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Research Article

FORMULATION AND CHARACTERIZATION OF FLOATING SODIUM ALGINATE BEADS OF AMOXICILLIN FOR PROLONGED GASTRIC RETENTION

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ABSTRACT

Sodium alginate (SA) floating beads containing amoxicillin were prepared by dripping method using calcium carbonate as gas generating agent. Hydroxyl propyl methyl cellulose (HPMC) was used in all the four formulations (A1, A2, A3 and A4) as swelling agent to control the release of the drug. Gas generating agent forms pores on the surface of the bead because of the rapid escape of CO2 during the curing process in precipitating media. Scanning electron microscopy (SEM) confirmed their porous and grossly spherical structure and size of the beads in the range of 800-1000µm. The drug entrapment efficiency was found to be 72.97-91.60%. A1 showed maximum drug entrapment efficiency and A4 showed least entrapment efficiency. The percentage porosity of beads was 78.99-96.03%. The porosity depends on the concentration of gas forming agent. The mechanical strength of the beads was 391-729 gm. All the formulations showed good floating time. The in- vitro release study was performed according to USP for 12 h. The cumulative percentage drug release was found to be 70.81 – 88.48%. The *In-vitro* dissolution study reveals that the concentration of gas generating agent affects the release rate.

KEYWORDS: Floating Alginate Beads, Sodium Alginate, HPMC, scanning electron microscopy

INTRODUCTION

Over the years there has been available a variety of drug modification and dosage forms, with which we have attempted to control the time course and specificity of drugs in the body. To maximize the utilization, it is necessary to deliver the drug to its target tissue in the correct amount at the proper time to elicit the desired response. Moreover, drug delivery must be continued at a rate such that the condition in question is cured or controlled in a minimum time with the fewest side effects[1].

Oral control release drug delivery formulations using biocompatible polymers have limited utilization if the system cannot remain in the vicinity of the absorption site for a longer time. Thus, site and time specific drug delivery have recently been of great interest in the pharmaceutical field to achieve overall therapeutic efficacy. A problem encountered with the conventional oral controlled release dosage forms is the inability to increase their residence time in the stomach and the proximal portion of the small intestine. The most convenient route for the drug delivery has historically has been by oral ingestion. However, oral controlled drug delivery system is complicated by gastric residence time which leads to incomplete drug release in the absorption zone and reduce the efficacy of the administered dose[2, 3].

To overcome these problems, several methods have been developed recently to extend gastrointestinal transit time of the dosage forms. One such method is floating drug delivery systems. Such systems have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. Although, the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the

residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in the plasma drug concentrations[4, 5].

In this investigation, it is intended to formulate and evaluate the floating sodium alginate beads for increasing the bioavailability of amoxicillin. They are also used as hydrophilic polymers in the development of controlled release formulation for the delivery of drugs.

Amoxicillin was chosen as the suitable drug candidate as it is stable in gastric acidic medium and has a low absorption window in gastrointestinal tract, it is also highly soluble at acidic pH and has no effect on food absorption. It has higher eradication rate in-vivo to H. pylori. Hence, increase in the gastric retention time of the drug in the stomach may improve its bioavailability and therapeutic efficacy[6].

MATERIALS AND METHODS

Amoxicillin was procured from Cipla Ltd Goa, Hydroxy propyl methyl cellulose K4M was procured from Colorcon Asia. Sodium alginate was procured from Snap Naturals and alginates Ltd Mumbai, India. All other chemicals were of analytical grade.

Preparation of Floating Sodium Alginate Beads

Floating SA beads of amoxicillin were prepared as shown in Table 1, using different proportions of SA, HPMC and $CaCo_3$. The weighed quantity of SA and HPMC were mixed with water to form a gel, and then drug was incorporated by triturating. The gas forming agent was added to the gel form. The resulting gel was dropped through a 26G syringe needle into 50ml of $CaCl_2$ solution (1%w/v) containing 10%v/v acetic acid. The solution containing beads were stirred using magnetic stirrer for about 10min. The beads were allowed to remain in the same solution for 2h to improve their mechanical strength. The thus formed beads were separated, washed initially with alcohol and subsequently with distilled water and then air dried[7].

Characterization of Beads

Size analysis and morphology of the beads

The size of sodium alginate beads was measured by taking 5-10 beads on glass slide under polarized light. The mean diameter was calculated by measuring the number of divisions covered by beads. The stage micrometer was previously calibrated using ocular micrometer. The surface morphological study was carried out using SEM[8, 9].

Drug entrapment efficiency of SA beads

Beads 10mg were dissolved in 100ml acidic buffer pH 1.2 and sonicated. The solution was filtered after sufficient dilution with acidic buffer (pH 1.2)[10, 11]. The solution was analysed spectrophotometrically at 272 nm and drug entrapment efficiency was calculated using the following equation,

EE = (actual drug content in the beads/ theoretical drug content) X 100

Bead porosity and mean pore diameter

The bead porosity was measured using porosimeter. The pressure was applied from 0 – 6000psi. The mercury intrusion data were recorded. Standard values for the contact angle and surface tension of mercury were used for calculations[7, 12].

Mechanical strength of beads

Ten beads of identical size were selected from each batch, and the crushing strength of each bead was determined using mercury load cell method[7].

In-vitro floating behaviour

The time taken for dosage form to emerge on the surface of the medium is called the buoyancy lag time, and the duration of time by which the dosage form constantly emerges on the surface of the medium is called total floating time. Weighed amount of beads from each batch was placed in USP XXIII type II dissolution apparatus containing 900ml of acidic buffer pH 1.2, using paddle at a rotational speed of 75rpm. The temperature of medium was maintained at $37^0C \pm 2^0C$. Initially all the beads start floating with zero floating lag time. Then, total floating time was determined [11, 13].

***In-vitro* drug release study**

Dissolution of the SA beads of each batch was carried out using USP type II apparatus using paddle. 900 ml of acidic buffer pH 1.2 was filled in a dissolution vessel and the temperature of the medium was set at $37^0C \pm 2^0C$**.** SA beads equivalent to 50mg drug were placed in each dissolution vessel and the rotational speed of paddle was set at 75rpm. Then, 5ml of sample was withdrawn at predetermined time interval for 12h and the same volume of fresh medium was replaced. The samples were analysed for drug content against acidic buffer pH 1.2 as blank at 272 nm using double beam UV spectrophotometer. The content of drug was calculated using the equation generated from standard curve. The cumulative percentage drug release was calculated[13, 14].

The matrix systems were reported to follow the zero order and diffusion mechanism for the release of drug. To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained were fitted into zero order, first order, Higuchi matrix, Peppas and Hixson Crowell model[15].

Stability study

The accelerated stability studies were conducted for selected formulations as per the ICH guidelines. The selected formulations were analysed for physical appearance, entrapment efficiency, in vitro floating ability and in vitro release study[16, 17].

RESULTS

Preparation of Floating Sodium Alginate Beads

Floating SA beads were successfully prepared for the delivery of amoxicillin to enhance absorption and bioavailability by increasing the gastric retention time. In concern to this approach, the primary necessity is to float the beads in gastric environment. In this study four formulations were prepared. In each formulation gas forming agent concentration was varied. The detailed composition of each formulation is given in Table 1.

Characterization of Sa Beads

Size Analysis and Morphology of Beads

Scanning electron microscopy of the formulation is shown in Fig I. The beads of the drug of all batches are almost grossly spherical. The SEM images illustrate the spherical shape with thin and incomplete calcium surface coating. Beads with higher gas forming agent concentration for A3 and A4 were more porous, rough and grossly spherical.

The size of SA beads is shown in Table I. The size of the beads was found to be in the range of 842.86, 938.17, 966.33 and 988.67μm for formulations A1, A2, A3 and A4. The bead size was found to increase with increase in the concentration of the gas forming agent which may be due to pore formation.

Drug Entrapment Efficiency of SA beads

The results of % drug entrapment efficiency are shown in the Table II. The high entrapment efficiencies are seen with lower concentration of gas forming agent as in A1 and A2 than A3 and A4. This may be due to increased porosity and pore diameter which is unable to retain the drug more effectively as seen with the formulations A3 and A4.

Mechanical strength of beads

Mechanical strength testing was performed to study the effect of gas forming agent. The high proportion of gas forming agent made the beads highly fragile and porous as seen in A3 and A4 and hence showed lower crushing strength than A1and A2. Higher mechanical strength of beads is important for avoiding breaking and distortion of beads during normal handling. The results of mechanical strength are given in Table II.

Percentage porosity and mean pore diameter of beads

Porosity and mean pore diameter was studied to determine the effects of gas forming agent on pore structure of the beads. The percentage porosity for the formulations A1, A2, A3 and A4 was 78.99%, 88.10%, 90.12% and 96.12% respectively. By increasing the ratio of gas forming agent as in A3 and A4, percentage porosity and mean pore diameter were increased. The results are shown in Table II.

***In-vitro* buoyancy behaviour**

The floating ability of the prepared beads was evaluated in acidic buffer pH 1.2. The wet beads had better floating ability than dry beads. The floating ability of sodium alginate beads is directly related to the gas content of the polymer matrix, which depends on the concentration of the gas forming agent. As the concentration of gas forming agent increases, the number of air trapped pores in the beads increases, which makes the beads to float. Wet beads contain greater proportion of CO2 gas than the dry ones and are thus more buoyant. Results of in vitro buoyancy studies are given in Table III.

***In-vitro* drug release studies**

Dissolution studies of all the four formulations of SA beads of amoxicillin were carried out using USP XXIII type II paddle dissolution apparatus for 12h. The cumulative percentage drug release for 12 hrs was found to be 70.81, 76.47, 82.83 and 88.48% for the formulation A1 to A4 respectively. The cumulative percentage drug release vs. time graph for all the formulation is shown in the Fig II. A1 is the best formulation selected among all on the basis of drug entrapment efficiency, drug release study, floating behaviour and mechanical strength.

The curve fitting results of the release rate profile of the designed formulations gave an idea on the release rate profile and the mechanism of the drug release. Fitting of the release rate data to the various models revealed that formulations A1 and A2 follows Peppa's model and A3 and A4 follow Higuchi matrix.

Stability studies

A stability study was conducted for the formulation A1 at $25^{oC}\pm2^{oC}$ with relative humidity 60% for a period of 30days. Stability testing results showed that there was no change in the physical appearance, entrapment efficiency, drug release pattern and floating behaviour of the SA beads at the end of 30days.

DISCUSSION

There were two principle objectives to this study. Firstly, use of $CaCO_3$ for the production of floating alginate beads by simple dripping method. The data presented here has established that the gas forming agent is highly effective for floating bead formation. The second objective was to assess the effects of gas forming agent on bead characteristics. The study has clearly shown that the amount of gas forming agent has a profound effect on bead size, morphology, floating ability, drug entrapment efficiency, pore diameter and % porosity, mechanical strength and release pattern.

SA beads were prepared by dripping method using 26G needle. HPMC K4 M was used as a swellable polymer for sustained release of the drug form the beads. The beads were formed due to the cross linking of sodium alginate with divalent calcium ions of the $CaCl_2$ solution. This mechanism is called ionotropic gelation.

The surface topography reveals that the beads were highly porous because of the rapid escape of the carbon dioxide during curing process. The number of observed pores appears to be directly related to the amount of gas forming agent.

The high entrapment efficiencies are seen with lower concentration of gas forming agent. This may be due to increased porosity and pore diameter which is unable to retain the drug more effectively. The high concentration of gas forming agent made the beads highly fragile and porous and showed lower mechanical strength.

The floating results were not affected by stirring speed of the paddle. The floating abilities persisted until disintegration of the beads began. Buoyancy of the beads is directly related to concentration of the gas forming agent. Instantaneous in vitro floating behaviour was observed for all batches which may be due to low apparent density provided by the porous nature of beads.

The maximum release of the drug may be due to higher concentration of the gas forming agent which increases the pore formation from which drug releases easily from the alginate matrix. A1 is the best formulation selected among all on the basis of drug entrapment efficiency, drug release study, floating behaviour and mechanical strength.

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Table I: Formulation Of Alginate Beads Of Amoxicillin And Their Sizes

Formulation Code	SA (%w/v)	HPMC (%w/v)	$CaCO_3$ (%w/v)	Amoxicillin (%w/v)	Bead size average (wet) µm ± S.D.	Bead size average (dry) µm ± S.D.
A1	3	0.3	1.5	1.5	234 ± .007	842.86 ± 005
A2	3	0.3	2.0	1.5	293 ± .005	938.17 ± 008
A3	3	0.3	3.0	1.5	367± .008	966.33 ±001
A4	3	0.3	3.0	1.5	388± .003	988.67 ± 004

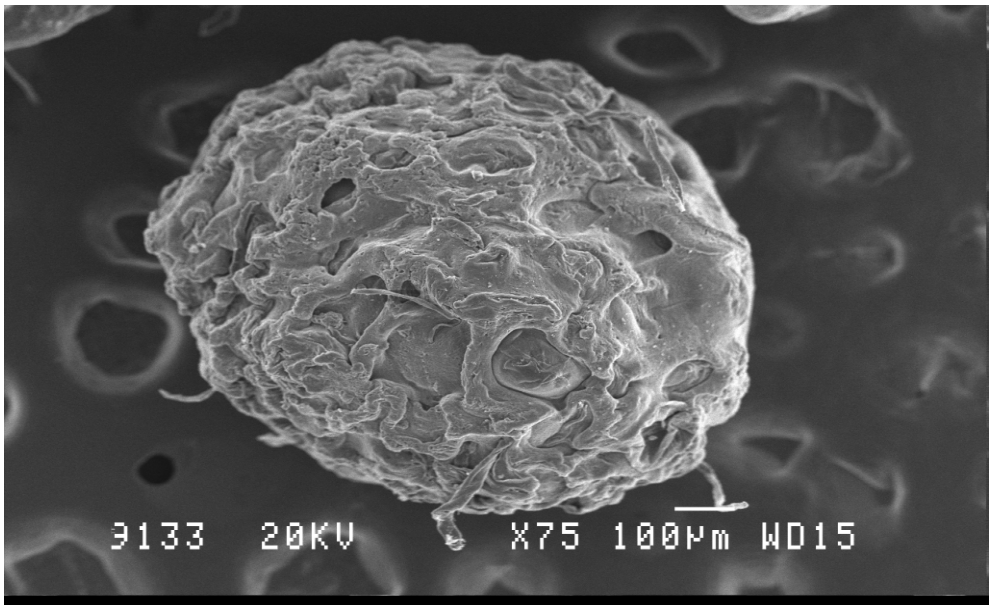
Table II: Effect Of Gas Forming Agent On Drug Entrapment Efficiency And Various Physical Properties Of Beads

Formulation	Drug entrapment efficiency (%)	Average mean Pore diameter µm ± S.D.	Porosity average (%) ± S.D.	Mechanical strength of beads (g)
A1	91.60	0.31± 0.003	78.99 ± 0.32	729 ± 0.83
A2	88.12	0.49 ± 0.14	88.10 ± 0.99	497 ± 0.38
A3	83.30	0.69 ± 0.38	90.12 ± 1.79	465 ± 0.1
A4	72.97	0.82 ± 0.33	96.03 ± 0.95	391 ± 0.03

Table III: Results Of Floating Property Of Formulations A1-A4

Formulation code	Floatation property	Duration of floatation (h)
A1	- +	More than 12 h
A2	- +	More than 12 h
A3	+ +	More than 12 h
A4	+ +	More than 12 h

- + partially floating, + + completely floating



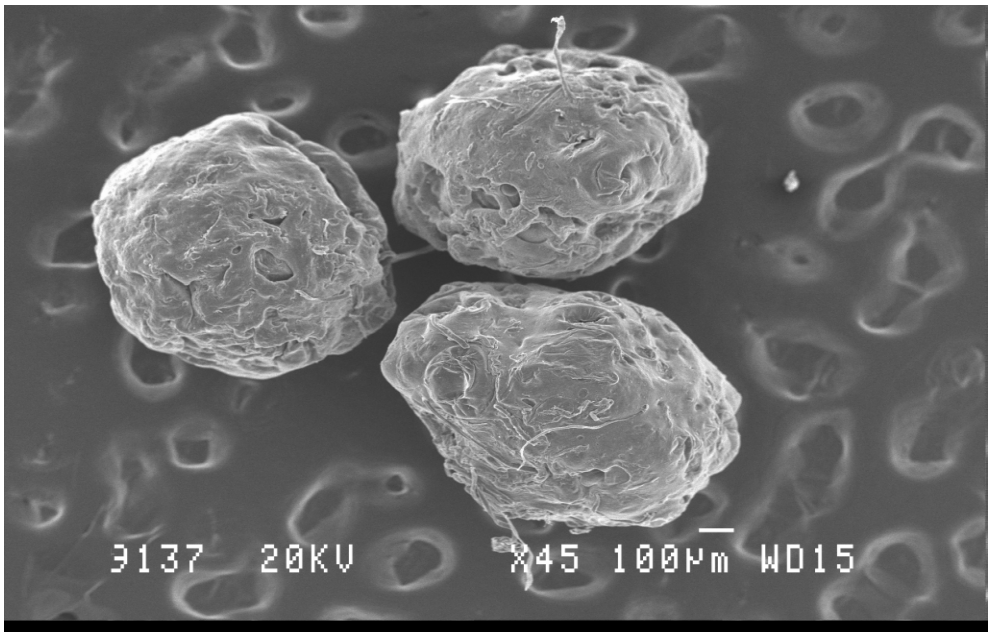
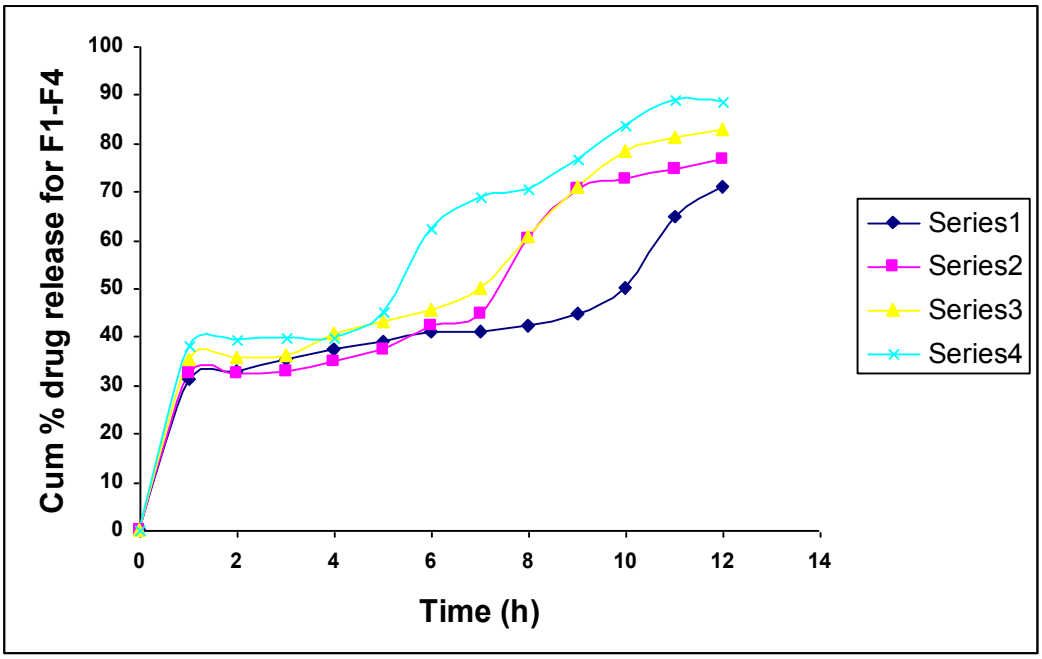


Figure I: Scanning Electron Microphotographs Of Floating Alginate Beads Of Amoxicillin



Series1- A1, Series2- A2, Series3-A3, Series4-A4.

Figure II: Comparison Of In Vitro Drug Release For Alginate Beads Of Amoxicillin F1-F4

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