Panacea Journal of Pharmacy and Pharmaceutical Sciences 2017:6(1);90-100

International Journal

PJPPS

Panacea Research Library

http://internationaljournal.org.in/journal/index.php/pjpps

Panacea Journal of Pharmacy and Pharmaceutical Sciences

ISSN: 2349 7025

Original Research Article **Volume 6 Issue 1**

PREPARATION AND EVALUATION OF MULTIPLE-UNIT FLOATING DRUG DELIVERY SYSTEM OF CLARITHROMYCIN

***Nimase P. K., More N. R.**

M. E. S's College of Pharmacy, A/P: Sonai, Tal: Newasa, Dist: Ahmednagar, Maharashtra

Article history:

Received: 9th May 2017

Received in revised form: 17th May 2017

Accepted: 17th May 2017

Available online: 31st May 2017

****Corresponding author:***

***Nimase P. K.**

E-mail: pradeepnimase@gmail.com

***Present address*:**

M. E. S's College of Pharmacy, A/P: Sonai, Tal: Newasa, Dist: Ahmednagar, Maharashtra.

Mob. No. 9527310032

These authors have no conflict of interest to declare.

Abstract:

Multiple-unit floating beads of clarithromycin were prepared from sodium alginate solution containing hydroxypropylmethylcellulose (K100M) and sunflower oil using the technique of three variables at three levels (3 power 3) factorial design and twenty-seven possible batches were prepared. These beads were evaluated for entrapment efficiency, drug loading, buoyancy and in vitro drug release. All formulations showed floating lag time below 2 minutes and showed total floating duration more than 10 hours. The result of in-vitro dissolution studies revealed that the formulation F14 was showing sustained release pattern of clarithromycin. The release rate, entrapment efficiency, drug loading and buoyancy was greater with formulation containing 2 percent sodium alginate solution and 5 percent calcium chloride solution along with 5 ml sunflower oil.

Keywords: Floating alginate beads; emulsion gelation; clarithromycin; controlled release.

INTRODUCTION

Gastro-retentive dosage forms are particularly appropriate for drugs, (1) that are locally active to the gastric mucosa in the stomach; with an absorption window in the stomach or in the upper small intestine; that are unstable in the intestine; with low solubility at high pH values.[3] One of the approach for gastro- retentive system is 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, antibiotics, peptides/proteins, and acid labile drugs[5].

Materials and methods:

Sodium alginate, hydroxyl propyl methylcellulose (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 hydroxyl propyl methylcellulose (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, a 3^3 full factorial design was utilized and the different batches were produced. The process parameters investigated are concentration of sodium alginate, concentration of calcium chloride, amount of sunflower oil, % entrapment efficiency, % drug loading and buoyancy[10]. Three factors were evaluated at three levels and experimental trials were performed at all possible

levels and 27 formulations were prepared[10]. (Table 1). Actual physical values of coded values are given in Table 2.

Table 1. Formulations using 3^3 full factorial design.

Formulation Code	Amount of Clarithromycin (mg)	Amount of HPMC K100M (mg)	Amount of Sodium alginate	Amount of Sodium 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 values.

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 lading 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].

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 talking 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[2].

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

The in-vitro dissolution studies of floating alginate beads was carried out by using 900ml of 0.1N HCl(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].

Kinetic modeling and mechanism of drug release:

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, and Peppas model using PSP-DISSO – v2 software. Based on the r-value, the best-fit model was selected[4].

Results:

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 %. The formulations F4, F11, F14 and F23 showed total floating duration 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

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.

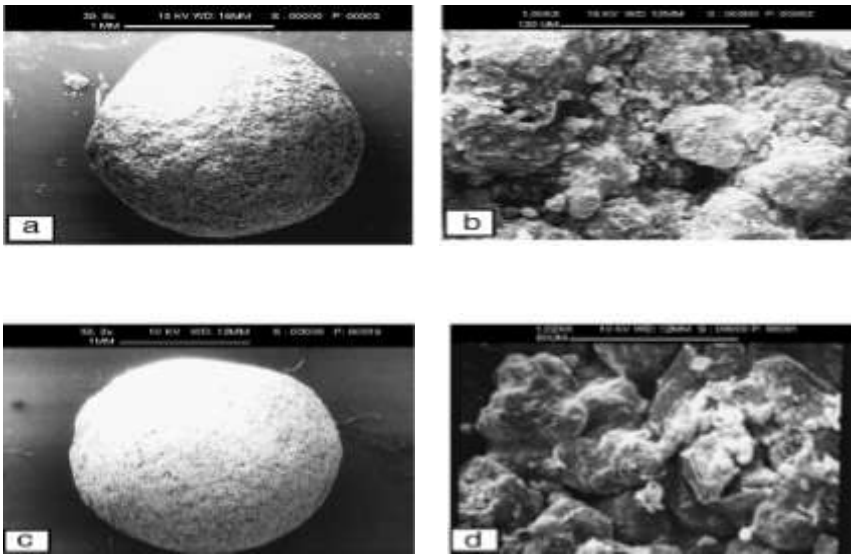


Fig. 1. SEM graphs of alginate beads (a) and (b) Surface morphology.

(c) and (d) cross-sectional view of floating alginate beads of clarithromycin.

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

From the results of in vitro dissolution studies (Table 4), it revealed that the floating alginate beads (F5, F8, F13 and F14) showed controlled release of clarithromycin for about 12 hr. Amongs the formulations, formulation F14 shows maximum % cumulative release within 1 hr, 6 hr and 12 hr. This suggested that formulation F14 was having the good sustained release of the clarithromycin up to the 12 hr. The beads showed excellent sustaining properties as compared to the conventional beads.

Table 4. 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				

Kinetic modeling and mechanism of drug release:

The results of in-vitro dissolution data analysis (Table 5) revealed that formulation F1 to F9 showed best fit in Korsmeyer-peppas model. The values of release exponent (n) were in between 0.5 and 1.0, suggesting non – Fickian diffusion. The best fit model for formulation F10 to F18 was found to be zero order, with correlation coefficient (R^2) ranging from 0.9919 to 0.9897. The formulations from F20 to F27 also showed best fit in Korsmeyer-peppas model, with correlation coefficient ranging from 0.9923 to 0.9958.

Table 5. Kinetic modeling of formulations F1-F27

Formulation	Zero order	First order	Higuchi	Korsmeyer Peppas	Diffusional exponent(n)
F1	0.9872	0.8946	0.9730	0.9946	0.7672
F 2	0.8668	0.8797	0.9799	0.9923	0.5237
F 3	0.8733	0.8629	0.9640	0.9994	0.6977
F 4	0.9658	0.8860	0.9672	0.9986	0.6900
F 5	0.9215	0.9164	0.9634	0.9903	0.6312
F 6	0.9174	0.9215	0.9749	0.9854	0.7411
F 7	0.9208	0.9130	0.9661	0.9829	0.6550
F 8	0.9670	0.8626	0.9704	0.9873	0.6608
F 9	0.9708	0.9641	0.9704	0.9894	0.6608
F10	0.9919	0.9812	0.9763	0.9750	0.5347
F11	0.9923	0.9822	0.9758	0.9323	0.6458
F12	0.9994	0.9768	0.9662	0.9794	0.6683
F13	0.9904	0.9833	0.9574	0.9992	0.7592
F14	0.9988	0.9716	0.9808	0.9803	0.7221
F15	0.9954	0.9630	0.9770	0.9754	0.5277
F16	0.9929	0.9799	0.9808	0.9829	0.5092
F17	0.9973	0.9840	0.9419	0.9873	0.6632
F18	0.9897	0.9616	0.9323	0.9873	0.6485
F19	0.9029	0.9734	0.9794	0.9750	0.6290
F20	0.8660	0.9409	0.9902	0.9923	0.7330
F21	0.8915	0.9391	0.9827	0.9834	0.7476
F22	0.8991	0.9524	0.9803	0.9949	0.6620
F23	0.8830	0.9404	0.9754	0.9891	0.6894
F24	0.8776	0.9523	0.9829	0.9933	0.5788
F25	0.9241	0.9818	0.9873	0.9904	0.5540
F26	0.9452	0.9732	0.9797	0.9833	0.7210
F27	0.8830	0.9894	0.9029	0.9958	0.7485

Discussion:

The results obtained revealed that 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 obtained results of microscopial examination indicated that as there is increase in the concentration of sunflower oil, the particle size of the beads increases. 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. The initial burst effect seen in SEM pictures was due to some amount of the drug, which might have been dragged to the surface during the processing. In- Vitro dissolution studied revealed that a new sustained release system of oil entrapped calcium alginate beads can be designed and prepared by an emulsion-gelation method. The sustaining properties of beads 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 highly water-soluble drug. In In-Vitro data analysis results formulations F10 to F18 showing zero order release kinetics suggesting that drug dissolution from the floating beads do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained.

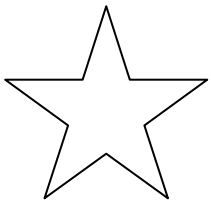
Conclusion:

The emulsion gelation method was successfully utilized for formulation of floating alginate beads of clarithromycin. 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. In-vitro dissolution study showed that, amongst the formulations, formulation F14 released clarithromycin for prolonged duration (12 h).The optimized formulation F14 showed best fit in zero order model. The floating alginate beads showed good stability at 4°C and at room temperature.

References:

1. S. Arora, J. Ali, A. Ahuja, R. K. Khar and S. Baboota. Floating Drug Delivery Systems: A Review AAPS Pharm. Sci. Tech. 2005; 6 (3): 47.
2. P. Sriamornsak , N. Thirawong and S. Puttipipatkhachorn. Morphology and buoyancy of oil-entrapped calcium pectinate gel beads. The AAPS Journal. 2004; 6: 24.
3. A. Streubel, J. Siepmann and R. Bodmeier. Floating microparticles based on low density foam powder. Int. J. Pharm. 2002; 241:279-292.
4. N. Rouge, P. Buri and E. Doelker. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int. J. Pharm. 1996; 136(1-2): 117-139.
5. Y. L. Patel, P. Sher and A. P. Pawar. The Effect of Drug Concentration and Curing Time on Processing and Properties of Calcium Alginate Beads Containing Metronidazole by Response Surface Methodology. AAPS Pharm. Sci. Tech. 2006; 86.
6. H. G. Brittain. In Analytical Profiles of Drug Substances and Excipients. . Vol. 24, Academic Press, California,
7. M. Nama, C. Gonugunta and P. Reddy Veerareddy. Formulation and Evaluation of Gastroretentive Dosage Forms of Clarithromycin. AAPS Pharm. Sci. Tech. 2008; 9(1): 231-237.
8. Y. D. Tang, S. S. Venkatraman, F. Y. C. Boey and L. W. Wang. Sustained release of hydrophobic and hydrophilic drugs from a floating dosage form. Int. J. Pharm. 2007; 336:159-165.
9. P. K. Choudhury and M. Kar. Preparation of alginate gel beads containing metformin hydrochloride using emulsion- gelation method. Tropical J. Pharm. Res. 2005; 4 (2): 489-493.
10. A. K. Seth and A. N. Mishra. Preparation and optimization of idoxuridine Liposomes. Ind. J. Pharm. Sci. 2005; 67(1): 89-95.

11. S. S. Badve, P. Sher, A. Korde and A. P. Pawar. Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery. Euro. J. Pharm. 2007; 65:85-93.
12. S. Sharma and A. Pawar. Low density multiparticulate system for pulsatile release of meloxicam Int. J. Pharm. 2006; 313:150-158.
13. S. Gupta and N. Aggarwal. Stomach-Specific Drug Delivery of 5-Fluorouracil Using Floating Alginate Beads. The AAPS Journal. 2007; 8 (2): 48.



How to cite this article:

Nimase PK, More NR. Preparation and evaluation of multiple-unit floating drug delivery system of clarithromycin. ***Panacea Journal of Pharmacy and Pharm. Sci. 2017:6(1);90-100***