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Research Article

DESIGN AND DEVELOPMENT OF ACECLOFENAC ALGINATE BEADS FOR SUSTAINED RELEASE DRUG DELIVERY

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ABSTRACT

Now the focus has been slightly moved to the patient's convenience and acceptance, where still the safety and efficacy remain integrated with design. Oral controlled release products are formulated to release active ingredient gradually and predictably over a 12 to 24hour period. The objective of the present study was to micro encapsulate the anti-inflammatory drug (aceclofenac) to provide sustained release and minimizing or eliminating drug release in the upper gastro intestinal track. Alginate beads of Aceclofenac were formulated by ionotropic gelation and the variables studied includes different concentrations of sodium alginate were evaluated with respect to particle size, surface characteristics, entrapment efficiency and *in vitro* release behavior. IR spectroscopic study confirmed the absence of any drug interaction. The mean particle size increases with increasing the polymer concentration. The shape of alginate beads has acceptable sphericity and surfaces were rough which were confirmed by SEM photograph. The entrapment efficiency in different formulation varied from 72% to 84%. The *in vitro* release profiles were also altered significantly by changing various parameters. The kinetic modeling of the release data indicates that Aceclofenac released from alginate beads followed by Higuchi's model. Studies demonstrated that Aceclofenac could be successfully prepared by ionotropic gelation technique with prolonged release characteristics.

Keywords: Aceclofenac, Alginate, Beads, Sustained release, Scanning electron microscopy.

INTRODUCTION

The goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site action, reducing the dose required, or providing uniform drug delivery. The beads of aceclofenac were prepared by ionotropic gelation technique [2].

A gel, in classical colloid terminology, is defined as a system which owes its characteristic properties to a cross – linked network of polymeric chains which form at the gel point. A considerable amount of research has been carried out in recent years to elucidate the nature of the cross-links and determine the structure of alginate gels. Alginate beads can be prepared by extruding a solution of sodium alginate containing the desired drug or protein, as droplets, into a divalent cross - linking solution such as Ca^{2+},Sr^{2+}, or Ba^{2+}.Monovalent cations do not induce gelation while Ba^{2+}. and Sr^{2+}, ions produce stronger alginate gels than Ca^{2+}.Other divalent cations such as Pb^{2+} ,Cu^{2+} ,Cd^{2+} ,CO^{2+}, Ni^{2+},Zn^{2+} ,and Mn^{2+} will also cross – link alginate gels but their use is limited due to their toxicity. The gelation and cross – linking of the polymers are mainly achieved by the exchange of divalent cations and stacking of these guluronic acids with the divalent cations, and the stacking of these guluronic groups to form the characteristic egg – box structure [1] shown in Figure.

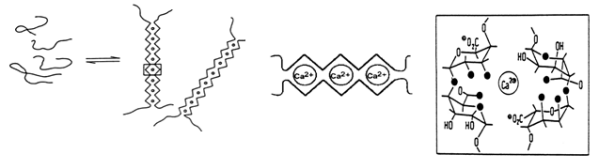


Fig. 1: Egg – box structure

Schematic representation of the egg-box association of the poly-l-L-guluronate sequences of alginate cross - linked by calcium ions. The upper section of the figure shows conversion of random coils to buckled ribbon like structures which contain arrays of Ca^{2+} ions. The bottom section shows the proposed stereochemistry of Ca^{2+} ion complexation. The oxygen atoms involved in the coordination sphere are shown as filled circles.

Aceclofenac is a non-steroidal anti-inflammatory drug, widely used in the management of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Usual therapeutic dose is 100 mg twice daily and half life is 3-4 hrs; thus it is necessary to be administered frequently in order to maintain the desired concentration. Therefore, Aceclofenac is an ideal candidate for sustained release formulation, resulting in more reproducible drug absorption and reducing the risk of local irritations compared to single dosage forms.

METERIALS AND METHODS

Aceclofenac was received as a gift sample from Macsur Pharma India Pvt Ltd, Puducherry, India. Sodium alginate AR was procured from Hi media biosciences Ltd, Mumbai, India. Calcium chloride AR was procured from S.D.Fine chemicals Ltd, Mumbai, India.

Formulation of Aceclofenac sodium alginate beads

The beads of Aceclofenac were prepared by ionotropic gelation technique. 100ml of Sodium Alginate (SA) solutions at different concentration were prepared by stirring sodium alginate powder in deionized water for 30 minutes then, an accurately weighed quantity of Aceclofenac was added to afford homogenous dispersions. The SA-drug dispersion were then added drop wise into a 100ml of cross linking solution (different concentration) using a 10ml of hypodermic syringe fitted with a 20 gauge needle and stirred at 500 rpm. The formed alginate beads were cured at different time interval. On expiration of this period the solution of cross linking agent was decanted and the alginate beads were washed repetitively for three times with 50ml deionized water. The alginate beads were thereafter dried at 60°C for 2hours in a hot air oven [2].

Table 1: Formulation chart

Formulation code	Drug (mg)	Sodium alginate (%w/v)	Cross-linking agent	Cross-linking (%w/v)	Curing time (min)
F1	200	2.5	$Cacl_2$	2	30
F2	200	2.5	$Cacl_2$	4	30
F3	200	3.5	$Cacl_2$	2	30
F4	200	3.5	$Cacl_2$	4	30
F5	200	5.0	$Cacl_2$	2	30
F6	200	5.0	$Cacl_2$	4	30

Evaluation

Physical Characterization

The particle size distribution analysis was performed by using an optical microscope. [3]

The shape and surface characteristics of beads were observed by scanning electron microscopy [4].

Determination of Drug Encapsulation Efficiency

Fifty milligrams of drug loaded alginate beads from each batch was placed in 100 ml conical flask containing 50 ml of phosphate buffer (pH6.8).The beads were agitated on mechanical shaker for 24 hours, to promote swelling and breakup of the cross - linked structure. Then solutions were filtered and the drug was quantified at 274 nm spectrophotometrically after appropriate dilution with buffer. The encapsulation efficiency (EE) was determined by using the following empirical relationship. Each determination was performed in triplicate manner. [5]

$$\text{Entrapment efficiency (\%)} = \frac{\text{Actual drug content (AC)}}{\text{Theoretical drug content (TC)}} \times 100$$

AC - Actual quantity of drug present in the beads a

TC - 100% theoretical quantity of drug present in the beads (actual initial dose)

***In Vitro* Drug Release Studies**

200 mg of drug loaded alginate beads were evaluated for *in vitro* drug release. The study was carried out in the USP XXXIV Type I apparatus using 900ml phosphate buffer (pH 6.8) solution and rotated at constant speed (100 rpm) and the temperature of the medium was maintained at 37°±0.5°C for 8 hours. A muslin cloth was tied over the basket to prevent the slippage of beads from the basket. An aliquot of the sample was periodically withdrawn at the regular time intervals and an equal volume was replaced with fresh dissolution medium. The test samples were filtered and analyzed spectrophotometrically at 274 nm after appropriate dilution with buffer. The percentage drug released at different time intervals were calculated. The *in vitro* drug release profiles were obtained by plotting the percentage release Vs time in hours. [6]

Dissolution Kinetics of Drug Release

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: Zero order (cumulative amount of drug released vs time), First order (log cumulative percentage of drug remaining vs time), Higuchi's model (cumulative percentage of drug released vs square root of time), and Korsmeyer's (log cumulative percentage of drug released vs. log time). [7]

RESULTS AND DISCUSSION

Physical Characterization

To establish the uniformity in size distribution of the prepared microbeads the particle size distribution analysis was performed as described in the methodology by using an optical microscopy technique. The various mean diameters described were also calculated. The results revealed that the size distribution of the prepared microbeads was found to be uniform and narrow. The above results were also evident from the following normal distribution graph obtained while plotting the mean size range and number of particles. The effect of concentration of polymer on the size of beads formed were studied and it was found that there was an increase in the average diameter of particles as there was an increase in the concentration of polymer. The graphs obtained were given in the following Figure.2.

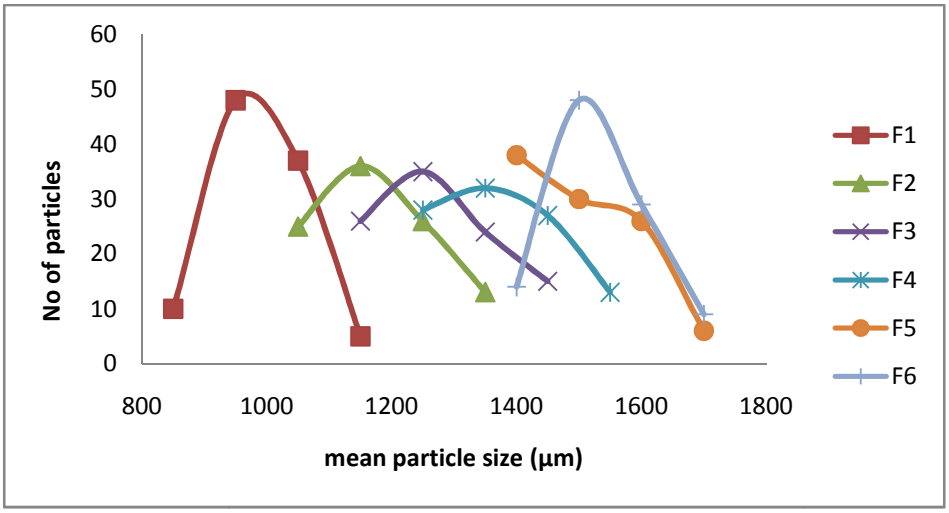
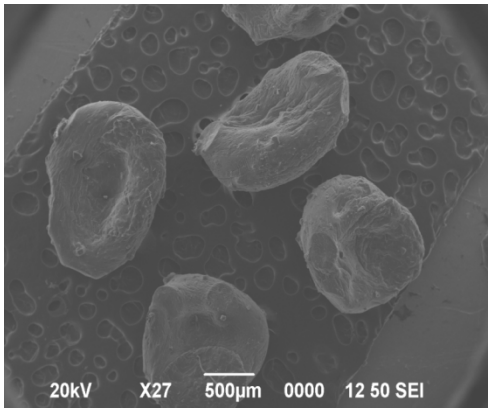
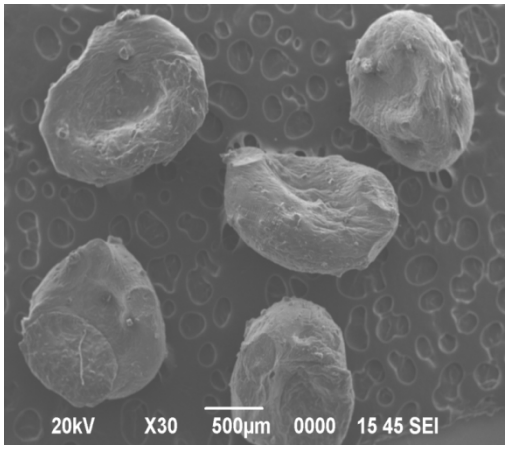


Fig. 2: Normal frequency distribution curve (F1-F6)



a) SEM of F1



b) SEM of F6

Fig. 3: SEM of formulation F1 and F6

The beads exhibiting acceptable sphericity and the presence of high intensity calcium peaks at the inner of the bead reveals that the presence of calcium is due to the cross links between calcium ions and carboxylate groups of alginate. The alginate beads were more or less spherical in shape and the exterior surfaces were rough. The spherical shape of the beads in wet state was usually lost after drying especially for beads prepared with low concentration of SA and cross -linking agent. With the increase of SA concentration the shape of the beads retained considerably. The shape and surface characteristics of beads were observed by scanning electron microscopy and are given in figure 3.

Determination of Drug Encapsulation Efficiency

The results indicated an increase in the concentration of sodium alginate and calcium chloride concentration increases the encapsulation efficiency.

Table 2: Average Entrapment Efficiency

S. No.	Formulation code	Concentration of sodium alginate (%w/v)	Concentration of $Cacl_2$ as cross linking agent (%w/v)	Entrapment Efficiency (%)
01	F1	2.5	2	72
02	F2	2.5	4	76
03	F3	3.5	2	76
04	F4	3.5	4	81
05	F5	5.0	2	79
06	F6	5.0	4	84

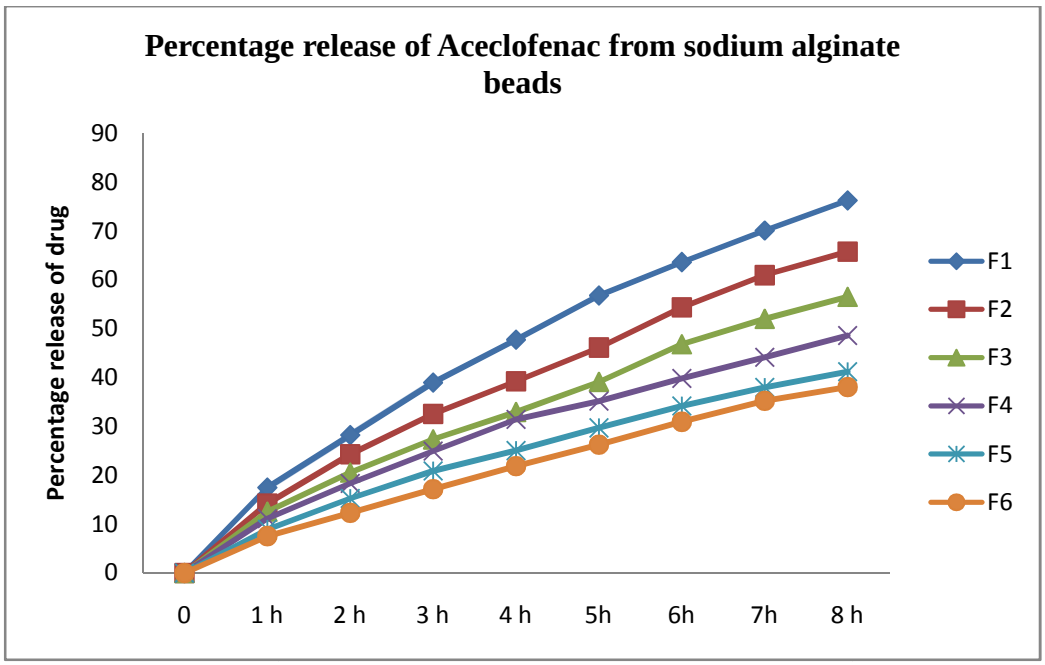


Fig. 4: *In vitro* release profile of Aceclofenac micro beads

In Vitro Drug Release Studies

The release profile for formulations (F1 – F6) is shown in Figure 4. The results indicated that the more sustained effect with increase in the concentration of sodium alginate. It was due to the number of the apparent cross – linking points formed within the calcium alginate beads increased with increasing alginate concentration in the formulation. It was also found that with increased concentration of $Cacl_2$, the drug release rate becomes more sustained. It is hypothesized that at higher $Cacl_2$ concentration a strong rigid gel is formed around the matrix, which may reduce the penetration of dissolution medium into core of the matrix, therefore decreasing the release rate.

Dissolution Kinetics of Drug Release

The release data obtained was subjected to zero order, first order, Higuchi's, Kosermayer's in order to establish the drug release mechanisms and kinetics of drug release from the tablet formulations. Criteria for selecting the most appropriate model were based on the best goodness of fit indicated by the value of regression coefficient(r). The *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's equation.

CONCLUSION

The study can be concluded that from the investigations proper selections of formulation parameters are important to achieve the desired particle size, drug loading efficiency and to sustain the release of drug from sodium alginate micro beads. It was observed that particle size increased as the polymer concentration increased. In case of drug loading efficiency, when the concentration of polymer and cross – linking agents was increased, the drug loading efficiency decreased. The results indicated that the more sustained effect with increase in the concentration of sodium alginate and $Cacl_2$.

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