Acta Pharmaceutica Sciencia
53: 551-562 (2011)

Development and Characterization of Floating Alginate Beads for Gastroretentive Drug Delivery System

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Abstract
The main object of this study was to involve in development and characterization of novel floating alginate beads of Ranitidine HCl having an air compartment in itself to increase its residence time in the stomach without contact with mucosa. Such floating alginate beads were prepared by Ion-gelation method, using various ratio of $CaCl_2$ as a crosslinking agent in ion gelation media. The presence of air compartment was observed in formulation FF_1, FF_2 and CFF_3, CFF_6 by visual examination but only FF_1 and CFF_3 were found to be buoyant. Average particle size of the formulation FF_1 and CFF_3 were found to be 1.36± 0.28 mm and 1.45±0.21 mm respectively. Surface morphology of formulations FF_1 and CFF_3 before and after complete dissolution test were studied by Scanning electron microscopy (SEM). *In-vitro* drug release studies of selected formulations were performed in 900 ml simulated gastric fluid (1.2 pH) without pepsin. Different drug release kinetics models were also applied for selected batches.

Keywords: Floating alginate beads, chitosan, calcium chloride ($CaCl_2$), Ranitidine HCl.

Introduction

In some circumstances prolonging the gastric residence time of a delivery system is desirable for achieving greater therapeutic benefit of the drugs. For example, drugs that are absorbed from the proximal part of the gastrointestinal tract (Fell et al. 2000), and drugs that are less soluble or are degraded by the alkaline pH may benefit by prolonged gastric retention (Fell 1999). In addition, for local effect sustained drug delivery to the stomach and proximal small intestine may be beneficial to treat certain conditions like ulceration. Prolonged gastric retention of a therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy leading to possible reduction of dose size (Garg et al. 2004). Gastroretentive drug delivery systems (GRDDS) can remain in the gastric region for several hours because of its lower density than that of the gastric fluid; hence significantly prolong the gastric residence time of drugs.

Multiparticulate dosage form pass through the gastro-intestinal tract (GIT) to avoid the vagaries of gastric emptying and thus release the drug more uniformly, which result in more reproducible drug absorption and reduce risk of local irritation. While single unit dosage

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form have the disadvantage of a release all-or-nothing emptying process.

In the present study multiunit floating beads of calcium alginate containing Ranitidine Hydrochloride are synthesized by emulsification/ gelation process. Ranitidine Hydrochloride is non- imidazole H_2 receptor blocker. The H_2 antagonists are competitive inhibitors of histamine at the parietal cell H_2 receptor. The half life of Ranitidine Hydrochloride is 2.8 to 3.1 h, its bioavailability is 50% by oral route. The recommended adult oral dosage of Ranitidine Hydrochloride for duodenum ulcer is 150 mg.

Material and Methods

Materials

Ranitidine Hydrochloride was purchased from Jackson laboratories Pvt. Ltd. Amritsar India. Sodium Alginate and Poly Vinyl Alcohol Cold (Average Molecular Weight 1,25000) were procured from Central drug house (P) LTD New Delhi, India. Ethylene Diamine Tetra Acetic Acid Di Sodium salt and n- Heptane were purchased from Qualigen Fine chemicals Pvt. Ltd. Mumbai, India. Calcium Chloride and Sodium Carbonate were purchased from Rankem Fine Chemicals Limited New Delhi, India. Chitosan from Crab Shell (degree of deacetylation $\geq$ 75%) was procured from Sigma- Aldrich, Denmark. All excipients and solvents were of analytical grade and double distilled deionised water was used in all experiments.

Preparation of Calcium Alginate Beads

Aqueous solution of sodium alginate (5% w/w) was dropped through an 18 gauze needle in to a medium constituted by n- Heptane, Calcium Chloride and Tween 20. The medium was stirred at 1000 rpm for 5 minutes at room temperature. The formed particles were separated from the medium, washed quickly with water and then di ethyl ether (Iannuccelli et al. 1998).

Preparation of Calcium Alginate Chitosan Beads

Aqueous solution of sodium alginate was dropped through an 18 gauze needle in to a medium constituted by n- Heptane, Calcium Chloride, Tween 20, Chitosan, and Acetic Acid. The medium was stirred at 1000 rpm for 5 minutes at room temperature. The formed particles were separated from the medium, washed quickly with water and then di ethyl ether. (Iannuccelli et al. 1998 and Basu et al. 2008)

Preparation of Floating Beads

Freshly prepared Calcium alginate and chitosan alginate beads were soaked in aqueous solution of sodium alginate and Poly Vinyl Alcohol for 10 minutes. The formulation parameters are enlisted in Table I. The coated beads were separated from coating solution and quickly rinsed with water and then di-ethyl ether. Then dried in the hot air oven at 40^0 C overnight (Iannuccelli et al. 1998).

Physicochemical Characterization

Presence of Air Compartment

Presence of air compartment was studied by optical microscopy of beads (Iannuccelli et al. 1998).

In –Vitro Buoyancy

Buoyancy of the formulation is determined by using USP Paddle type (USP XXIII) dissolution apparatus at 100 rpm and $37^\circ \pm 0.5^0$ C in simulated gastric fluid (SGF). 100 beads were placed in the 900 ml of simulated gastric fluid without pepsin at $37^0 \pm 0.5^0$ C and the buoyancy of floating beads was visually measured after 24 h.

Particle Size

Particle size of floating beads was measured by optical microscopy using optical microscope (Radical Instruments, India) (Iannuccelli et al. 1998).

Scanning electron microscopy

Floating Beads obtained before and after complete dissolution were examined for their surface morphology by scanning electron microscope (Leo Electron microscopy Ltd. U.K.). The floating beads were dried at 50^0C for 6 h and stored between sheets of wax paper in dessicator before examination. The samples were coated with gold paladium for 120 second and examined under scanning electron microscope (Iannuccelli et al. 1998).

Drug content and loading efficiency

To determine the loading efficiency, a weighed quantity of beads equivalent to 100 mg of Ranitidine HCl was allowed to dissolve in a solution of 0.5 M sodium carbonate and 0.05 M Di sodium EDTA on magnetic stirrer at 1000 rpm for over night. Resultant solution was filtered to remove shell fragment, the estimation of drug was carried out by measuring the absorbance at the λ_{max} 314 nm using UV double beam Spectrophotometer (UV – 1700 Pharma Spec. UV–Visible Spectrophotometer. Shimadzu, Japan).(USP, 2008) The Loading efficiency was calculated as follows: (Equation-1)

$$\text{Loading efficiency} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \times 100 \quad (1)$$

In-vitro dissolution studies

The drug release rate from beads was determined using USP XXIII basket type dissolution test apparatus (Electrolab TDT-08L). A weighed quantity of beads equivalent to 300 mg of drug was placed in basket. The dissolution test was carried out in 900 ml simulated gastric fluid (1.2-pH) without pepsin at 100 rpm and 37.5±0.5^{0}C temperature (Sriamornsak et al. 2004). At specified time interval, 5ml aliquots were withdrawn, filtered and diluted with the same medium and assayed at 314 nm for Ranitidine HCl using a double beam UV Spectrophotometer (UV–1700 Pharma Spec. UV–Visible Spectrophotometer. Shimadzu, Japan). Sample withdrawn were replaced with the equal volume of the same dissolution medium. All the experiments as specified above were conducted in triplicate.

Release models and kinetics

Generally the release of drug from alginate beads is controlled by various factors such as surface area, coating thickness, permeability of membrane, solubility of drug and pore former agent. Release kinetics of drugs from the formulation (FF_1 and CFF_3) were determined utilizing various mathematical equations like (a) zero order rate Eq. (2) describes the systems, where the drug release is independent of its concentration. (b)The first order equation Eq. (3) describes the release from systems, where release rate is concentration dependent. (c) Higuchi model Eq. (4), the drug release from insoluble matrix is directly proportional to square root of time and is based on Fickian diffusion. (d) The Hixson–Crowell cube root law Eq. (5) describes the release from the systems, where it depends on the change in surface area and diameter of the particles or tablets with time and mainly applies in case of system, which dissolute or erode over time (Vyas et al. 2004).

$$Qt = k_0 t \quad (2)$$

$$\ln Q_t = \ln Q_0 - k_1 t \quad (3)$$

$$Q_t = k_H t^{1/2} \quad (4)$$

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t \quad (5)$$

Where Q_t is the amount of drug release in time t, Q_0 is the initial amount of the drug in tablet and $k0$, k_1, k_H and k_{HC} are release rate constants for zero order, first order, Higuchi model and Hixson–Crowell rate equations, respectively. In order to define a model, which will represent a better fit for the formulations, dissolution data were further analyzed by Peppas and Korsenmayer equation Eq. (6)

$$Mt / M\alpha = kt^n \qquad (6)$$

where Mt is the amount of drug released at time t and $M\alpha$ is the amount released at time α

Drug release data obtained was applied to different drug release models in order to establish the drug release mechanism and kinetics. Criteria for selecting the most appropriate model was based on best goodness of fit and smallest sum of squared residuals (Vyas et al. 2004).

Results and Discussion

The beads forming the system were composed of a calcium alginate or chitosan alginate as a core separated by an air compartment from a membrane of calcium alginate and PVA (Table 1).

Table 1. Different composition of formulation

Ingredients	Formulation					
	Simple Alginate Beads (gm)			Chitosan Alginate Beads (gm)		
	F_1	F_2	F_3	CF_1	CF_2	CF_3
Sodium Alginate	5	5	5	5	5	5
Ranitidine HCl	8	8	8	8	8	8
Water	100	100	100	100	100	100
	Ion Gelation Media					
Calcium Chloride	1	5	10	1	5	10
Tween 20	1	1	1	1	1	1
N – Heptane	20	20	20	20	20	20
Chitosan	-	-	-	0.625	0.625	0.625
Acetic Acid	-	-	-	3	3	3
Water	80	80	80	80	80	80

All formulation was characterized for their physiochemical parameters like presence of air compartment, *in-vitro* buoyancy, particle size, and drug content (Table 2-6).

Table 2. Different coating materials and methods

Material	Formulation											
	Simple Alginate Beads (gm)						Chitosan Alginate Beads (gm)					
	FF_1	FF_2	FF_3	FF_4	FF_5	FF_6	CFF_1	CFF_2	CFF_3	CFF_4	CFF_5	CFF_6
Sodium Alginate	5	5	5	5	5	5	5	5	5	5	5	5
PVA Cold	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Beads Used	F_1	F_1	F_2	F_2	F_3	F_3	CF_1	CF_1	CF_2	CF_3	CF_3	CF_3
Washing	Method											
	-	+	-	+	-	+	-	+	-	+	-	+

(-) = Without Washing, (+) = With Washing

Table 3. Observation for presence of air compartment formulation

Calcium Alginate Beads						Chitosan Alginate Beads					
FF_1	FF_2	FF_3	FF_4	FF_5	FF_6	CFF_1	CFF_2	CFF_3	CFF_4	CFF_5	CFF_6
+	-	-	-	-	+	-	-	+	-	-	+

(-) = Air Compartment Absent, (+) = Air Compartment Present

Table 4. Observations of *in –vitro* buoyancy

Parameters	Formulations											
	Calcium Alginate Beads						Chitosan Alginate Beads					
	FF_1	FF_2	FF_3	FF_4	FF_5	FF_6	CFF_2	CFF_3	CFF_4	CFF_5	CFF_6	
Buoyancy	+	-	-	-	-	-	-	-	+	-	-	-
Floating Time (Hours)	72	0	0	0	0	0	0	0	72	0	0	0
Buoyancy (%)	100	0	0	0	0	0	0	0	100	0	0	0

Table 5. Particle size observation of beads

Formulation	Particle Size (mm) (n = 40)
FF_1	1.36 ± 0.28
CFF_3	1.45 ± 0.21

Table 6. Observation of average pore diameter of the pore present at the membrane

Formulation	Average Pore Size (μm) (n = 15)
FF_1	17.73 ± 5.75
CFF_3	18.07 ± 6.76

Formulation FF_1, FF_6, CFF_3, and CFF_6 were found to show the presence of air compartment but only formulation FF_1 and CFF_3 were found to be buoyant. Average particle size of formulation FF_1 and CFF_3 were found to be 1.36 ± 0.28 mm and 1.46 ± 0.21 mm respectively and all the formulation were found within limit. The drug loading efficiency of the formulation FF1 and CFF_3 were found to be 57.25% and 76.04 % respectively (Table 7).

Table 7. Observations of loading efficiency and drug content of the beads

Formulation	Drug Content (mg)	Loading Efficiency (%)
FF_1	57.25	57.25
CFF_3	76.04	76.04

The $t_{80\%}$ values determined from percent cumulative drug release versus time plots and release rate diagrams confirmed the effect of chitosan on the release rate of ranitidine hydrochloride (Figure 1 and 2).

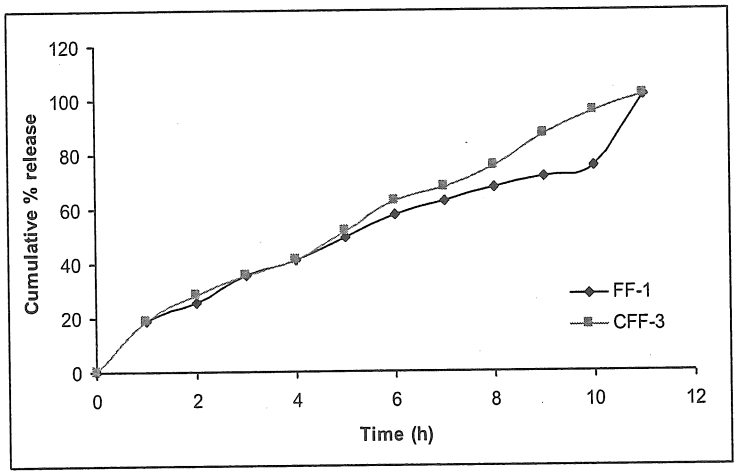

Figure 1. Dissolution profiles of different floating beads

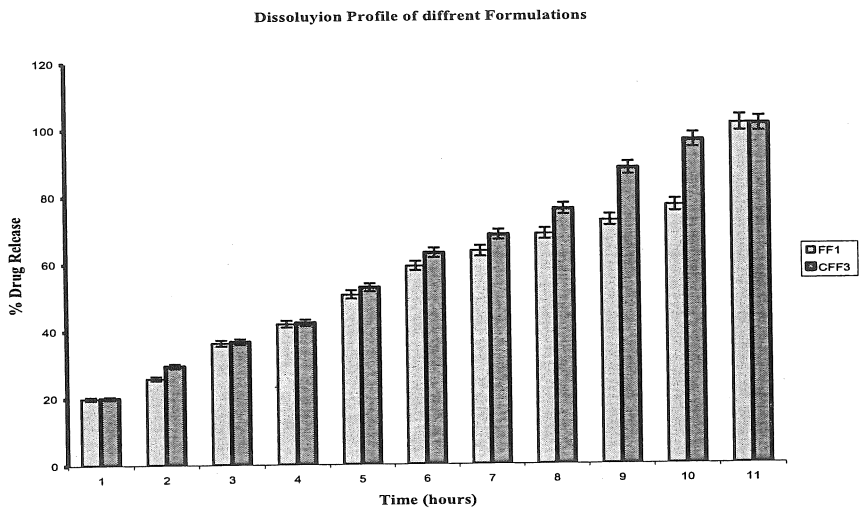

Figure 2. Bar diagram of dissolution profile of different formulations

Formulation CFF_3 showed slower release ($t_{80\%}$ in 9 h) compared to formulation FF_1 ($t_{80\%}$ in 8 h). Change in the concentration of calcium chloride in the formulations leads to change in buoyancy. This may be due to the absence of air compartment or due to accumulation of beads resulting in the absence of air compartment, or due to collapsed air compartment. Formulations FF_2, CFF_1, CFF_2, and CFF_4 were found to be non buoyant due to absence of air compartment, while formulations FF_3, FF_4, FF_5, and CFF_5 were found to be non buoyant due to accumulation of beads. Formulation FF_6 and CFF_6 were found to be non buoyant due to collapsed alginate membrane. The formulations FF_2, FF_3, FF_4, FF_5, CFF_1, CFF_2, CFF_4, CFF_5, and CFF_6 were found to be non buoyant so these formulations were not taken for further studies. On the basis of presence of air compartment and *in-vitro* buoyancy study, appropriate

concentration of calcium chloride was found to be 1% for floating calcium alginate beads and 4% for the chitosan alginate beads (Figure 3).

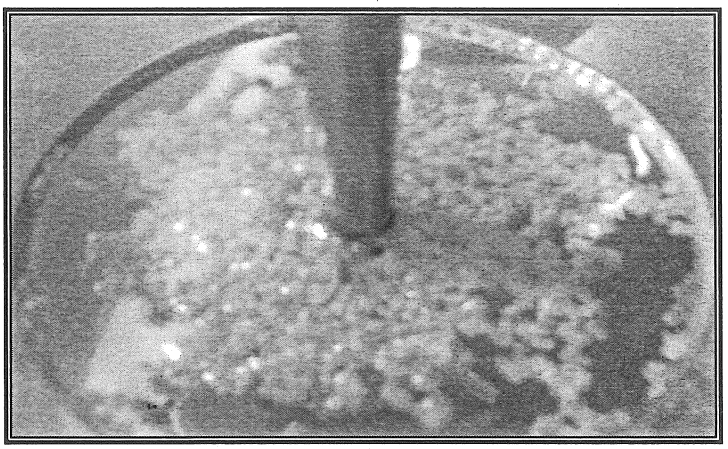

Figure 3. Photograph of floating beads after 24 hours during buoyancy study

Formulations FF_1 and CFF_3 obtained before and after complete dissolution were studied by SEM (Figure 4, 5, 6 and 7).

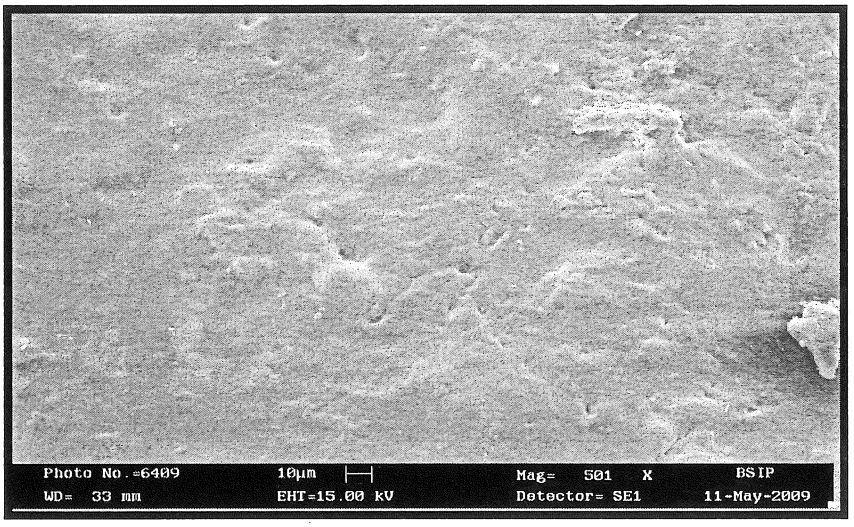

Figure 4. Scanning electron photomicrograph of calcium alginate beads before dissolution (501 X)

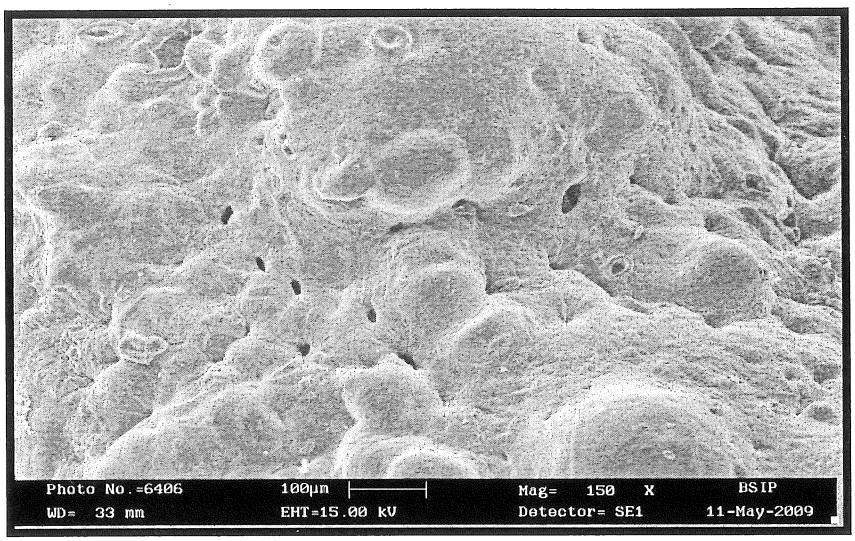

Figure 5. Scanning electron photomicrograph of calcium alginate beads showing the presence of pore on the surface after dissolution (150 X)

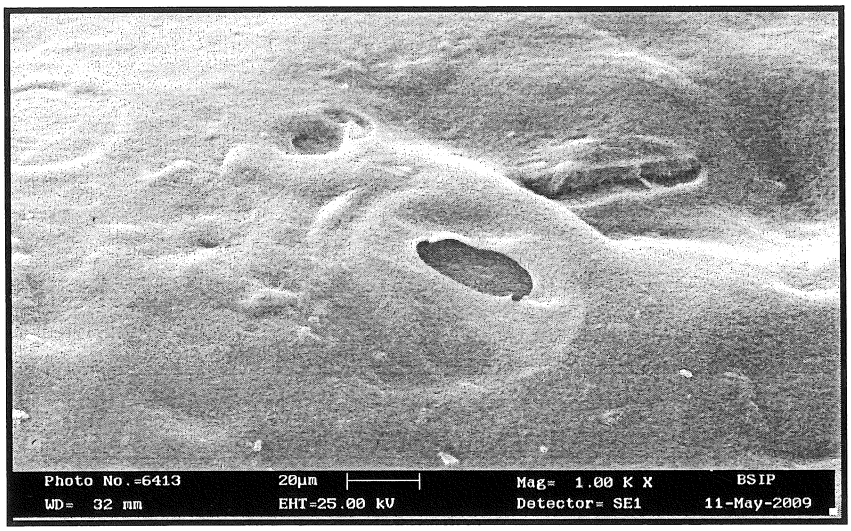

Figure 6. Scanning electron photomicrograph of chitosan alginate beads before dissolution (1000 X)

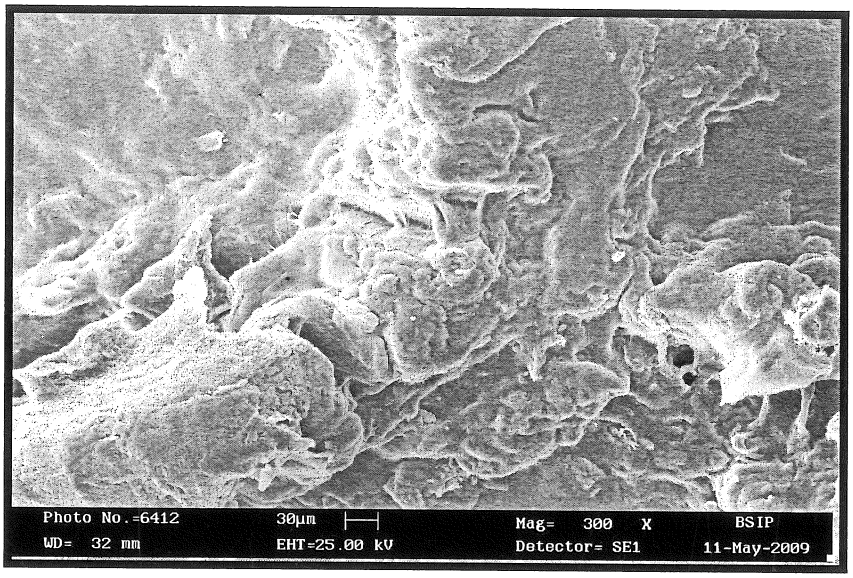

Figure 7. Scanning electron photomicrograph of chitosan alginate beads showing the presence of pores on the surface after dissolution (150 X)

Formulations showed rough and non-porous region before dissolution. After dissolution, formulations showed more rough and micro porous region. The pore size were found 17.73 ± 5.75 µm and 18.07 ± 6.76 µm for formulation FF_1 and CFF_3 respectively. Results of SEM also showed that membrane did not show swelling and rupturing. Broken surface of all the formulations showed the presence of air compartment (Figure 8 and 9).

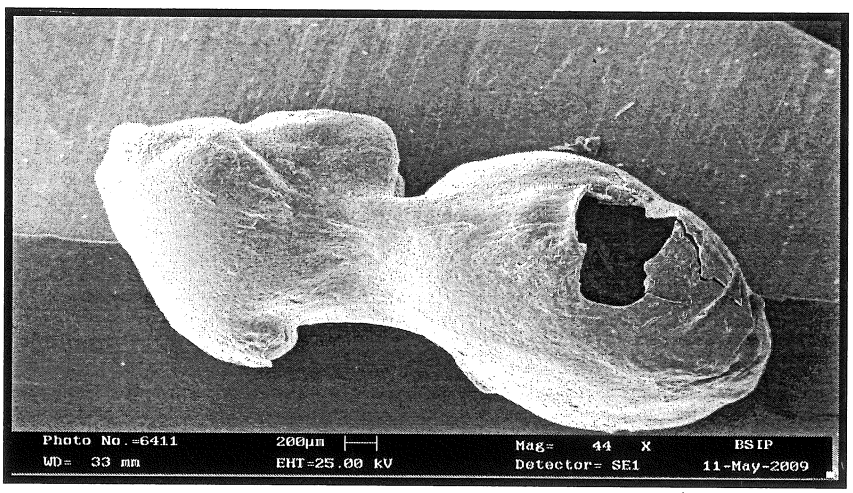

Figure 8. Scanning electron photomicrograph of chitosan alginate beads showing the presence of air compartment before dissolution (44 X)

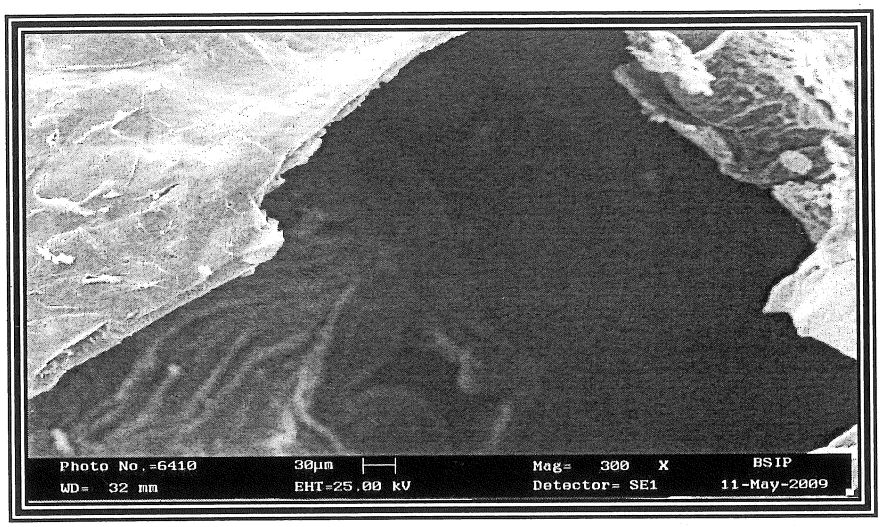

Figure 9. Scanning electron photomicrograph of calcium alginate beads showing the presence of air compartment (300 X)

The linear nature of the plots between percent cumulative drug release and time suggest that formulation FF_1 did not follow zero order kinetics, which is confirmed by the less correlation co-efficient. The linear nature of the curves obtained for first order, Higuchi model and Hixson–Crowell model suggests that the release from the formulations may follow any one of these models. While considering the higher correlation co-efficient values, the release data seem to better fit with first order models. Hixson–Crowell and Higuchi model moreover showed comparatively small correlation co-efficient. The linear nature of the plots between percent cumulative drug release and time suggest that the formulation FF_1 did not follow first order kinetics, which is confirmed by the less correlation co-efficient. The CFF3 formulation showed higher correlation coefficient values of 0.9984 which confirm that it follow zero order kinetics (Table 8).

Table 8. Regression analysis and correlation co-efficient values for dissolution data of formulation according to various kinetic models.

Kinetics Model	Parameters	Formulation	
		FF_1	CFF_3
Zero Order	R	0.9801	0.9984
	K_0	7.153	8.359
First Order	R	0.9982	0.9178
	K_1	1.361×10^{-1}	1.178×10^{-1}
Higuchi Order	R	0.9679	0.9851
	K_H	31.428	36.692
Hixson–Crowell model	R	0.9786	0.991
	K_{HC}	2.0 x 10-1	2.323×10^{-1}
Peppas -Korsenmayer model	R	0.9888	0.9928
	n	0.6636	0.714
	K	6.636×10^{-1}	7.14×10^{-1}

Summary and Conclusion

As a new oral drug delivery system for gastric retention, air compartment multiple unit beads were successfully developed by coating with microporous semipermeable membrane of calcium alginate and PVA. The prepared air compartment multiple unit system does not require any effervescent agents (sodium carbonate, calcium carbonate) or low density imparting agent (oils). The core consisted of a matrix of calcium alginate or chitosan and calcium alginate containing ranitidine hydrochloride. The core beads were prepared by ion gelation method and coated by using a conventional dip coating method. Air compartment present in the formulations helps in the floating of alginate beads. The scanning electron microscopy (SEM) study was applied to elucidate the mechanism of release from the air compartment multiple unit beads. The effect of different formulation variables including concentration of gelating agent and method of coating to select the optimal formulation. Result of SEM showed that the *in-situ* delivery pores were formed in predetermined time after coming in to contact with dissolution medium. The single step *in-vitro* buoyancy study at pH 1.2 was performed to determine the buoyancy. Formulation CFF_3 and FF_1 were considered as the optimum formulations on the basis of in-vitro buoyancy study. The single step dissolution study at pH 1.2 was performed to determine the release pattern of formulations CFF_3 and FF_1. The dissolution results indicated that $FF_1$was able to deliver drug at an approximate First order up to 11 h. The dissolution results indicated that CFF_3 was found to be able to deliver the drug at an approximate zero order up to 11 h. The preparation of air compartment multiple unit floating beads was effected through conventional techniques thus eliminating the use of sophisticated technologies like spray drying or freeze drying. The designed device may act as one of the promising formulation for gastro retentive drug delivery system in the treatment of peptic ulcer.

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Received: 26.07.2011
Accepted: 30.12.2011