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Preparation and Evaluation of Starch coated Alginate Microsphere of Diclofenac potassium

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Abstract: The aim of this study was to prepare and characterize the microsphere of diclofenac potassium by using biodegradable polymers. To improve the sustained delivery properties, diclofenac Potassium (DP) was multi-layered with alginate and starch. An attempt was made to formulate a sustained release dosage form of diclofenac potassium, to minimise frequent dosing as well as reducing or eliminating local side effects by avoiding the drug release in the upper gastro-intestinal tract. To prepare single and multilayered beads, ionotropic gelation technique was applied using various combinations of alginate and starch polymers. The morphology of the beads was investigated by SEM and Granulometric studies. The entrapment efficiency of drug was also determined. The formulations were found to be effective in providing controlled release of drug for a longer period of time. FT-IR studies were carried out for characterisation of beads.

Key words: Microsphere; Alginate; starch; Diclofenac potassium; SEM; FTIR.

INTRODUCTION

Diclofenac potassium (DP) is a mono potassium salt of benzoic acetic acid derivative (mol. wt 334.25). It is a very popular and most useful non-steroidal anti-inflammatory agent which is widely used in rheumatoid arthritis[1]and other inflammatory conditions[2]. The biological half life of diclofenac potassium is about 1-2 hours and the usual oral dose is 50mg, 2-4 times a day[3] and diclofenac potassium is more potent than diclofenac sodium[4]. Therefore it requires multiple dosing to maintain therapeutic blood level of the drug. The most frequent adverse side effects of diclofenac potassium on long term administration are gastrointestinal disturbances, hyper acidity, peptic ulceration and gastrointestinal bleeding[5,6]. Hence an attempt was made to formulate a sustained release dosage form with diclofenac potassium, which provides the initial loading dose and the microsphere of diclofenac potassium for the maintenance dose to minimize the frequent dosing as well as the adverse effects.

From the literature survey it was found that, synthetic polymeric materials don't exhibit the biodegradability and bio-incompatibility. On the other hand, to dissolve the synthetic polymers, organic solvents are required. Problems of possible toxicity, explosion hazards and especially environmental pollution[7] associated with the use of organic solvents have been raised recently. Natural polymers are devoid of toxicity and biodegradability problems[8]. Hence alginate and starch are used as coating materials as they are free of organic solvent as well as eco-friendly[9].

Alginates are natural polysaccharide polymers isolated from marine brown algae. Algenic acid is converted to its sodium salt and form sodium alginate. A linear chain consisting of ß-D-mannuronic acid and α-L-guluronic acid residues arranged in block in a polymer chain, these homogeneous blocks are

separated by blocks made of random or alternating units of d-mannuronic acid and l-guluronic acids[10]. Alginates offer various applications in drug delivery, such as in matrix type alginate gel beads[11] in liposome, in modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering applications[12].

In a comparative study, alginate formulation appeared to be better than the polylactide-co-glycolide(PLG) formulations in improving the bioavailability of two clinically important antifungal drugs- clotrimazole and econazole. The nanoparticles were prepared by the emulsion –solvent-evaporation techniques in case of PLG and by the cation – induced controlled jellification in case of alginate.

Starch is a naturally occurring polysaccharide, biocompatible, biodegradable, and adhesive and nontoxic[13,14]. It also shows a high degree of swelling and forms gel like system when in contact with aqueous medium. In addition starch microspheres do not produce immune response[15]. $CaCl_{2\ a}$ divalent metal was used as a cross linking agent in manufacturing of diclofenac potassium microsphere[16].

MATERIALS AND METHODS

Materials

Diclofenac potassium IP was received as a gift sample from U S Vitamins Ltd, Gujarat, India. Sodium alginate, starch and calcium chloride (analytical grade) were purchased from Loba Chemicals and Qualigens India Ltd, respectively. All other ingredient used of analytical grade.

Methods

Preparation of microbeads

Starch-alginate coated diclofenac potassium beads were prepared by ionotropic gelation technique followed by Fattah et. al[17]and Bert et al[18] with some modifications. A blend of sodium alginate and starch were dispersed in distilled water at different concentrations and homogenized for 1h. Drug polymer solution was prepared by dispersing the drug slowly into previously prepared alginate-starch slurry with continuous and uniform stirring for 3hours. A gelation medium was prepared separately by dissolving calcium chloride in distilled water. Bubble free dispersion medium was extruded through glass syringe (20G) into the gently agitated $CaCl_2$ solution. The agitation was carried out by magnetic stirrer at 200rpm. Beads were formed instantly. After 10mins the beads were removed by filtration from the solution and washed with de-ionized water. The beads were dried at 30^0C under reduced pressure till they attained constant weight. This method was repeated for different formulations by changing the quantities of starch, alginate and $CaCl_2$.

Yield of beads

To determine the yield following formula was employed.

$$\text{Yield of beads} = \frac{W2}{W1} \times 100$$

Where W_1 = the weight summation of drug, polymers and cross linking agents, W_2 = the weight of the beads prepared experimentally. The mean of three determinations was reported in Table-2.

TABLE 1 : Quantities of different ingredients used in preparing microbeads.

Formulation Code	Sodium alginate (mg)	Starch (mg)	Drug (mg)	Cross linking Agent ($CaCl_2$) (mg)	Stirring speed (rpm)
S1	200	100	200	5	200
S2	200	200	200	5	200
S3	200	100	200	10	200
S4	200	200	200	10	200
S5	200	50	200	5	200
S6	200	50	200	10	200
S7	200	300	200	5	200
S8	200	300	200	10	200
S9	100	100	200	5	200
S10	100	100	200	10	200
S11	300	100	200	5	200
S12	300	100	200	10	200

TABLE 2 : Percentages of yield and the drug entrapment as well as the mean diameter of microbeads.

Bead Code	Yield (%)	Entrapment (%)	Mean Diameter (mm)
S1	79.25	92.30	0.78
S2	77.10	89.73	0.92
S3	72.44	88.33	0.93
S4	74.21	90.88	0.96
S5	86.63	88.32	0.98
S6	70.68	88.70	0.80
S7	68.36	83.26	0.85
S8	78.97	81.42	0.92
S9	72.38	89.47	0.96
S10	79.45	86.58	0.87
S11	83.12	84.25	0.89
S12	89.52	81.12	0.94

Determination of drug entrapment efficiency

To evaluate the drug content inside the beads, the digestion method was applied. The drug – loaded beads (50mg) were pulverized and incubated in 50ml of 0.1N NaOH solution at room temperature for 24h. After the interval the solution was stirred, filtered, diluted and assayed spectrophotometically at 276nm.

$$\text{The drug entrapment efficiency} = \frac{X2}{X1} \times 100$$

Where X_1 = the theoretical amount of the drug present in the beads, X_2 = the experimental amount of the drug present in the beads. The mean of three determinations was reported in Table-2.

Particle size analysis

The particle sizes of the prepared microbeads were determined using the optical microscopy method. It was the most direct method for size distribution measurement. The prepared microbeads were mounted in light liquid paraffin and the diameters of 100 particles were measured by means of an optical microscope equipped with a calibrated ocular micrometer. Then the mean diameter was calculated and represented in Table-2.

***In vitro* release study**

The dissolution profile of DP- microsphere was determined by using USP (Type-I) basket type dissolution test apparatus taking 900ml of phosphate buffer (pH 7.4) solution. The study was carried out for eight hours. The dissolution medium was maintained at a temperature of 37 ± 1^0C. The basket was covered by 100 mesh nylon cloth and rotated at 50 rpm. The 10ml of sample was taken at every 1h interval and simultaneously equal quantity of the corresponding blank dissolution medium was added to the dissolution apparatus. The sample was filtered and suitably diluted to determine the absorbance at 276nm in double beam UV spectrophotometer (CHEMITO-2500). Cumulative percentages of drug release from the microbeads were determined at different intervals and plotted in figure 5 & figure 6.

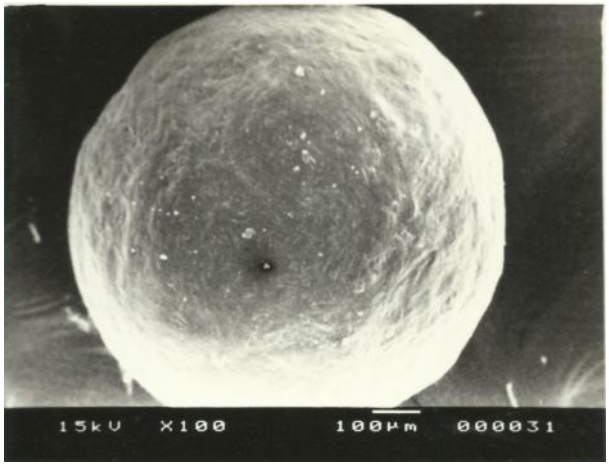

FIGURE 1: SEM photograph (X100) of blank sodium alginate and starch combination microsphere.

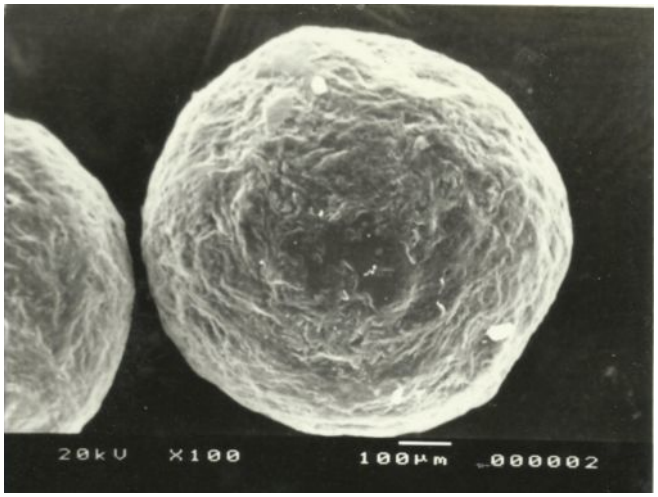

FIGURE 2 : SEM photograph (X100) of DP loaded sodium alginate and starch combination microsphere.

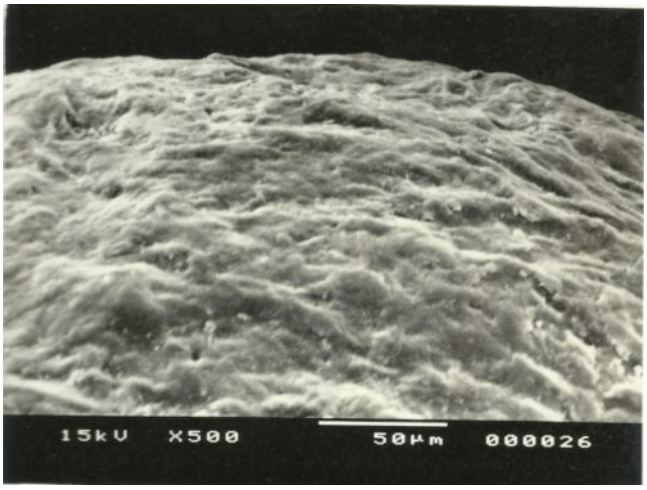

FIGURE 3 : SEM photograph (X500) of DP loaded sodium alginate and starch combination microsphere.

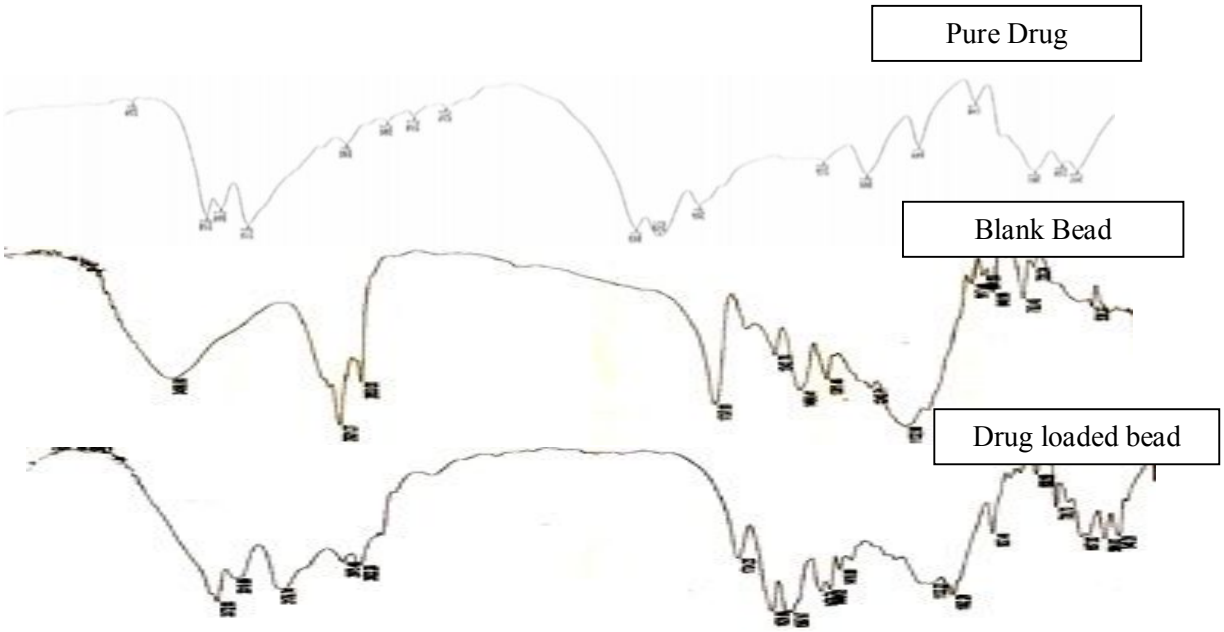

FIGURE 4: Comparative study of the FT-IR spectrum of pure drug, blank bead and the drug loaded beads.

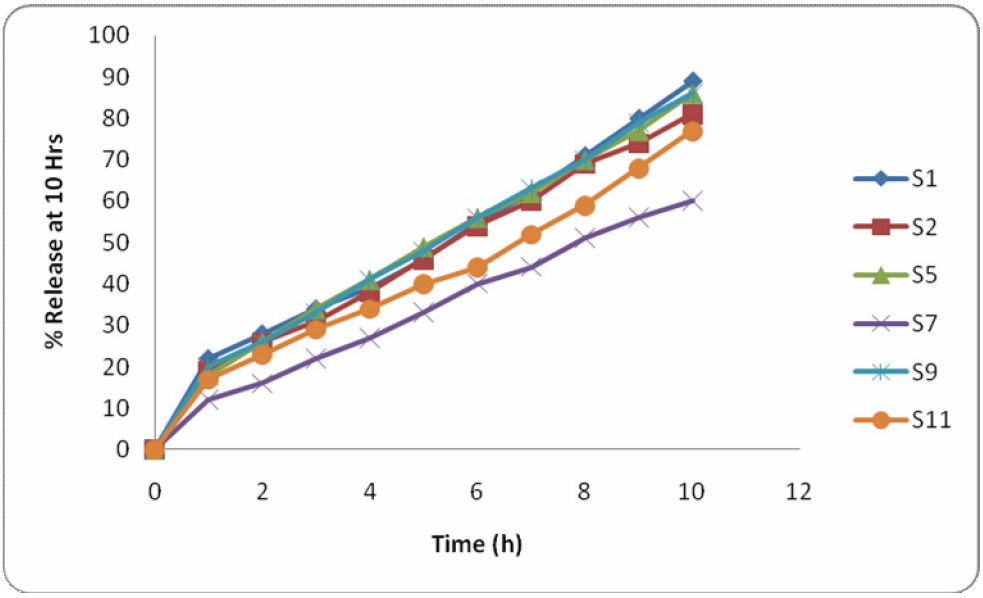

FIGURE 5: Cumulative percentage of drug release vs. time (h) [Effect of Polymer concentration]

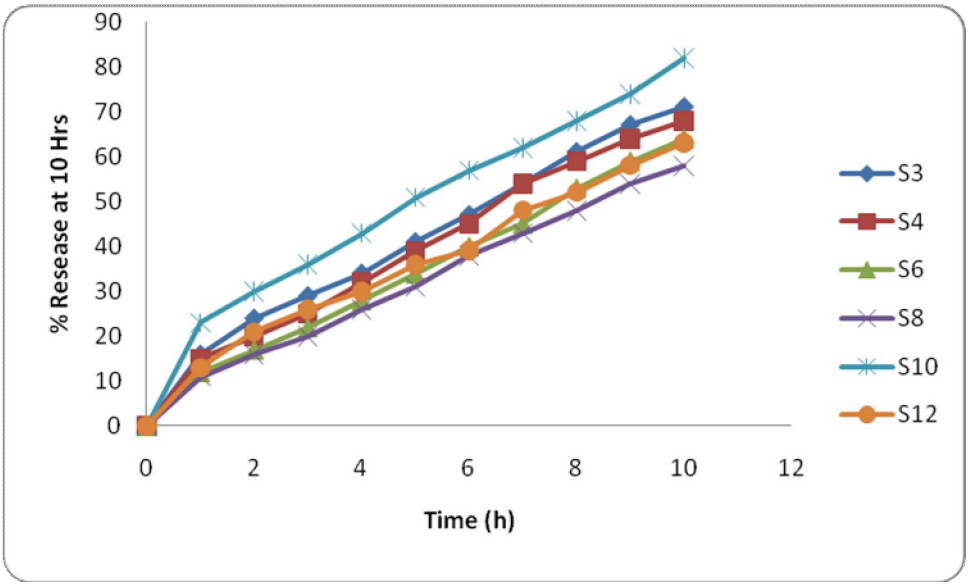

FIGURE 6: Cumulative percentage of drug release vs. time (h) [Effect of Cross linking agent concentration]

RESULTS AND DISCUSSIONS

The microbeads were sufficiently hard and spherical in shape. The beads were characterized for their particle size by microscopic method, drug loading efficiency and scanning electron microscopy.

Scanning Electron Microscopy (SEM) Analysis: From the scanning electron microscopy analysis (Fig 1-3) it was found that, microspheres prepared by ionotropic gelation method were spherical, non-aggregated and porous. The surface of the blank microsphere were smooth where as drug loaded placebos were slightly rough than blank placebos. The study of drug loaded beads showed the presence of drug particles on the surface and that might be factor for initial release of drug by bursting effect.

***In-vitro* release study**: The *in-vitro* release patterns of diclofenac potassium in different formulations were studied and were shown in fig 5-6, the physico-chemical properties of the beads were tabulated in the table-2. The release pattern showed the initial bursting effect, followed by slow release. Starch has a popular swelling effect, which provide the busting effect to the release and also starch increases the porosity of the matrix of alginate-starch beads. The release pattern

showed that microsphere with smaller diameter released higher quantity of the drug when larger particles released lesser. This involved a very common phenomenon that the smaller particles of having the same weight of larger particles have higher surface areas. On the other hand the result also demonstrated that, the higher concentration of polymers were responsible for the slower release of drug and lower release rate. Higher concentration of polymers produced the non-shrinkable, hard shell and skeletal structure matrices, which were the reasons behind the slower release of the drug.

Calcium chloride was used as cross linking agent. Release rate of drug decreased with the increasing amount of the cross linking agent. Hardness of the shell of beads was due to the presence of cross linking agent. Lowering of $CaCl_2$ results the loose bonding of surface of beads. The results indicated that, the release characteristics of diclofenac potassium depends upon the drug-polymer ratio, concentrations of alginate and starch, concentration of cross linking agent i.e. $CaCl_2$.

CONCLUSION

Diclofenac potassium loaded microspheres were prepared successfully by ionotropic gelation method using the combination of sodium alginate and starch polymers in different ratios. It was observed that the prepared microspheres were spherical, free flowing, high percentage entrapment efficiency and high percentage of yielding capacity.

The *in-vitro* controlled release of DP from the prepared microspheres formulations have been established in this study. However, the *in-vitro* release characteristics of the drug from the microspheres are subject to confirmation in animal and human studies for coming into conclusion of enhanced bioavailability and reduced dose frequency to improve patient compliance, which is under progress in our laboratory.

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