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RESEARCH ARTICLE

FORMULATION AND *IN VITRO* EVALUATION OF GASTRORETENTIVE FAMOTIDINE HOLLOW MICROSPHERES

G. Lakshmana murthy[1], Dr. S. Jeevanandham[2], Dr. G. Prathap Kumar[3]

[1]Jagans college of Pharmacy, Nellore, Andhrapradesh

[2]Assistant Professor, Department of Pharmaceutics, School of Pharmacy, University of Gondar

[3]M.R.R College of pharmacy, nandigama, Andhrapradesh

**Corresponding Author's Email:*

ABSTRACT

The main aim of this study is to develop a gastro retentive multiple unit floating drug delivery system for a drug which is poorly absorbed from lower gastrointestinal tract of famotidine. The hollow micro spheres were prepared by the emulsion solvent diffusion technique using eudragit RS 100 as a release rate controlling polymer in the ratios 1:1, 1:2 ,1:3,and 1:4.The prepared microspheres were evaluated for drug-polymer compatibility, micromeritic properties, drug entrapment efficiency, in-vitro buoyancy and drug release studies. The mean particle size increased with increase in the polymer concentration. The micromeritic properties were found to be improved when compared to pure drug .Scanning electron microscopy confirmed the hollow structure with smooth external surface. The drug and polymer were found to be compatible as seen in IR studies. The entrapment efficiency of formulation E1-E4 were 70.42%, 70.12%, 69.22% and 67.78% and for the formulation C1-C4 were 72.19%, 68.67%, 67.14% and 66.87%, cellulose acetate containing microspheres showed a desirable high drug content and entrapment efficiency respectively. The microspheres floated up to 10 h over the surface of the gastric buffer medium and the buoyancy percentage was found to be in the range of 60-39% of E1-E4and C1-C4. In-vitro drug release studies showed that the prepared microspheres exhibited prolonged drug release for more than 12 hours. The mechanism of drug release wasfound to be a combination of both peppas and zero order release kinetics. The developed floating microspheres of aceclofenac may be used for prolonged drug release for at least 12 h for maximizing the therapeutic efficacy along with patient compliance.

Keywords: Famotidine, Ethyl acetate, acetone, Eudragit RL100, Higuchi's model, PVA, scanning electron microscopy.

INTRODUCTION

Famotidine is a histamine H_2-receptor antagonist that inhibits stomach acid production, and it is commonly used in the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD/GORD). It is commonly marketed by Johnson & Johnson/Merck under the trade names Pepcidine and Pepcid and by Astellas under the trade name Gaster. Unlike cimetidine, the first H_2 antagonist, famotidine has no effect on the cytochrome P450 enzyme system, and does not appear to interact with other drugs.[1]

Oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. The reasons for this are essentially physiological and usually affected by the GI transit of the form, especially its gastric residence time (GRT), which appears to be one of the major causes of the overall transit time variability.[2]

Gastroretentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged periods. As the system floats over gastric contents, the drug is released slowly at a desired rate resulting in increased gastric retention with reduced fluctuations in the plasma drug concentration. 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[3-8].

PREFORMULATION STUDIES

Preformulation testing is an investigation of physical and chemical properties of drug substance alone and when combined with excipients. It is the first step in the rational development of dosage form.

ANALYSIS OF FAMOTIDINE

Indentification of drug by IR Spectra

The IR spectrum of famotidine in KBr dispersion was analysed using ABB Bomen model MB 104 Fourier Transform Infrared Spectrophotometer. From the IR spectrum obtained interpretations were made and compared with that of standard.

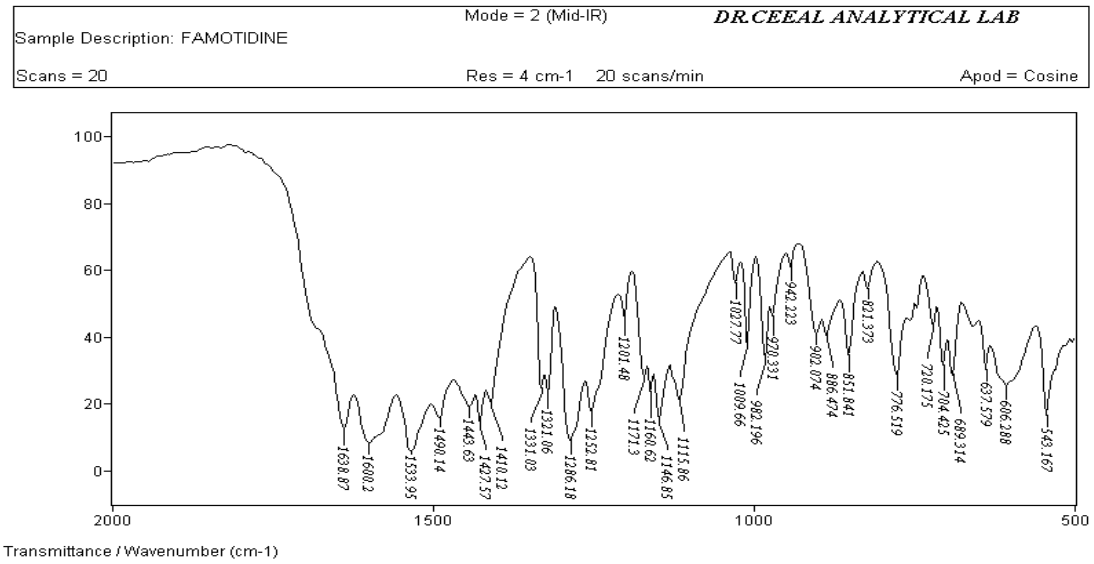


Figure 1: IR Spectra of Famotidine

Standard calibration of famotidine in 0.1N HCl

Procedure

In a 100 ml standard flask, stock solution was prepared by dissolving 100 mg of famotidine in 5 ml methanol and made up to the volume with 0.1N HCl. From this stock solution (1%w/v), serial dilutions were made by withdrawing 5 ml, 10 ml, 15 ml, 20 ml and 25 ml and transferred individually into 10 ml standard flask and the volume was made up to the mark using 0.1N HCl. The absorbance of resulting solutions was measured using shimadzu UV-1601 spectrophotometer at 265 nm and the values are given in fig 2.

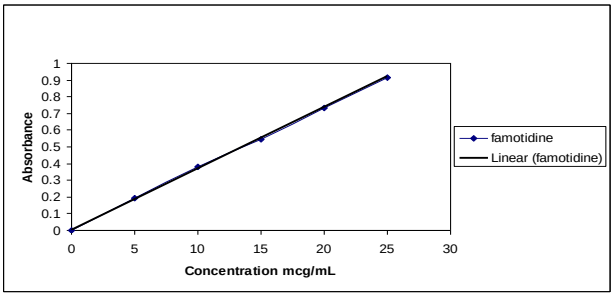


Figure 2: Standard calibration of famotidine in 0.1N HCl

MATERIALS AND METHOD:

FORMULATION DEVELOPMENT

Preparation of famotidine floating hollow microspheres using Eudragit RL 100

Microspheres were prepared by emulsion solvent diffusion method[9]. Four different ratios (E1-E4) of floating hollow microspheres of famotidine were prepared by using Eudragit RL 100 as polymer calculated quantity (as mentioned in table 4) of Eudragit RL 100 and Glyceryl monostearate were dissolved in 20 ml of mixture of ethanol and dichloromethane (1:1) to get a homogenous polymer solution. Famotidine was dispersed uniformly in the polymer solution and then it was poured slowly in to 200 ml of 0.75% w/v polyvinyl alcohol in distilled water. The emulsion formed was stirred continuously for 2 hours using propeller type agitator at 1500 rpm. The temperature was maintained at 40^{o}C. The finely dispersed droplets of the polymer solution of drug were solidified in the aqueous phase via diffusion of the solvent, leaving the cavity of microspheres filled with water. Hollow microspheres formed were filtered using nylon cloth and washed repeatedly with distilled water.

Table 1: (formulation of famotidine floating hollow microspheres E1-E4)

Sl.No.	Ingredients	Quantity			
		E1 (1:1)	E2 (1:2)	E3 (1:3)	E4 (1:4)
1	Famotidine	500 mg	250 mg	250 mg	250 mg
2	Eudragit RL 100	500 mg	500 mg	750 mg	1000 mg
3	Glyceryl monostearate	250 mg	250 mg	375 mg	500 mg
4	Ethanol : Dichloromethane (1:1)	20 ml	20 ml	20 ml	20 ml
5	Polyvinyl Alcohol (0.75% w/v)	200 ml	200 ml	200 ml	200 ml

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Preparation of famotidine floating hollow microspehers using cellulose acetate

Four different ratio of (C1 (1:1), C2 (1:2), C3 (1:3), C4 (1:4)) famotidine floating hollow microspheres were prepared using cellulose acetate were prepared by same procedure as that of Eudragit RL 100. The solvent system used was acetone: ethyl acetate in the ratio of 1:1. Calculated quantities for four different ratios are mentioned in table 2

Table 2: formulation of famotidine floating hollow microspheres C1-C4

S.No.	Ingredients	Quantity			
		C1 (1:1)	**C2 (1:2)**	**C3 (1:3)**	**C4 (1:4)**
1	Famotidine	500 mg	250 mg	250 mg	250 mg
2	Cellulose acetate	500 mg	500 mg	750 mg	1000 mg
3	Glyceryl monostearate	250 mg	250 mg	375 mg	500 mg
4	Acetone : ethyl acetate (1:1)	20 ml	20 ml	20 ml	20 ml
5	Polyvinyl Alcohol (0.75% w/v)	200 ml	200 ml	200 ml	200 ml

CHARACTERIZATION OF MICROSPHERES

Particle size

The size distribution in terms of $d_{(avg)}$ of microspheres of formulations (E1-E4) and (C1-C4) using optical microscopic method with the help of a calibrated ocular micrometer[57] . The results are shown in fig 3.

Entrapment efficiency

To determine the entrapment efficiency 50 mg of microspheres was taken in a 50 ml standard flask, 10 ml of methanol was added to solubilize and made up to the volume with distilled water. The drug content was determined by measuring the absorbance at 265 nm using Shimadzu UV 1601 spectrophotometer.

The percentage drug entrapment efficiency of microspheres were calculated by using the formula

$$\% \text{ entrapment efficiency} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

The results are shown in table 4

Buoyancy percentage

Floating behavior of hollow microspheres was studied in a USP XXIV dissolution apparatus (Type II) by spreading the microspheres (300 mg) on a 0.1mol L^{-1} HCl containing 0.02% between 80 as a surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 hrs, both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed. Buoyancy percentage was calculated using the formula.

$$\% \text{ buoyancy of microspheres} = \frac{\text{Weight of buoyant microspheres}}{\text{Initial weight of buoyant microspheres}} \times 100$$

The results are shown in Table 5.

***In vitro* drug release study**

The release rate of famotidine from microspheres was determined using USP dissolution testing apparatus I (Basket type). The dissolution test was performed using 900 ml of 0.1N HCl, at 37 ± 0.5°C at100 rpm[10]. Withdrawn samples (5 ml) were analyzed spectrophotometrically at 265 nm. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition. All experiments were performed in triplicate. Linear regression was used to analyze the *in vitro* release mechanism.

Mechanism of drug release

The *in vitro* data was treated according to Zero order, First order, Higuchi, Korsmeyer Peppas and Hixson-Crowell equation and the coefficient of correlation was determined.

Zero order Equation - % released = K.time

First order Equation – log (fraction unreleased) = K/2.303 x time

Higuchi Equation - % released = K. time $^{0.5}$

Korsmeyer Peppas Equation - %released = K.time ^{n}

Hixson Crowell Equation– (fraction of unreleased) $^{1/3 =}$ *1-K.time*

The results are given in Table-7 and in fig 4

Refabrication and evaluation of selected famotidine floating hollow microspheres

Microspheres of selected formulations E1-A and C1-A were prepared based on the prototype formulation (E1 and C1) to assess the reproducibility. The method of preparations of E1-A and C1-A were same as that of E1 and C1 respectively.

Table 3: Refabrication of selected formulations E1-A and C1-A

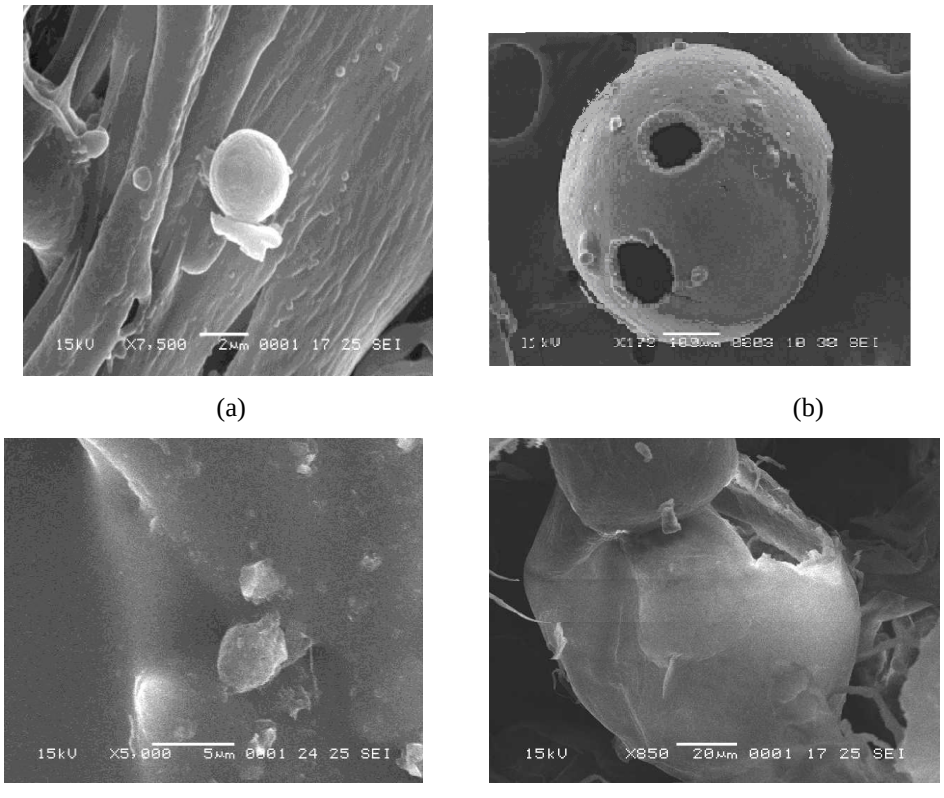
SL. No.	Ingredients	Quantity	
		E1-A	C1-A
1	Famotidine	500 mg	500 mg
2	Cellulose Acetate	-	500 mg
3	Eudragit RL 100	500 mg	-
4	Glyceryl monostearate	250 mg	250 mg
5	Ethanol : Dichloromethane (1:1)	20 ml	-
6	Ethyl Acetate : Acetone (1:1)	-	20 ml
7	Polyvinyl Alcohol (0.75%)	200 ml	200 ml

Characterization of the Selected Formulations (E1-A and C1-A)

Characteristics of microspheres such as particle size, drug content, entrapment efficiency, percentage buoyancy and *in vitro* release were evaluated.

MORPHOLOGY: Size and Shape

The external and internal morphology of the microspheres were studied by scanning electron microscopy (SEM). The samples for SEM were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Afterwards, the stubs containing the coated samples were placed in the scanning electron microscope (JSM-6360A, JEOL, Tokyo, Japan) chamber. The samples were then randomly scanned and photomicrographs were taken at the acceleration voltage of 15 kV to investigate the internal morphology, hollow microspheres were cut with a knife. The SEM photomicrographs of formulations E1-A and C1-A are shown in fig 3.



(a) (b)

(c) (d)

Figure 3: Scanning electron microphotographs of floating hollow microspheres of famotidine: (a) & (b) surface and cross-sectional morphology of C1-A respectively (c) & (d) surface and cross-sectional morphology of the formulation E1-A respectively.

RESULTS:

Characterization of particle size:

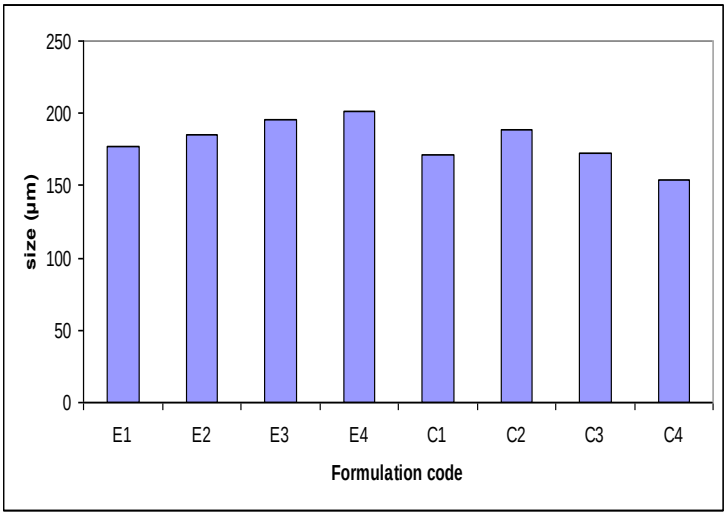


Figure 4: Particle size distribution of formulations E1-E4 and C1-C4

Table 4: Drug entrapment efficiency in formulations (E1-E4 and C1-C4)

Sl.No.	Formulation code	Entrapment efficiency (%)			Mean ± SD
		1	2	3	
1	E1	71.05	70.28	69.95	70.42 ± 0.56
2	E2	71.2	69.18	69.98	70.12 ± 1.01
3	E3	69.24	70.18	68.25	69.22 ± 0.96
4	E4	69.03	67.04	67.29	67.78 ± 1.08
5	C1	72.25	71.11	73.21	72.19 ± 1.05
6	C2	68.98	69.01	68.64	68.87 ± 0.20
7	C3	67.19	66.91	67.34	67.14 ± 0.21
8	C4	67.56	66.14	66.92	66.87 ± 0.71

Table 5: Buoyancy percentage of formulations E1-E4 and C1-C4

Sl.No.	Formulation code	Buoyancy (%) after 12 h			Mean ± SD
		1	2	3	
1	E1	70.17	69.11	68.36	69.21 ± 0.09
2	E2	67.15	68.05	66.52	67.24 ± 0.76
3	E3	66.16	67.29	65.95	66.46 ± 0.72
4	E4	64.29	64.64	63.99	64.30 ± 0.32
5	C1	71.11	70.75	71.84	71.23 ± 0.55
6	C2	65.34	64.61	66.1	65.35 ± 0.74
7	C3	59.26	59.97	61.21	60.14 ± 0.98
8	C4	58.86	59.12	60.37	59.45 ± 0.80

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 6: *In vitro* release data

***In vitro* release data of famotidine from the formulationE1,E2,E3,E4&C1,C2, C3,C4**							
E1	**E2**	**E3**	**E4**	**C1**	**C2**	**C3**	**C4**
24.32 ± 0.57	18.57 ± 0.46	14.46 ± 0.22	12.87 ± 0.85	19.74 ± 0.25	15.66 ± 0.18	13.26 ± 0.48	10.39 ± 0.32
26.48 ± 0.05	21.69 ± 0.29	18.28 ± 0.65	13.80 ± 0.14	22.66 ± 0.27	19.27 ± 0.38	15.88 ± 0.24	12.33 ±0 .48
28.51 ± 0.23	26.23 ± 0.17	20.43 ± 0.61	16.89 ± 0.26	28.00 ± 0.23	22.32 ± 0.83	18.79 ± 0.69	15.33 ± 0.71
31.53 ± 0.65	29.95 ± 0.62	24.57 ± 0.57	18.99 ± 0.12	33.23 ± 0.37	26.69 ± 0.14	22.15 ± 0.10	17.93 ± 0.68
34.49 ± 0.18	32.01 ± 0.54	28.10 ± 0.16	20.52 ± 0.82	37.73 ± 0.85	30.29 ± 0.67	26.08 ± 0.85	20.06 ± 0.15
37.68 ± 0.54	34.92 ± 0.23	30.58 ± 0.68	23.72 ± 0.17	41.92 ± 0.44	34.85 ± 0.64	29.62 ± 0.32	22.19 ±0. 74
41.45 ± 0.71	37.70 ± 0.11	34.63 ± 0.74	27.57 ± 0.66	45.30 ± 0.90	37.77 ± 0.44	34.02 ± 0.48	26.51 ± 0.49
44.18 ± 0.11	41.70 ± 0.98	36.80 ± 0.50	29.51 ± 0.71	49.53 ± 0.45	41.93 ± 0.62	37.17 ± 0.74	30.56 ± 0.73
47.84 ± 0.47	45.36 ± 0.41	40.25 ± 0.40	32.32 ± 0.52	53.78 ± 0.21	44.96 ± 0.93	40.70 ± 0.87	33.94 ± 0.73
51.10 ± 0.22	49.39 ± 0.12	43.08 ± 0.52	34.36 ± 0.55	57.64 ± 0.23	50.03 ± 0.18	43.25 ± 0.29	35.87 ± 0.78
62.53 ± 0.96	50.57 ± 0.83	45.86 ± 0.26	36.41 ± 0.32	63.30 ± 0.19	52.60 ± 0.34	47.37 ± 0.26	39.42 ± 0.51

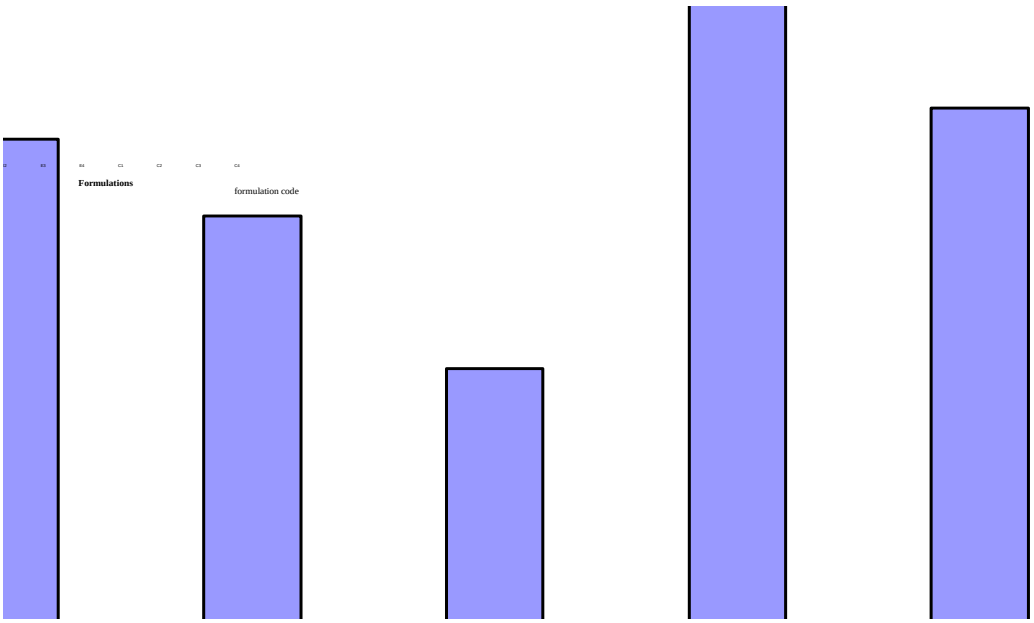


Figure 5: Comparison of *in vitro* drug release profile of formulations E1-E4 and C1-C4

Table 7: *In-vitro* kinetics data for formulations E1-E4 and C1-C4

Formulation Code	**Coefficient of correlation (r^2)**					
	0 order	**1st order**	**Higuchi**	**Korsmeyer Peppas**		**Hixson crowell**
				r^2 value	**'n' value**	
E1	0.8585	0.9903	0.990	0.865	0.285	0.891
E2	0.8848	0.9407	0.974	0.966	0.337	0.9253
E3	0.9175	0.9579	0.986	0.968	0.384	0.9466
E4	0.9184	0.9486	0.974	0.932	0.365	0.9398
C1	0.9238	0.991	0.995	0.865	0.285	0.9612
C2	0.9359	0.9718	0.984	0.963	0.408	0.9631
C3	0.9503	0.9764	0.982	0.956	0.434	0.97
C4	0.9585	0.9733	0.969	0.963	0.408	0.9698

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 8: Characterization of selected formulations E1-A and C1-A

[a]Mean ± SD, n = 3

S.No.	Parameter	Observation[a]	
		E1-A	C1-A
1	Mean Particle Size (µm)	171.5 ± 1.818	165.2 ± 2.164
2	Entrapment Efficiency (%)	70.1 ± 0.45	72.05 ± 0.95
3	Buoyancy (%)	69.05 ± 0.15	70.95 ± 0.35

Table 9: *In vitro* release data of famotidine from the formulation E1-A

[a]Cumulative % Drug release	[a]Cumulative % Drug release
E1-A	C1-A
24.60 ± 0.65	19.05 ± 0.39
27.11 ± 0.52	21.56 ± 0.11
29.15 ± 0.11	27.30 ± 0.63
32.17 ± 0.21	32.46 ± 0.53
35.06 ± 0.36	36.27 ± 0.99
38.33 ± 0.58	41.34 ± 0.96
41.60 ± 0.85	44.93 ± 0.71
44.97 ± 0.39	48.88 ± 0.62
48.84 ± 0.48	52.99 ± 0.32
51.89 ± 0.87	57.60 ± 0.17
62.15 ±0. 43	63.05 ± 0.76

***In vitro* drug release profile of formulations E1-A and C1-A**

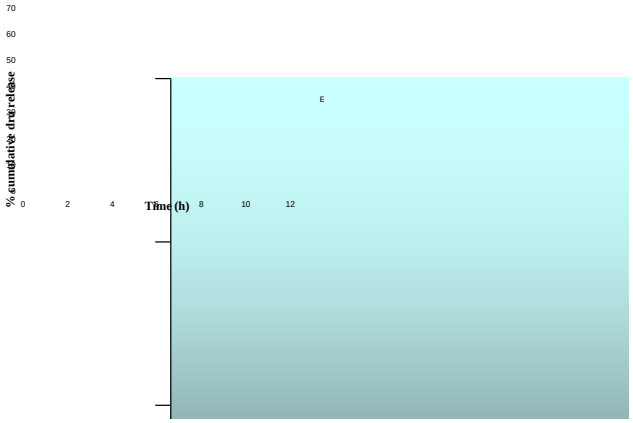


Figure 6: *In vitro* drug release profile of formulations E1-A and C1-A

Table 10: *In vitro* kinetics data for refabricated formulations E1-A and C1-A

Formulation Code	Coefficient of correlation (r^2)					
	0 order	1st order	Higuchi	Korsmeyer Peppas		Hixson crowell
				r^2 value	'n' value	
E1-A	0.856	0.989	0.990	0.875	0.282	0.895
C1-A	0.935	0.988	0.991	0.980	0.422	0.968

RESULTS & DISCUSSION

The results indicated that the mean particle size or average diameter $d_{avg)}$ of microspheres was in the range of 153.6-201.9. Cellulose acetate polymer containing microspheres were smaller in size than that of Eudragit RL 100 coated microspheres.

The results shown in table 5 indicate the percentage of entrapment efficiency of formulations E1-E4 and C1-C4. The drug content of all formulations was determined spectrophotometrically. The entrapment efficiency of formulation E1-E4 were 70.42%, 70.12%, 69.22% and 67.78% and for the formulation C1-C4 were 72.19%, 68.67%, 67.14% and 66.87%. The results shows cellulose acetate containing microspheres showed a desirable high drug content and entrapment efficiency.

The results shown in table 6 indicate the percentage buoyancy formulations E1-E4 and C1-C4. The percentage buoyancy of formulations E1-E4 at the end of 12 h were found to be 69.21%, 67.24%, 66.46% and 64.3% and for the formulations C1-C4 at he end of 12 h were 71.23%, 65.35%, 60.14% and 59.45%. The results indicates that increase in concentration of polymers, Eudragit RL 100 and cellulose acetate decreases the floating time. Formulation C1 of cellulose acetate coated microspheres and E1 of Eudragit RL 100 coated microspheres were found to be best.

The results shown in table 7 indicate the *in vitro* drug release data of formulations E1-E4 and C1-C4. The cumulative percentage drug release of E1-E4 at the end of 10 h were 62.53%, 50.64%, 45.86% and 36.41% it indicates that increase in concentration of Eudragit RL 100 decreases the release rate of drug. The cumulative drug release of C1-C4 at the end of 10 h was 63.30%, 52.60%, 47.37% and 39.42%. Increase in concentration of cellulose acetate tends to control the release of famotidine from the formulations.

The data obtained for *in vitro* release were fitted in to equations for the zero order, first order and Higuchi release models. The interpretation of data was based on the value of the resulting regression coefficient. The *in vitro* drug

release showed the highest regression coefficient values for Higuchi's model, indicating diffusion to be the predominant mechanism of drug release. The formulation E1 and C1 using Eudragit RL 100 and cellulose acetate respectively showed constant rate of release and hence these two formulations were chosen as best and refabricated table no 8.

The results shown in table 9, indicate the $d_{(avg)}$ of microspheres of formulations E1-A and C1-A were found to be 171.5 µm and 165.2 µm respectively. The percentage entrapped and buoyancy percentage after 12 h were found to be 70.1% (E1-A), 72.05% (C1-A) and 69.05% (E1-A), 70.95% (C1-A) respectively. The percentage cumulative drug release of E1-A and C1-A at the end of 10 h were found to be 62.15% and 63.05% respectively. The data's obtained were compared respectively with that of E1 and C1. The results were almost similar and hence showed good reproducibility.

CONCLUSION

The formulation using Eudragit RL 100 and cellulose acetate showed a constant rate of release. Thus, prepared floating hollow microspheres of famotidine may prove to be potential candidates for a multiple-unit drug delivery device adaptable for any intragastric condition.

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 ISSN: 2250-1177 CODEN (USA): JDDTAO