethyl acetate	Insoluble
6	Ether	Insoluble
7	Haxane	Insoluble
8	Chloroform	Insoluble
9	DMF	+++

++++ Very soluble less than 1 part, +++ Freely soluble: 1-10 parts, ++ sparingly soluble: 30-100 parts,+ Slightly soluble: 100-1000 parts,- Practically insoluble: > 1000 parts

Table 6: Partition coefficient values of famotidine

S. No.	Solvent System	Partition coefficient
1	n-Octanol/Buffer solution (pH 1.2)	3.67
2	n-Octanol/Buffer solution (pH 7 .4)	4.24

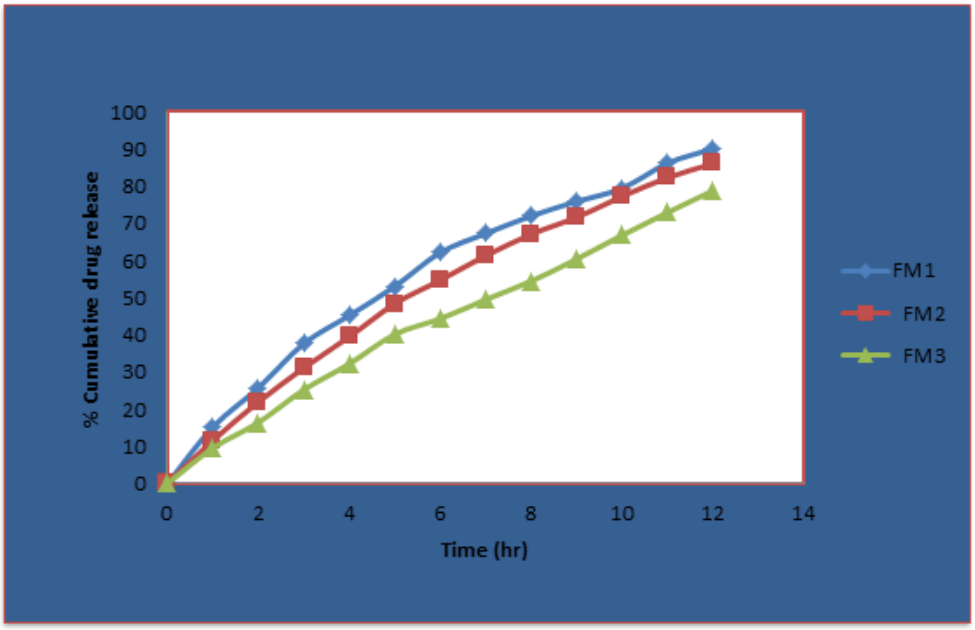


Figure 5.1: *In-vitro* drug release profile of famotidine from floating microspheres formulations FM1 to FM3 (pH 1.2)

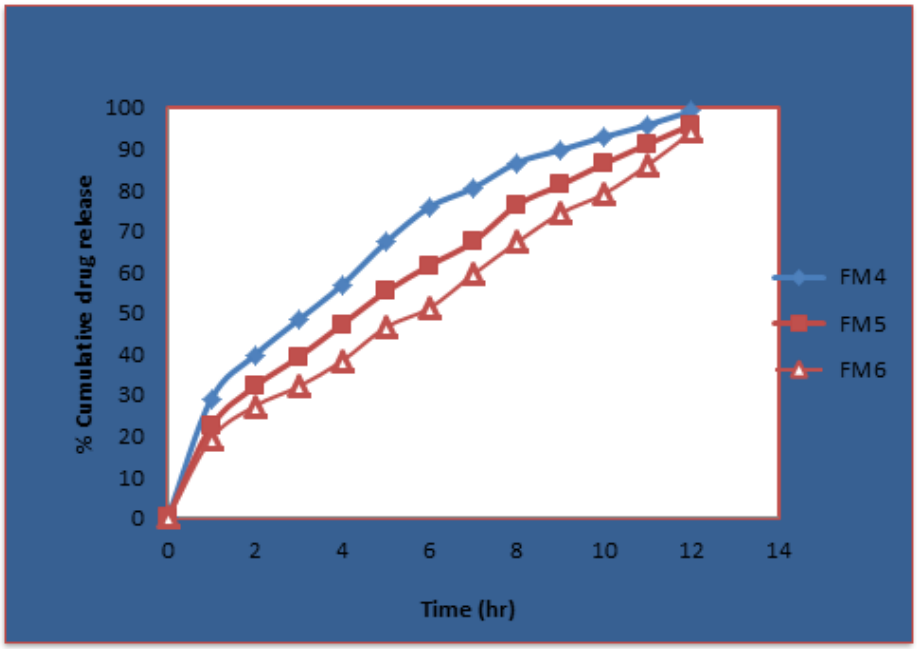


Figure 5.2: *In-vitro* drug release profile of famotidine from floating microspheres formulations FM4 to FM6 (pH 1.2)

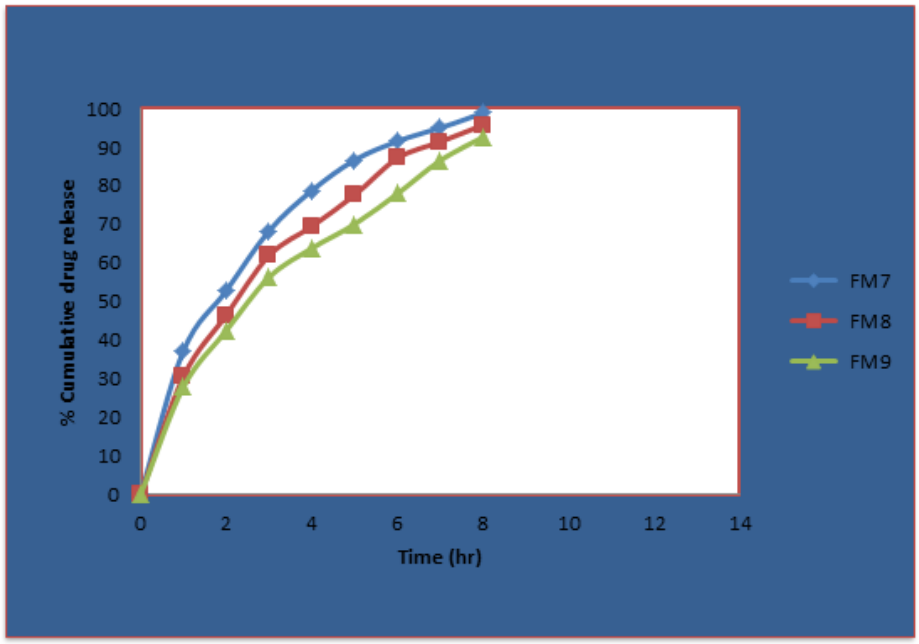


Figure 5.3: *In-vitro* drug release profile of famotidine from floating microspheres formulations FM7 to FM9 (pH 1.2)

Table 6 : In-vitro drug release profile of famotidine from floating microspheres of various formulations (pH 7.4)

Time (h)	% Cumulative drug release*								
	FM1	FM2	FM3	FM4	FM5	FM6	FM7	FM8	FM9
1	15.89 ±1.89	12.97 ±2.34	12.17 ±1.66	21.14 ±1.65	13.45 ±1.43	16.13 ±1.17	40.66 ±2.66	33.16 ±1.09	30.23 ±1.53
2	27.79 ±2.41	24.62 ±2.8	19.49 ±1.81	31.93 ±1.64	24.89 ±2.06	20.29 ±2.14	52.23 ±1.40	48.25 ±1.63	45.11 ±2.57
3	35.93 ±2.44	36.39 ±2.89	24.43 ±0.72	42.71 ±0.69	35.13 ±1.57	25.13 ±1.52	71.39 ±1.68	66.43 ±1.92	57.62 ±3.33
4	48.61 ±2.63	37.44 ±0.71	36.18 ±1.54	48.19 ±0.88	41.86 ±2.11	36.71 ±0.00	83.44 ±1.84	73.70 ±1.79	63.57 ±2.05
5	55.76 ±1.91	46.19 ±1.53	43.50 ±2.44	56.78 ±1.00	50.53 ±1.24	41.89 ±1.65	89.98 ±2.28	82.84 ±2.16	74.07 ±1.59

6	66.61 ±2.19	55.71 ±2.42	45.94 ±1.87	66.76 ±0.86	57.93 ±0.61	47.99 ±0.81	94.47 ±1.84	90.78 ±1.84	78.12 ±1.03
7	68.89 ±1.33	63.18 ±1.91	52.37 ±1.17	71.92 ±1.33	62.98 ±2.03	55.32 ±0.93	95.57 ±1.38	92.35 ±1.97	89.59 ±1.54
8	76.69 ±2.19	69.91 ±2.09	54.96 ±1.91	80.23 ±0.54	71.24 ±1.67	59.34 ±1.49	97.45 ±0.47	94.97 ±2.60	94.89 ±2.43
9	79.28 ±3.10	73.61 ±1.34	64.98 ±2.75	86.13 ±1.41	77.80 ±0.96	64.78 ±1.81	98.55 ±1.47	97.89 ±2.67	98.4 ±3.24
10	84.15 ±1.89	78.57 ±1.52	68.74 ±1.17	92.96 ±1.38	82.98 ±1.74	69.93 ±1.28			
11	87.98 ±1.77	80.55 ±1.79	73.16 ±1.31	95.11 ±0.51	88.51 ±1.56	78.14 ±1.06			
12	91.56 ±1.10	84.30 ±2.63	81.17 ±1.61	97.93 ±1.30	93.72 ±1.28	86.42 ±2.61			

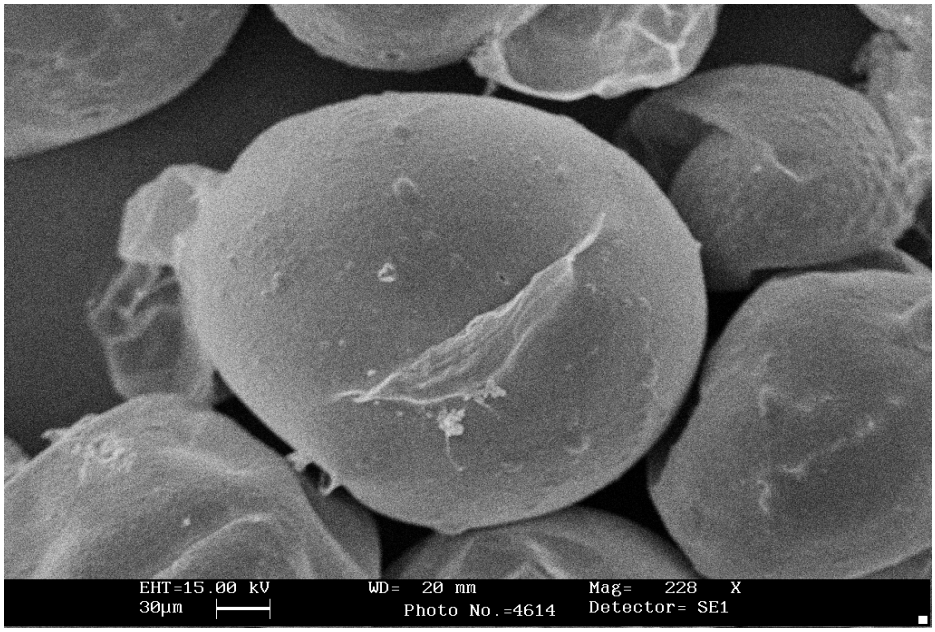


Figure 5.7: *SEM View* of floating microspheres of famotidine F4

The sample of famotidine obtained as gift sample from M/s Cadila Pharmaceutical, Ahmedabed (India) was subjected to preformulation studies. The melting point of the drug was found to be 164ºC which exactly matched with the value reported in the monograph supplied along with drug. Famotidine was also identified by IR and UV spectroscopy. The identification of famotidine sample was confirmed by characteristic band attributable to the different function group present in the drug molecule. The solution of famotidine in both SGF (pH 1.2) was scanned in the range of 200-400 nm using SYSTRONICS 2202 UV/visible spectrophotometer). In order to estimate famotidine in experimental protocol, standard curve of drug was prepared in SGF (pH 1.2) at 292 nm. The estimation procedure was found to be fairly reproducible and acceptably sensitive for the concentration range of 2-20 µg/ml. A correlation coefficient of standard curve of famotidine is given in table 3 and 4. Greater than 0.993 was obtained which indicated that drug followed Beer Lambert's law. The method is convenient, quick, less expensive and fairly sensitive.

The equilibrium solubility of famotidine was determined in various solvent systems and found to be freely soluble in glacial acetic acid and DMF. The result was shown in table 5

The partition coefficient of famotidine was different buffer solution of varying pH where the formulations were expected to release the drug. The value of partition coefficient indicates the pH dependency. The result was shown in table 6. Partition

Coefficient of drug in n-Octanol/Buffer solution (pH 1.2) was found to be 3.67 and n-Octanol/Buffer solution (pH 7.4) was found to be 4.24.

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