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Original Article

Formulation, development and evaluation of oil entrapped calcium alginate floating beads of atenolol for antihypertensive drug

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ABSTRACT

Atenolol, a competitive beta (1)-selective adrenergic antagonist, has the lowest lipid solubility of this drug class. Although it is similar to metoprolol, atenolol differs from pindolol and propranolol in that it does not have intrinsic sympathomimetic properties or membrane-stabilizing activity. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract.The elimination half-life of atenolol is up to 6 to 7 hours. The oral doses of 50 mg or 100 mg both b-blocking and anti-hypertensive effects persist for at least 24 hours. In the present work an attempt has been made to prepare oil entrapped floating calcium alginate beads containing Atenolol to target the drug to stomach mucosa for prolonged period of time. Beads were prepared by using sodium alginate, mustard oil, olive oil and prepared by using emulsion gelation technique to improve gastric retention. The prepared beads were evaluated for physical characterization floating lag time, total floating time, swelling index and in vitro drug release studies. The prepared beads were found to be spherical, free flowing and remain buoyant for 24 hrs with a short floating lag time. It was found that the cumulative drug release from all formulations was found to be between 91.74 to 99.042.

Key Words: Beads, Atenolol, Sodium alginate, Mustard oil, Olive oil.

INTRODUCTION

Oral delivery systems that can precisely control the release rate of target drug in a specific site of gastro -intestine (GI) have an enormous impact on the health care system. Gastroretentive drug delivery system is an approach to prolong gastric residence time and appropriate for drugs which should be locally active in the gastric mucosa in the stomach. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach [1], low density (floating) systems that causes buoyancy in gastric fluid [2]. Muco-adhesive systems that causes bioadhesion to stomach mucosa , unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, superporous hydrogel systems , magnetic systems etc [3]. Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force forover 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours [4]. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa [5]. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. A number of techniques have been used to produce sustained release or controlled drug delivery system. They include the use of barrier embedding in slowly creditable barrier coating, embedding in slowly erodible beads, matrix, skeleton type matrix polymer resin beads, passage sponge formation and chemical complexation. Atenolol (2nd generation - β blocker) is a β_1 selective antagonist (cardio

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selective). The elimination half-life of atenolol is 6 to 7 hours and there is no alteration of kinetic profile of drug by chronic administration. Following intravenous administration peak plasma levels are reached within 5 minutes. Atenolol loaded calcium alginate beads were prepared by Emulsion gelation method [6]. The method involves aqueous and organic solvent free environment. Positively charged calcium ion and the negatively charged polymer as pectin; casin and sodium alginate etc. can cause instaneous gelation of polymer [7] .

EXPERIMENTAL

Materials: Atenolol was obtained as Gift sample from Caraco pharmaceutical laboratories ltd. Sodium alginates was obtained from Loba Chemie laboratory. Calcium chloride was obtained from Qualigens Fine Chemicals. Olive and mustered oil was obtained from Qualigens fine chemicals.

Table-1 Composition Of Floating Beads Of Atenolol

Sl. No.	Ingredients	Mass (mg)
1	Atenolol	50
2	Sodium alginate	200-300
3	Oil	10-14%
4	Water	10 ml

Method:

Emulsion gelation method was selected for the preparation oil entrapped beads. Emulsion gelation method is simpler than the ones used so far for preparation of other floating dosage form. Atenolol loaded calcium alginate beads were prepared by the emulsion–gelation method [8]. In this method, the sodium alginate solution was prepared in water in different ratio. Oil in concentrations (10%, 12% and 14% w/w), was then added to the polymer solution to make mixtures. To ensure emulsion stabilization, the mixtures were homogenized at 10,000 rpm using a homogenizer for 10 min. Atenolol was then dispersed in the formed emulsion. The bubble-free emulsion was extruded; using a 23G syringe needle into 250 ml gently agitated (5%) calcium chloride solution at room temperature. The emulsion gel beads were allowed to stand in the solution for 20 min before being separated and washed with distilled water. The beads were air-dried at room temperature.

Table-2 Formula Of Floating Beads Of Atenolol (F1-F9)

Formulation	Atenolol (mg)	Sodium Alginate(mg)	Olive Oil(ml)	Mustard Oil(ml)	Water(ml)
F1	50	200	10	10	10
F2	50	250	10	10	10
F3	50	300	10	10	10
F4	50	200	12	12	10
F5	50	250	12	12	10
F6	50	300	12	12	10
F7	50	200	14	14	10
F8	50	250	14	14	10
F9	50	300	14	14	10

EVALUATION

Study of Homogeneity and Uniformity of Beads:

To prepare uniform beads (i.e. of the same size and density) it is essential that synthesis conditions such as viscosity, rate of falling of drops, stirring rate and distance between syringe and gelation medium, be maintained constant during the course of the formation of beads. Variation in any of these parameters during the bead formation process may result in the production of non-homogenous and non-uniform beads, affecting the overall results to an appreciable extent [9]. Also, process homogeneity was greatly influenced by emulsion homogenization which yields fine dispersion of oil and water with size uniformity. Without homogenization, the oil might separate out from the solution and uneven sized beads were formed [10].

Scanning electron microscopy:

The size of Beads was determined using microscope (Olympus NWF 10x, Educational Scientific Stores, India) fitted with an ocular micrometer and stage micrometer. Scanning electron microscopy (SEM) (Leo 430, Leo Electron Microscopy Ltd, Cambridge, England) was performed to characterize the surface of the formed Beads [9-11].

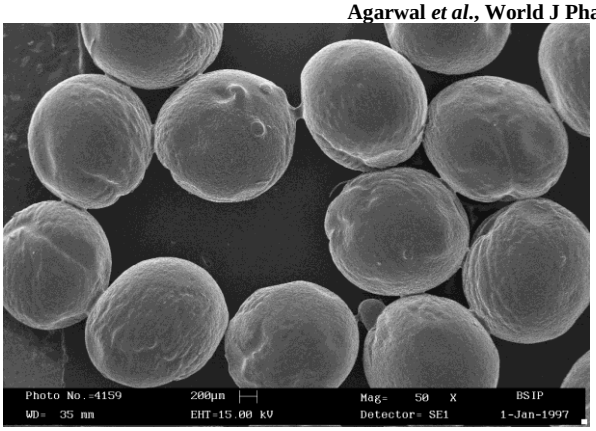

Fig No.1 Olive Oil

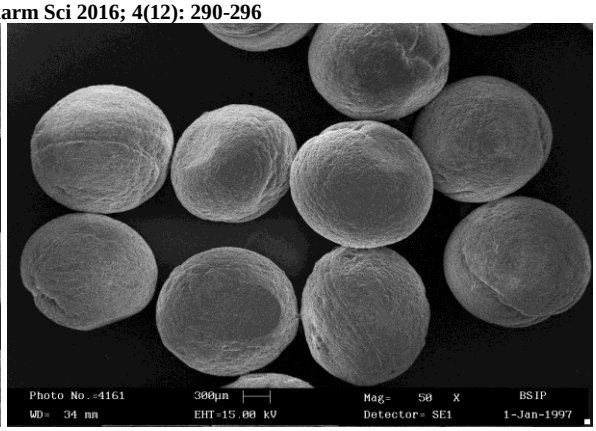

Fig No.2 Mustard Oil

Flow properties: The flow properties of Beads were characterized in terms of angle of repose, carr index and hausner ratio For determination of angle of repose (θ), the Beads were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The Beads were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The tan-1 of the height of the pile / radius of its base gave the angle of repose. Beads were poured gently through a glass funnel into a graduated cylinder cut exactly to 10ml mark. Excess Beads were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Hausner ratio (HR) and carr index (IC) were calculated according to the two equations given below; [12]

$HR = \rho t/\rho b$; $IC = (\rho t\% \rho b)/\rho t$

Floating lag time and total floating time determination: The time between the introduction of the beads into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in 0.1N HCl maintained at 37ºC in using USP dissolution apparatus [13].

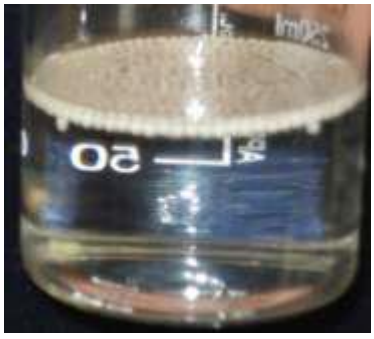

Fig. 3: In vitro (%) percent buoyancy:

Beads (90mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N hydrochloric acid. The medium was agitated with a paddle rotating at 100 rpm for 11 hrs. The floating and the settled portions of Beads were recovered separately. The Beads were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the Beads that remained floating and the total mass of the Beads Development and evaluation of floating Beads of atenolol [14].

Drug content: Practical drug content was analyzed by using the following procedure, The beads equivalent to 50 mg of Atenolol were taken and dissolved in 100 ml of 0.1 N HCL. This solution was kept overnight for the complete dissolution of the drug from floating beads in 0.1N HCl. This solution was filtered and further diluted to make a conc. of 10 µg/ml. The absorbance of the solutions was measured at 254 nm using double beam UV-Visible spectrophotometer against 0.1N HCl solution as blank and calculated for the percentage of drug present in the sample [14].

Swelling studies: Weight gain or water uptake can be studied by considering the swelling behaviour of Floating dosage form. The study is done by immersing the dosage form in 0.1N HCl at 37ºC. The beads were periodically removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen beads were then reweighed and swelling index is measured in the terms of percent weight gain, as given by equation SU = (Wt – Wo) X 100 / Wo In which Wt and Wo are the weights of the dosage form at time t and initially, respectively [15].

In vitro drug release studies: The drug release was studied using a USP dissolution apparatus type I at 50 rpm in 0.1N hydrochloric acid as dissolution medium (900 ml) maintained at 37±0.5°C. A sample (10 ml) of the solution was with-drawn from the dissolution apparatus hourly and the

samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 µ membrane filter and diluted to a suitable concentration with 0.1 N hydrochloric acid. Absorbance of these solutions was measured at 237 nm using UV-Visible spectrophotometer and Cumulative percentage drug release was calculated [8].

MATHEMATICAL MODELS

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$C = k_o t$ ------ (1)

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$LogC = LogCo - kt / 2.303$-------- (2)

Where, C0 is the initial concentration of drug and K is first order constant.

$Q = Kt^{1/2}$---------- (3)

Where, K is the constant reflecting the design variables of the system.

$Q0^{1/3} - Qt^{1/3} = K_{HC}\, t$------- (4)

Where, Qt is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation. The following plots were made:

Zero order release kinetics: Cumulative% drug release vs. time.

First order release kinetics: Log cumulative of % drug remaining vs. time.

Higuchi Model: Cumulative % drug release vs. square root of time.

Korsmeyer-Peppas Model: Log cumulative % drug release vs. log time.

Hixson-Crowell cube-root Model: Cube root of drug % remaining in matrix vs. Time [16, 17]

Fig.4. Drug Release Profile Of Floating Beads Of Atenolol

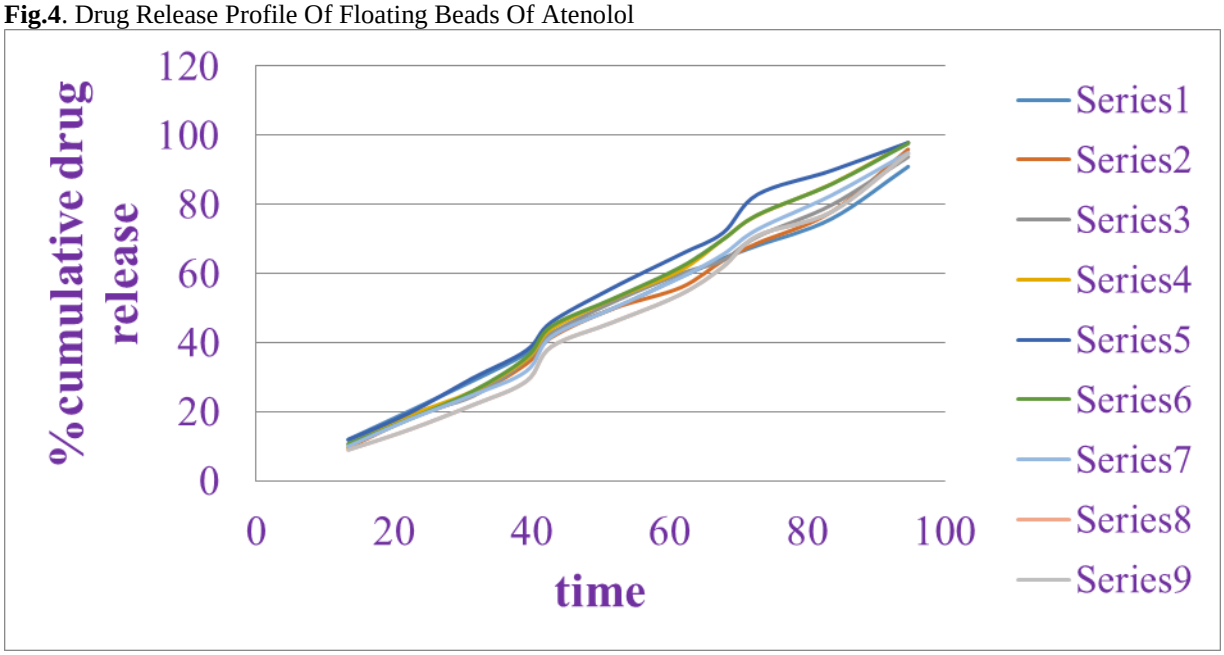

Table 3: Kinetic Data Of Various Models For Release Study

Formulation no.	Zero order	First order	Higuchi Model	Peppas Model		Hixson Model
				R	N	
F1	0.998	0.822	0.950	0.992	1.103	0.912
F2	0.987	0.840	0.945	0.996	1.065	0.925
F3	0.998	0.714	0.953	0.996	0.965	0.853
F4	0.996	0.811	0.943	0.994	1.002	0.912
F5	0.996	0.756	0.952	0.997	0.982	0.905
F6	0.998	0.810	0.941	0.992	1.044	0.922
F7	0.999	0.768	0.952	0.996	0.993	0.909
F8	0.994	0.801	0.963	0.998	0.971	0.915
F9	0.998	0.784	0.960	0.995	0.906	0.887

Physical Evaluation:

Table No 4. Result of Size of Beads, Oil Leakage, Shape and Weight Of 100 Beads For Olive Oil

Formulation code	Sod. Alginate	Olive oil	Size of the beads	Oil leakage	Shape	Wt of 100 beads
F1	-1	-1	94	YES	Spherical	150
F2	-1	0	99	No	Spherical	155
F3	-1	+1	95	No	Spherical	148
F4	0	-1	98	No	Spherical	159
F5	0	0	100	No	Spherical	160
F6	0	+1	100	YES	Spherical	170
F7	+1	-1	99	NO	Spherical	180
F8	+1	0	97	No	Spherical	200
F9	+1	+1	100	No	Spherical	212

Table No. 5. Result of Size of Beads, Oil Leakage, Shape and Weight Of 100 Beads For Mustard Oil

Formulation code	Sod. Alginate	Mustard Oil	Size of the beads	Oil leakage	shape	Wt of 100 beads
F1	-1	-1	80	No	spherical	150
F2	-1	0	82	Yes	spherical	160
F3	-1	+1	100	No	spherical	143
F4	0	-1	98	No	spherical	154
F5	0	0	83	No	spherical	166
F6	0	+1	96	No	spherical	172
F7	+1	-1	97	No	spherical	180
F8	+1	0	97	No	spherical	200
F9	+1	+1	99	NO	spherical	212

Table No. 6. Result of Floating Time, Floating Lag Time, Drug Content and Drug Release For Olive Oil

Formulation code	Sod. Alginate	Olive oil	Floating Lag Time (Sec)	Floating Time (Hrs)	(%) Drug Content	(%) Drug Release in 12 hrs
F1	-1	-1	28	24	42.92	97.708
F2	-1	0	22	24	61.50	94.920
F3	-1	+1	10	24	68.14	99.042
F4	0	-1	88	24	57.59	98.440
F5	0	0	53	24	50.95	98.861
F6	0	+1	32	24	51.73	97.828
F7	+1	-1	116	nf	44.09	95.939
F8	+1	0	35	24	53.25	98.767
F9	+1	+1	17	24	96.89	99.744

Table No.7.Result Of Floating Time, Floating Lag Time, Drug Content And Drug Release For Mustard Oil

Formulation code	Sod. Alginate	Mustard oil	Floatng Lag Time	Floating Time	(%) Drug Content	(%) Drug Release 12 hrs
F1	-1	-1	55	24	38.62	97.388
F2	-1	0	40	24	30.44	90.263
F3	-1	+1	32	24	36.42	91.300
F4	0	-1	40	24	41.09	99.809
F5	0	0	37	24	44.91	98.781
F6	0	+1	20	24	50.25	98.855
F7	+1	-1	40	24	42.65	99.828
F8	+1	0	33	24	56.08	98.140
F9	+1	+1	22	24	44.23	92.664

Table No. 8. Result Of Beads Density, (%) Buoyancy, Swelling Studies And Flow Property For Olive Oil

Formulation code	Sod. Alginate	Olive oil	Beads Density:	percent buoyancy:	Swelling studies:	Flow property
F1	-1	-1	0.42	100	12.50	+
F2	-1	0	0.54	92	11.10	+ +
F3	-1	+1	0.57	100	10.00	+ +
F4	0	-1	0.42	90	22.21	+ + + +
F5	0	0	0.50	100	20.00	+ + + +
F6	0	+1	0.54	99	11.1	+ +
F7	+1	-1	0.50	Nf	11.00	+ + + +
F8	+1	0	0.55	98	11.05	+ + + +
F9	+1	+1	0.57	100	9.09	+ + + +

Table No. 9. Result Of Beads Density, (%) Buoyancy, Swelling Studies And Flow Property For Mustard Oil

Formulation code	Sod. alginate	Mustard oil	Beads Density:	percent buoyancy:	Swelling studies:	Flow property
F1	-1	-1	0.52	90	18.75	+ + + +
F2	-1	0	0.70	98	13.33	+ +
F3	-1	+1	0.71	100	10.26	+ + +
F4	0	-1	0.55	100	11.11	+ + + +
F5	0	0	0.62	99	09.52	+ + + +
F6	0	+1	0.77	100	05.00	+ + + +
F7	+1	-1	0.55	100	15.00	+ + + +
F8	+1	0	0.56	100	10.26	+ + + +
F9	+1	+1	0.52	100	09.52	+ + +

RESULT AND DISCUSSION

Percentage Drug Content: Percentage drug content in the formulation F9 For olive oil and H8 for mustard oil was found to be in the range of 96.89 to 56.08% . It showed uniform dispersion of drug in polymer system.

Percentage Buoyancy: Buoyancy percentage was calculated as the ratio of the mass of the Beads that remained floating and the total mass of the Beads Development and evaluation of floating Beads of atenolol. In vitro buoyancy was more than 70% after 24 hrs indicate satisfactory performance of proposed formulation. The percent buoyancy of formulation decreased as polymer concentration increased.

Particle size: The particle size of Atenolo beads as measured as 80 to 100 (µm). The particle size of the beads was affected by factor such as preparation technique, polymer concentration, needle size and stirring time. The mean particle size of Atenolol beads was in range value (table) depending upon the types of polymer used. The particle size increased as the amount of polymer was increased in each preparation.

Flow properties: The flow properties of all formulation were within the acceptable range and therefore they could be easily filled into capsule

Swelling studies: The amount of polymer directly affected the solvent transfer rate thus, as the

polymer concentration increased the swelling index also increased. In vitro swelling studies were carried in 0.1NHCL at 37^0C and degree of swelling index for each was determined gravimetrically. Swelling index for all formulation increased as the concentration of polymer increased.

In vitro drug release studies: In vitro drug release from the floating beads of Atenolol (for mustard oil and olive oil) was found to be from 91.30 to 100.04%. Among all formulation, f3 was found to be the best formulation for olive oil as its release 99.04%, f7 was found to be the best formulation for mustard oil as its release 99.82% in a sustained manner with constant fashion over extended period of time .The release study was further investigated for the kinetic studies. Various kinetic models were applied. In vitro drug release data fitted into various kinetic models suggest that the all formulations obey zero order models from the $^*n^*$ values obtained (Table-2).

CONCLUSION

Oil entrapped floating calcium alginate beads of atenolol were successfully prepared using sodium alginate as polymer and oil by emulsion gelation method. The floating time of beads was found to be more than 24 hrs suggesting that the method used for prepration was effective. The floating time was significantly increased as the amount of oil was increased in each formulation. The floating lag time of beads was found to be less than 60 second suggesting that the method used for preparation was effective. The floating lag time was significantly decreased as the amount of oil was increased in each formulation. Percent buoyancy of formulation decreased as polymer concentration increased. In vitro buoyancy was more than 70% after 24 hrs indicate satisfactory performance of propose formulation. The mean particle size of beads was in range depending upon the type of polymer used. The particle size increased significantly as the amount of polymer was increased in each preparation.The best formulation of oil entrapped floating calcium alginate beads of atenolol for olive oil was found to be F-3 99.04% and for mustard oil was found to be F-7 99.82 %, drug release in 12 hrs. Hence finally it was concluded that the prepared oil entrapped floating calcium alginate beads of atenolol may prove to be potential candidate for safe and effective sustained drug delivery over an extended period of time which can reduce dosing frequency.

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