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Research Article

Formulation and evaluation of controlled release alginate microspheres using locust bean gum

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ABSTRACT

The microspheres were prepared by ionic cross-linking technique. Chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for microspheres. For slowing the rate of release from microspheres the hydrophilic polymer Locust bean gum was used in different concentration with model drug as Diclofenac sodium, so that the drug will be release constantly for 12hrs. The formulation prepared showed the angle of repose within acceptable range having a good flow property. The drug entrapment efficacy of all the formulation was in the range of 90.6–98.9%. The drug entrapment efficacy of microspheres increases with increase in concentration of hydrophilic gums. I*n vitro* drug release from microspheres was studied. The microspheres containing 1.5% of Locust bean gum shows 97.8% drug release. The values of co-efficient correlation (r) were calculated and were found to be linear for first order release as compare to zero order release. Stereo microscopy invade that the microspheres are spherical in shape and with porus surface. Stability studies reveled that polymers used were stable and compatible with the drug and there is no significant effect on physical characteristics, drug content and dissolution profile of the microsphere.

Key words: Microspheres, Diclofenac sodium, Locust bean gum, Sodium alginate, Calcium chloride.

INTRODUCTION

One of the common methods of controlling the rate of drug release is microencpsulation. The encapsulation technique (e.g. solvent evaporation, coacervation-phase separation) normally involve water insoluble polymer as carriers, which requires large quantity of organic solvent for there solubilization[1,2]. As a result the process become vulnerable to safety hazards, toxicity and increases the cost of production making the technique non reproducible, economically and ecologically at an industrial scale. These concerns demand a technique free from any organic solvent, which can be fulfilled by the microspheres prepared by Ionotropic gelation technique, it has been widely examined and developed. The mechanism of Microsphere formation is based on electrostatic interaction between amine groups of polymer and negatively charge group of polyanion such as tripolyphosphate. Chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for Microsphere formation. The gelation of alginate is cause by forming an egg box junction to associate divalent metal ions of alginate polymer chain. Sodium alginate has been used as matrix material to achieve a control release drug delivery due to its hydrogel forming properties. Gelation of an anionic polysaccharide, sodium alginate, the primary polymer, was achieved with oppositely charged counter ions i.e. Ca^{++} to form microparticals which were further made sustained by using divalent polymer[3] The principle of gelation is based on the formation of tight junction between the glucoronic acid residues of sodium alginate. The number of apparent cross-linking points formed within the calcium alginate gel beads increase with increase alginate concentration. The increase in the apparent cross linking density delayed the alginate gel disintegration in phosphate buffer due to the retardation of Ca^{++} exchange with Na^{++} and eventually increase lag time. The increase alginate gel density per unit volume was also thought to affect the decrease pore size within the gel, and thus drug release becomes slow[4].

MATERIALS AND METHOD:

Diclofenac sodium was obtained as gift sample from Alkem Laboratories Ltd., Mumbai, Locust bean gum was obtained as gift sample from Crystal Colloids Ltd. Mumbai Sodium Alginate from Sulbha Gums Bangalore, other chemicals used were of analytical grade.

Preparation of Microspheres[7,8,9]:

The microspheres were prepared by ionic cross-linking technique. The alginate solution comprising 2.5% sodium alginate, 1.25-2% locust bean gum, 1% of plasticizer and 100mg of drug were prepared by initially dissolving the polymer in 50% deionized water using gentle heat. On complete dissolution the weighed quantity of drug was added and was mixed thoroughly, to this, solution of sodium alginate was added to afford homogeneous dispersion. The dispersion was added drop wise via 20 gauge hypodermic needle fitted with a 10ml

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Table N0. 1: Compositions of various formulations of microspheres

Formulation Code	Diclofenac sodium (%w/v)	Sodium Alginate (%w/v)	Locust bean gum (%w/v)	Calcium chloride (%w/v)	Glycerol (%w/v)
F1	1.5	1.5	1.25	5	1
F2	1.5	1.5	1.50	5	1
F3	1.5	1.5	1.75	5	1
F4	1.5	1.5	2.00	5	1

Table No. 2: Drug entrapment efficacy and Angle of repose of microspheres

Formulation Code	Drug entrapment efficacy*(%)	Angle of Repose* (ø)
F1	90.6	25°
F2	94.4	26°
F3	96.7	26°
F4	98.6	28°

* Mean of three readings.

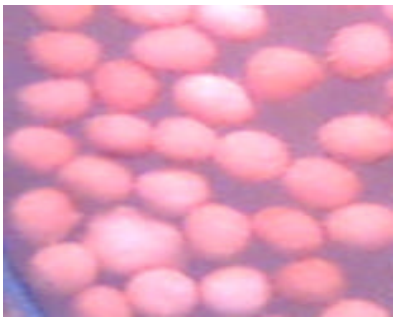

Figure No.1:Photomicrographs of controlled release microspheres (60X)

Figure No. 2: Shows spherical shape of controlled release microspheres (60X)

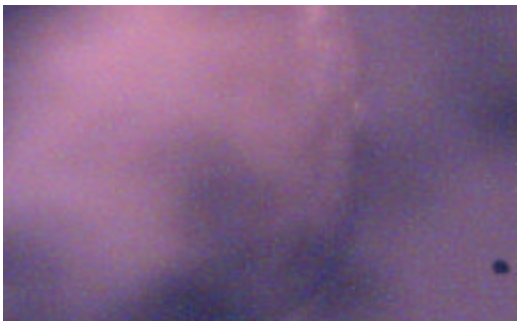

Figure No. 3: Shows pore visibility of controlled release microspheres (200X)

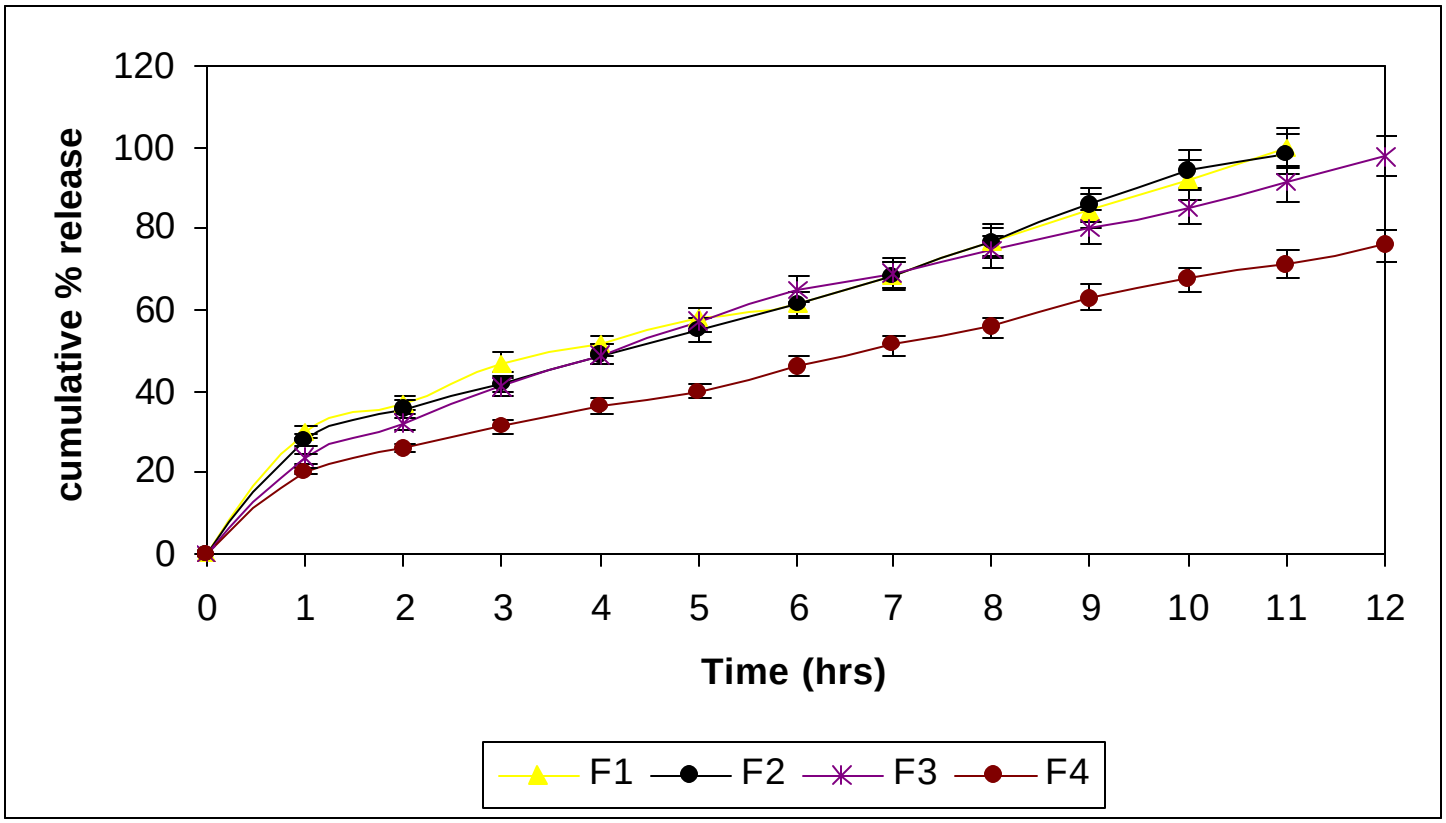

Figure No. 4: In *vitro* Drug Release of Diclofenac sodium microspheres

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syringe into 50ml 5%w/v of cross linking agent (Calcium chloride) solution, being stirred at 200rpm for 10min. The droplets from the dispersion instantaneously gelled into discrete drug-polymer-alginate matrices upon contact with the solution of cross-linking agent. The formed microspheres were further allowed to stir in the solution of cross-linking agent for an additional 2hrs. On expiration, cross-linking agent was decanted and microspheres were washed with 3 x 50ml volume of deionized water. The microspheres were there after dried at 80°C for 2hrs in a hot air oven. Compositions of various formulations are shown in Table No.1.

Evaluation of Microspheres:

Drug Entrapment Efficacy[10]-

Accurately weighed microspheres equivalent to 100mg were suspended in 100ml of simulated intestinal fluid of pH 7.2±o.1 and kept for 24hrs. Next day it was stirred for 5min and filtered. After suitable dissolution, Diclofenac sodium content in the filtrate was analyzed spectrophotometrically at 278nm using Shimadzu UV spectrophotometer. Finally, drug encapsulation efficiency is calculated by-

$$\text{Drug Entrapment Efficiency} = \frac{\text{Actual drug content X 100}}{\text{Theoretical drug content}}$$

The drug entrapment efficacy of microspheres is shown in Table No. 2.

Flow Property[11]-

Angle of repose method was employed to assess the flowability. Microspheres were allowed to fall freely through the funnel fixed at 1cm above the horizontal flat surface until the apex of conical pile just touched the tip of the funnel. The angle of repose (ø) was determined by formula.

$$ø = \tan^{-1}(h/r),$$

Where, h- Cone height of microspheres,

r- Radius of circular base formed by the microspheres on the ground.

The flow property of microspheres is shown in Table 2

Stereo Microscopic study-

Stereo microscopic study was conducted by Intel play stereo microscope to study surface morphology of the microspheres. The stereo microscopic photographs of the microspheres are shown in Figure No. 1, 2 and 3.

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

The *in vitro* dissolution study was carried out using six station dissolution rate test apparatus USP at 50rpm. The dissolution medium consisted of 900ml simulated gastric fluid (pH 1.2) for first 2hrs followed by simulated intestinal fluid (pH 7.2) from 2 to 12hrs. Aliquots of 5ml were withdrawn every one-hour and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots withdrawn were diluted suitably, filtered and analyzed at 278nm spectrophotometrically. All the release studies were conducted in triplicate and the mean values were plotted versus time with standard deviation less than three indicating reproducibility of result. The plot of percentage cumulative drug release against time (Hrs.) is shown in Figure No. 4

Stability Studies[12]-

Stability study was carried out on the optimized formulation F3. The formulation was wrapped in aluminium foil and then placed in an amber colored bottle. It was stored at 40 ± 2°C, 75% ± 6% relative humidity for 6 months. Microspheres were evaluated for *in vitro* drug release after Two, Four and Six month. Result obtained was compared with the data obtained for zero time at room temperature and humidity (Temperature 28 ± 2°C and humidity 42% ± 2%).

RESULT AND DISCUSSION:

Chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for microspheres. For slowing the rate of release from microspheres the hydrophilic polymers was added in different concentration so that the drug will be release constantly for 12hrs. The formulation prepared showed the angle of repose within acceptable range having a good flow property. The drug entrapment efficacy of all the formulation was in the range of 90.6 – 98.6%. The drug entrapment efficacy of microspheres increases with increase in concentration of hydrophilic gums. Diclofenac sodium *in vitro* release from microspheres was studied in acid buffer (pH 1.2) for initial 2hrs and phosphate buffer (pH 7.2) for the period of 10hrs. The release pattern of microsphere was slow and spread over extended period of time. The formulation F3 containing 1.75% of locust bean gum shows sustained drug release for 12hrs. Formulation F4 containing 2% of locust bean gum shows slow release where as formulations F1 and F2 shows faster drug release due to less percentage of locust bean gum. The values of co-efficient correlation (r) were calculated and were found to be linear for first order release as compare to zero order release. Stereo microscopic photographs indicated that the microspheres are spherical in shape and with porus surface. Stability studies reveled that polymers used were stable and compatible with the drug and the formulations were stable.

CONCLUSION:

Controlled release microspheres were successfully prepared employing ionotropic gelation technique. The method of preparation was found to be simple, and in different concentrations locust bean gum can be effectively blended with sodium alginate and Diclofenac sodium to form microspheres without using organic solvents. Microspheres prepared are spherical in shape and having porus surface. The drug entrapment capacity is above 90%, with increase in the percentage of locust bean gum there is increase in drug entrapment efficacy. The microspheres were found to be effective in sustaining the drug release for 12hrs. Drug release was diffusion controlled and followed first order kinetics. Stability studies revealed that there was no significant change in drug content and dissolution profile of microspheres. The process of

drug release from the polymer-drug matrix involves solvent penetration into the dry matrix, gelation of the polymer, dissolution of the drug, and diffusion of drug through resultant layer. Concomitantly, the outer layer becomes fully hydrated and dissolves.

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