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Preparation and evaluation of floating calsium alginate beads of clarithromycin

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ABSTRACT

The objective of this investigation was to develop an intra gastric floating drug delivery system of clarithromycin and also attempts were made to sustain the release of clarithromycin. Multiple-unit floating beads of clarithromycin were prepared from sodium alginate solution containing Hydroxypropylmethylcellulose (K100M) and sunflower oil by using emulsion-gelation method. These beads were evaluated for entrapment efficiency, drug loading, buoyancy and in vitro drug release. All formulations were the floating lag time below two minutes and shows total floating duration more than ten hours. It was observed that entrapment efficiency, drug loading and buoyancy was greater with formulation containing two percent sodium alginate solution and five percent calcium chloride solution along with 500mg HPMC and five ml sunflower oil (i.e.F14) and also the result of in-vitro dissolution studies reveals that the formulation F14 gave sustained release pattern of clarithromycin upto 12 hrs.

Key words: Floating alginate beads; emulsion gelation; clarithromycin; controlled release.

INTRODUCTION

Gastro-retentive dosage forms have been a topic of interest in terms of their potential for controlled drug delivery. [1] These dosage forms are particularly appropriate for drugs: (1) that is locally active to the gastric mucosa in the stomach, for example, antibiotic administration for *Helicobacter pylori* eradication in the treatment of peptic ulcer disease. [2]; (2) with an absorption window in the stomach or in the upper small intestine; (3) that are unstable in the intestine or colonic environment; and (4) with low solubility at high pH values. [3] It is widely accepted that gastric emptying of conventional dosage forms in humans is affected by numerous factors and the time taken shows wide inter and intra subject variation. This variability, in turn can lead to unpredictable tmax and bioavailability, since many drugs absorb to the greatest extent in the upper part of the small intestine. [4] A drug that is released from a dosage form in a controlled manner in the stomach will empty together with fluids and will have the whole surface area of the small intestine available for absorption. Several approaches of gastro-retentive dosage forms have been proposed and investigated, such as bioadhesive delivery systems in which

bioadhesive polymers adhere to the mucin-epithelial surfaces. [4] Another approach is density controlled delivery systems or floating dosage forms, which remain buoyant on gastric contents because they have a lower density than gastric fluids. [1]

Calcium alginate gel beads have been developed in recent years as a unique vehicle for drug delivery system. Various categories of drug have been encapsulated such as nonsteroidal anti-inflammatory drugs, enzymes, peptides/proteins, and acid labile drugs. [5] Clarithromycin was selected as a model drug for incorporation in calcium alginate beads. Clarithromycin, a macrolide antibiotic is widely used as an anti-bacterial as well as to prevent recurrence of peptic ulcer disease caused by *Helicobacter pylori.* [6] The beads were evaluated with respect to micromeretic properties, floating property, drug content, entrapment and encapsulation efficiency, *in vitro* drug release.

In the present investigation, a controlled release formulation of clarithromycin capable of providing detectable blood levels over 10 hr was formulated using expandable and swellable hydrocolloid polymer along with the sunflower oil. [7] The polymer used was sodium alginate which is an inexpensive, nontoxic product extracted from kelp. Sodium alginate has been used as thickening and gelling agent. Additionally it also reduces interfacial tension between an oil and water phase and is efficient for preparation of emulsion. Hydroxypropylmethylcellulose (K100M) was also used to achieve a controlled drug release. [8]

MATERIALS AND METHODS

Materials

Sodium alginate, hydroxypropylmethylcellulose (K100M) and calcium chloride were obtained from Colorcon Asia Pvt. Ltd. (Goa, India.). Clarithromycin was donated by Biochem Pharmaceutical (Daman, India.). All other chemicals used were of analytical grade.

Formulation of clarithromycin floating beads

Clarithromycin floating beads were prepared using emulsion-gelation method. Sodium alginate and hydroxypropylmethylcellulose (K100M) were dissolved in water with stirring. Sunflower oil was added to polymer solution followed by clarithromycin. The homogenized mixture was extruded into calcium chloride solution with gentle agitation at room temperature. The formed beads were allowed to stand for 30 min in the solution for curing then separated by filtration and dried at room temperature and used for further studies. [9]

Process variables and process optimization

To investigate the contribution of formulation variables on the release profile of clarithromycin from alginate beads, the different batches were produced and analyzed for size, shape, ease of preparation, drug loading, entrapment efficiency, buoyancy and drug release. The formulation parameters investigated are concentration of sodium alginate, concentration of calcium chloride, amount of sunflower oil, % entrapment efficiency, % drug loading and buoyancy.

Three factors were evaluated at three levels and experimental trials were performed at all possible levels and 27 formulations were prepared as shown in Table 2. Actual physical values of coded variables are given in Table 2. [10]

Table 1.Different formulations prepared

Formulation Code	Amount of Clarithromycin (mg)	Amount of HPMC K100M (mg)	Amount of Sodium alginate	Amount of Calcium chloride	Amount of Sunflower oil (ml)
F1	250	500	1%	4%	2
F2	250	500	2%	4%	2
F3	250	500	3%	4%	2
F4	250	500	1%	5%	2
F5	250	500	2%	5%	2
F6	250	500	3%	5%	2
F7	250	500	1%	6%	2
F8	250	500	2%	6%	2
F9	250	500	3%	6%	2
F10	250	500	1%	4%	5
F11	250	500	2%	4%	5
F12	250	500	3%	4%	5
F13	250	500	1%	5%	5
F14	250	500	2%	5%	5
F15	250	500	3%	5%	5
F16	250	500	1%	6%	5
F17	250	500	2%	6%	5
F18	250	500	3%	6%	5
F19	250	500	1%	4%	10
F20	250	500	2%	4%	10
F21	250	500	3%	4%	10
F22	250	500	1%	5%	10
F23	250	500	2%	5%	10
F24	250	500	3%	5%	10
F25	250	500	1%	6%	10
F26	250	500	2%	6%	10
F27	250	500	3%	6%	10

Table 2: Actual physical values of the coded variables

Coded value	Concentration of sodium alginate (X1)	Concentration of calcium chloride (X2)	Amount of sunflower oil. (X3)
-1	1%	4%	2 ml
0	2%	5%	5 ml
1	3%	6%	10 ml

Evaluation of beads

Determination of drug loading and encapsulation efficiency

Drug loading was determined by dissolving 25 mg of floating alginate beads in 50 ml HCl buffer (pH 1.2.) The prepared solution was filtered through 45 µm filter paper and assayed spectrophotometrically at 760 nm. The drug loading was calculated according to formula;

% drug loading = (Amount of drug in beads/Amount of beads) × 100

Percentage encapsulation efficiency was calculated using following formula,

Percentage encapsulation efficiency= AQ / TQ × 1OO

Where AQ is the actual drug content of beads and TQ is the theoretical quantity of drug present in beads. [11]

Microscopical characteristics of beads
Floating alginate beads of clarithromycin were evaluated for particle size by taking 50 beads by using Motic microscope. The average particle size was calculated.

Determination of Moisture Content
The formulations were subjected to moisture content study by using an IR moisture balance by placing the beads at 60 °C for 10 min. [5]

Buoyancy study
The time between the introduction of the floating alginate beads into the medium and the time taken to rise on the surface was measured as floating lag time and the duration for which the formulation constantly floated on the surface of the medium was measured as total duration of floating. [12]

SEM of floating beads
Morphological characterization of the floating alginate beads of clarithromycin was done by taking scanning electron micrograph (Model Jeol JSM-5200). Cross-sectional views were obtained by cutting the bead with a razor blade. The samples were coated to 200 Aº thickness with gold- palladium prior to microscopy. A working distance of 20 nm, a tilt of 0º and accelerating voltage of 15 KV were the operating parameters. Photographs were taken within the range of 50- 500 magnifications.

***In-Vitro* drug release studies**
The in-vitro dissolution studies of floating alginate beads was carried out by using 900ml of 0.1N HC1(pH 1.2) maintained at 37± 0.5 ^{0}C at 100 rpm using USP XXIV dissolution test apparatus. The samples were removed periodically and assayed on UV spectrophotometer at 760 nm. [13]

RESULTS AND DISCUSSION

The floating beads of clarithromycin were prepared by emulsion-gelation method and influence of amount of sunflower oil on floating property and particle size of the beads, as well as concentration of hydroxypropylmethylcellulose (K100M) on the release profile of clarithromycin from floating alginate beads were studied.

Drug loading capacity of beads ranged from 28.11% to 39.99 % and encapsulation efficiency was in the range 75.97% to 91.44 %. There was no considerable effect of amount of sunflower oil on drug loading and encapsulation efficiency of clarithromycin. The percentage efficiency was high because bead formation was carried out in distilled water in which clarithromycin is insoluble and with a lesser possibility of leaching of clarithromycin during encapsulation. The formulations F4, F11, F14 and F23 showed total floating duration of more than 10 hr. Drug loading, encapsulation efficiency and total floating duration of the prepared floating beads of clarithromycin are shown in Table 3.

Table 3. Comparative study of pharmaceutical parameters of the floating beads

Formulations	%DEE	% DL	B (hr)	Formulations	%DEE	% DL	B (hr)
F1	81.68	31.19	9	F15	78.56	34.68	9
F2	83.11	36.74	10	F16	80.55	29.77	7
F3	80.08	32.24	8	F17	79.94	34.56	8
F4	79.91	31.91	9	F18	77.23	32.55	7
F5	88.69	37.64	11	F19	78.44	31.66	6
F6	81.36	30.46	8	F20	81.58	34.16	7
F7	78.64	31.00	10	F21	75.97	31.24	8
F8	80.19	35.94	9	F22	87.20	38.11	6
F9	81.98	30.42	9	F23	82.53	33.69	11
F10	78.24	29.54	7	F24	80.14	30.70	10
F11	82.59	36.19	11	F25	80.04	28.91	6
F12	79.21	28.11	7	F26	82.63	34.12	6
F13	80.00	35.63	9	F27	79.55	29.33	7
F14	91.44	39.99	12				

% DEE = % drug entrapment efficiency, % DL= % drug loading, B= buoyancy

Microscopical characteristics of beads

Microscopical characteristic of beads are shown in the Table 4. It was observed that the particle size of formed beads varies between the 0.6 mm to 1.6 mm. The obtained results indicated that as there is increase in the concentration of sunflower oil, the particle size of the beads increases.

Determination of moisture content

Low moisture content in all the floating alginate beads indicated the effectiveness of the adopted drying conditions. Low moisture level ensures better stability of the clarithromycin in the beads Table 4.

Table 4. Particle size and moisture content of the floating alginate beads

Formulations	Particle size(mm)	%Moisture content	Formulations	Particle size(mm)	%Moisture content
F1	0.655±0.02	0.96±0.48	F15	0.812±0.02	2.44±0.46
F2	0.621±0.01	0.98±0.45	F16	0.964±0.001	1.67±0.57
F3	0.72±0.01	0.99±0.44	F17	0.851±0.01	1.82±0.58
F4	0.625±0.02	1.28±0.47	F18	0.785±0.03	1.41±0.66
F5	0.710±0.03	1.48±0.56	F19	1.256±0.03	1.54±0.68
F6	0.749±.001	2.32±0.68	F20	2.004±0.01	2.33±0.74
F7	0.824±0.07	1.49±0.54	F21	1.096±0.05	1.76±0.72
F8	0.917±0.01	2.20±0.59	F22	0.989±0.04	2.60±0.59
F9	0.955±0.02	2.11±0.64	F23	1.573±0.02	2.30±0.60
F10	0.865±0.02	1.76±0.63	F24	1.660±0.002	2.48±0.49
F11	0.781±0.01	1.74±0.79	F25	1.01±0.05	1.87±0.73
F12	0.736±0.04	1.29±0.74	F26	1.04±0.02	2.40±0.47
F13	0.716±0.02	2.42±0.51	F27	1.11±0.04	1.63±0.64
F14	0.844±0.05	1.66±0.56			

SEM of floating beads

The surface and cross-sectional SEM pictures for different formulations of floating beads are shown in Fig. 1. The SEM picture shows the presence of oil droplets throughout the alginate matrix. The initial burst effect seen was due to some amount of the drug, which might have been dragged to the surface during the processing.

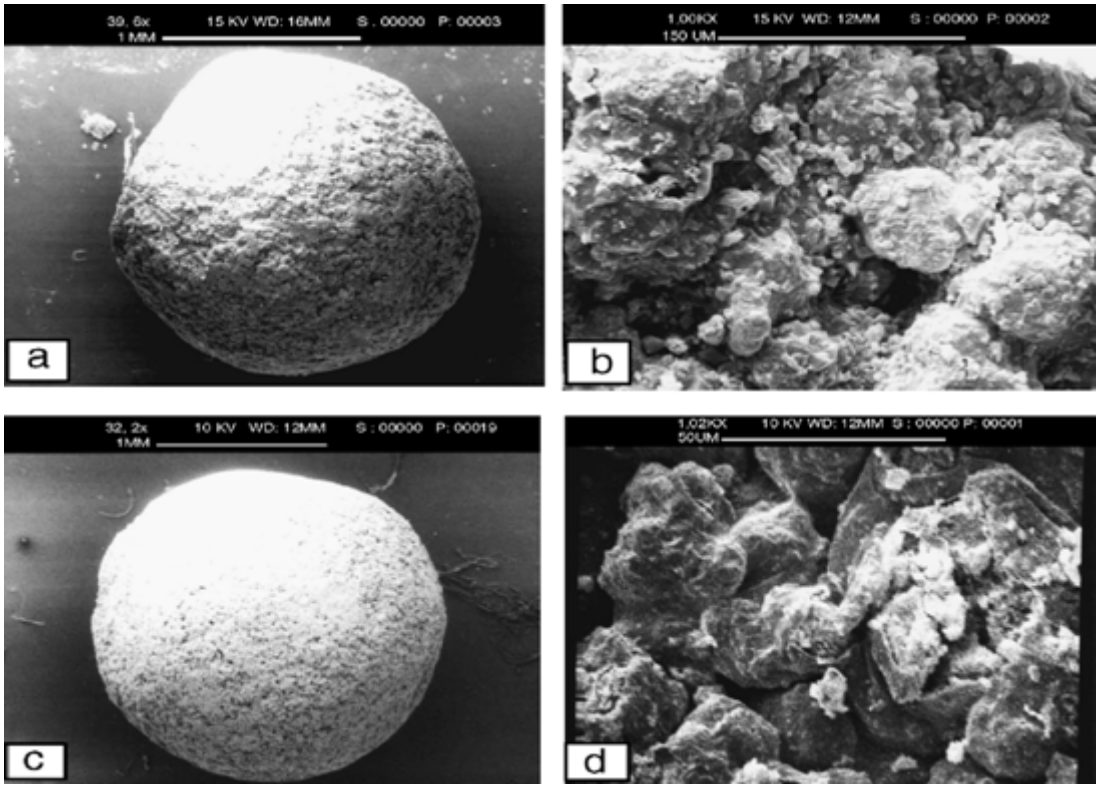

**Fig. 1. SEM graphs of alginate beads (a) and (b) Surface morphology.
(c) and (d) cross-sectional view of floating alginate beads of clarithromycin.**

Table 5. Percent cumulative release of Formulations

Formulations	% cumulative release			Formulations	% cumulative release		
	Q1	Q6	Q12		Q1	Q6	Q12
F_1	19.54	38.11	89.36	F15	21.28	41.90	85.75
F_2	19.11	45.35	92.71	F16	17.72	46.49	19.74
F_3	21.56	43.33	87.91	F17	20.25	41.59	82.77
F4	18.32	43.79	88.20	F18	19.26	40.31	81.88
F5	20.10	47.08	93.11	F19	16.34	38.22	78.49
F6	19.77	42.57	85.40	F20	17.63	36.16	77.34
F7	18.44	41.14	80.79	F21	19.33	41.72	82.59
F8	21.46	47.63	91.64	F22	18.99	37.91	78.34
F9	19.71	39.55	79.17	F23	20.70	45.20	92.74
F10	19.36	38.10	78.50	F24	19.34	39.11	79.90
F11	20.74	45.25	92.00	F25	20.20	37.17	75.33
F12	18.59	38.67	79.20	F26	21.79	46.71	90.26
F13	20.23	47.76	93.22	F27	19.76	42.23	85.82
F14	21.78	46.28	94.11				

***In-Vitro* drug release studies**

The *in vitro* dissolution studies of the prepared batches were performed to investigate the dependant variable i. e. percentage drug release at 1 hr (Q1), 6 hr (Q6), and 12 hr (Q12). From the results of in vitro dissolution studies, it revealed that the floating alginate beads (F5, F8, F13 and F14) showed controlled release of clarithromycin for about 12 hr. Amongst the formulations, formulation F14 shows maximum % cumulative release within 1 hr, 6 hr and 12 hr. also. This suggested that formulation F14 was having the good sustained release of the clarithromycin up to

the 12 hr. Hence it can be concluded that a new sustained release system of oil entrapped calcium alginate beads were designed and prepared by an emulsion-gelation method and it's morphological and release characteristics were studied. The prepared beads were easy to prepare and evaluate. The beads showed excellent sustaining properties as compared to the conventional beads which were due to incorporation of HPMC K100M. Thus, oil entrapment technique can become a useful tool for the development of multiparticulate system even for a water-insoluble drug.

CONCLUSION

The emulsion gelation method was successfully utilized for formulation of floating alginate beads of clarithromycin. The adopted method for estimation of clarithromycin showed good linearity. The formulated floating alginate beads have shown higher percentage of drug loading, encapsulation efficiency, particle size and very low moisture content. The scanning electron photomicrographs of floating alginate beads reveals that the beads are almost spherical and the matrix showed densely populated sunflower oil droplets, which provides floating property. The rheological parameters like angle of repose and bulk density reflects better flowability of floating alginate beads. In-vitro dissolution study showed that, amongst the formulations, formulation F14 released clarithromycin for prolonged duration (12 h). Formulated floating beads of clarithromycin showed good swelling behavior. The optimized formulation F14 showed best fit in zero order model.

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