



# Development and Evaluation of Sustained Delivery of Diclofenac Sodium from Hydrophilic Polymeric Beads

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## ABSTRACT

Sustained-release polymeric beads containing diclofenac sodium were fabricated with hydrophilic polymers, sodium carboxymethyl cellulose (Na CMC), and sodium alginate (Na alginate). Particulate beads of Na CMC and Na alginate were prepared by the ionotropic gelation method using calcium chloride as a cross-linking agent. Beads of diclofenac sodium were prepared with different concentrations of polymers. Prepared beads were evaluated for their yield, particle size, drug entrapment efficiency, release behavior and tested for the presence of incompatibility using FTIR measurement. The drug entrapment efficiency varied between 73 and 92% in different formulations. For the same concentration of polymer, the release of diclofenac sodium from the beads was observed to be 82.69% and 91.33% for Na CMC and Na alginate, respectively, at the end of 10 h. The drug in beads maintained its identity after bead formation as observed by the FTIR study. From the study it could be concluded that multiparticulate beads of diclofenac sodium could be successfully prepared by the ionotropic gelation technique with high entrapment efficiency and sustained-release characteristics.

**Key words:** Diclofenac sodium, ionotropic gelation, sodium alginate, sodium carboxy methyl cellulose

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## INTRODUCTION

Over the past few decades, many sustained-release (SR) drug delivery systems have been developed using a variety of techniques in the presence of polymeric matrices. The use of hydrophilic polymers in the development of SR formulations for the delivery of drugs for oral route has proven to be advantageous over the conventional drug delivery systems. The ability of the hydrogels to swell and regulate the release of encapsulated drugs by controlling cross-linking makes them attractive as materials in the controlled release of drugs. Among the different polymers, swollen cellulose derivatives are widely used for obtaining controlled-release drug delivery systems.<sup>[1]</sup> Sodium alginate has been used as a matrix material to achieve a

controlled-release drug delivery due to its hydrogel-forming properties.<sup>[2,3]</sup>

The SR formulations of non-steroidal anti-inflammatory drug (NSAID) have been proved to minimize the side effects.<sup>[4]</sup> Diclofenac sodium is a non-steroidal anti-inflammatory agent, which is widely used in long-term therapy for rheumatoid arthritis. The biological half-life of diclofenac sodium is about 1-2 h, therefore it requires multiple dosing to maintain therapeutic drug blood level. The most frequent adverse side effects of diclofenac sodium on long-term administration are gastro-intestinal disturbances, peptic ulceration, and perforation.<sup>[5]</sup> In order to eliminate these adverse effects, enteric coated and/or SR forms have been developed and commercialized.<sup>[6-9]</sup>

Diclofenac sodium is poorly soluble in water and acidic pH (1-3) but is rapidly soluble in alkaline pH (5-8).<sup>[10]</sup> Hence, an attempt was made to formulate a SR dosage form containing beads of diclofenac sodium for controlled release, which eliminates the need for multiple dosing thereby increasing patient compliance and decreasing the occurrence of adverse effects.<sup>[11]</sup> The preparation of beads involves simple and reproducible methods. The hydrophilic carriers and polymers used were non-toxic, relatively less expensive, and easily available.

The main objective of this study was to develop the suitable micro-particulate bead system of diclofenac sodium for prolonged release delivery by varying the concentration of sodium alginate and sodium carboxymethyl cellulose.

## MATERIALS AND METHODS

Diclofenac sodium was received as a gift sample from Kaushick Therapeutics Pvt. Ltd. Sodium carboxymethyl cellulose (Na CMC) was received from Central Drug House Pvt. Ltd, New Delhi, and sodium alginate (Na alginate) and calcium chloride was purchased from Qualigens Fine Chemicals, Mumbai. All other chemicals and solvents were of analytical grades.

### Preparation of beads

Na CMC and Na alginate beads containing diclofenac sodium in ratios of 1:1, 1:1.5, and 1:2 were prepared based upon the methods previously proposed with some modification.<sup>[12,13]</sup> The drug dispersions were prepared by dispersing diclofenac sodium in 1-3% Na CMC and 1-3% Na alginate in deionized distilled water. Diclofenac sodium beads of Na CMC and Na alginate were prepared by dropping drug-polymer dispersions through a 20-gauge disposable syringe needle into 5% aqueous counter ion solutions (100 ml) of calcium chloride, which was gently agitated with a magnetic stirrer. The stirrer speed was kept constant at 1500 rpm. The formed beads were allowed to stand in solution for 1 h to be cured and then collected by filtration. These beads were washed with deionized water twice before drying in air for 24 h. The dried beads were sieved and used. The various ratios of drug and carriers, and formulation of beads are summarized in Tables 1 and 2.

### Measurement of bead size

The particle size was measured by taking 5-10 particles on a glass slide under polarized light. The mean diameter was calculated by measuring the number of divisions of the ocular micrometer covering the spheres. The stage

**Table 1: Ratio of drug and polymer used in preparation of diclofenac sodium beads**

Combination for beads	Drug	Na CMC	Na alginate
F1	1	1.0	-
F2	1	1.5	-
F3	1	2.0	-
F4	1	-	1.0
F5	1	-	1.5
F6	1	-	2.0

**Table 2: Composition and physico-chemical properties of diclofenac sodium beads**

Formulation code	Yield of beads* (%)	Drug entrapment* (%)	Mean diameter* (mm)
F1	82.75	82.82	0.86
F2	80.20	73.24	0.91
F3	77.63	69.56	0.96
F4	79.63	92.41	0.89
F5	76.66	85.28	0.92
F6	73.40	77.42	1.01

\*Average of three determinations.

micrometer was previously used to standardize the ocular micrometer.

### Drug entrapment efficiency

An accurately weighed quantity of beads containing 100 mg of drug was suspended in 100 ml of phosphate buffer pH 7.4 and was kept for 24 h. After the stipulated time, the mixture was stirred at 500 rpm for 15 min on a magnetic stirrer. Then the mixture was subjected to filtration. Five milliliters of this solution was diluted to 100 ml with phosphate buffer pH 7.4, and the absorbance of the resulting solution was spectrophotometrically measured at 276 nm.

### In vitro release drug studies for diclofenac sodium beads

The release of the drug from the Na CMC and Na alginate beads was tested using a dissolution tester (Disso test, Electro lab) equipped with eight baskets. The baskets were covered with 100-mesh nylon cloth to prevent the escape of the beads. The dissolution rates were measured at  $37 \pm 2^\circ\text{C}$  under 50 rpm paddle speed. Accurately weighed quantities of beads containing diclofenac sodium equivalent to 100 mg were added to 900 ml of 0.1 N HCl (pH 1.2). The test was carried out for 2 h and then continued in phosphate buffer (pH 7.4) for next 8 h. The samples were withdrawn at regular time intervals, filtered, and suitably diluted to determine the absorbance at 276 nm in the UV-visible spectrophotometer (Elico SL164).

### FTIR Study

FTIR spectra of diclofenac sodium, drug-loaded Na CMC,

and Na alginate were obtained in KBr pellets using a Perkin – Elmer model 883 spectrophotometer.

### RESULTS AND DISCUSSION

Diclofenac sodium has high solubility in the alkaline medium and may not show prolonged effect. Therefore, to sustain the drug release and absorption, diclofenac sodium beads were prepared with hydrophilic polymers like Na CMC and Na alginate by the ionotropic gelation technique using calcium chloride as a cross-linking agent. The gelation of alginate is caused by forming an egg box junction to associate divalent metal ions of the alginate polymer chain.<sup>[14,15]</sup> Among the cellulose derivatives, carboxymethyl cellulose can form insoluble salts when the polymer chains share polyvalent metal ions by a cross-linking technique, i.e. a reaction with divalent or trivalent metal ions ( $Ca^{2+}$ ,  $Al^{3+}$ , or  $Cr^{3+}$ ) was proposed.<sup>[1]</sup> The formed beads were sufficiently hard and their physical parameters such as particle size and friability were determined and found within acceptable limits.

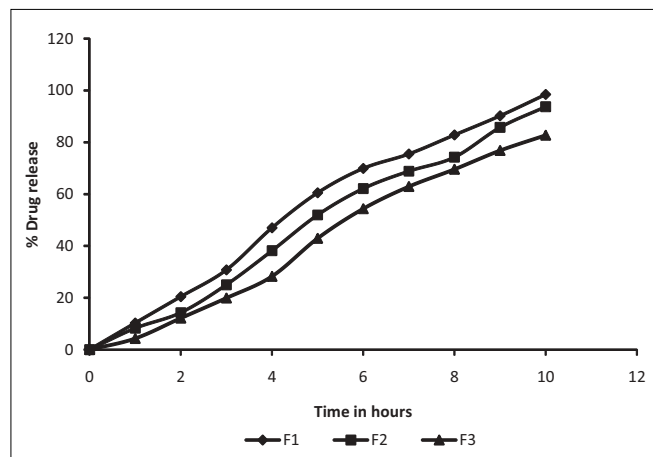


Figure 1: Drug release profile of diclofenac sodium from Na CMC beads

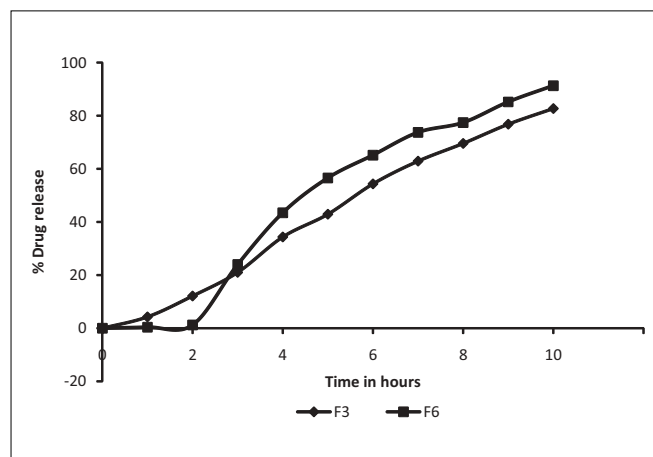


Figure 3: Comparison of drug release profile of formulation III and VI

The mean particle size of the beads increases with the increase in the concentration of Na alginate and Na CMC, at 5% fixed concentration of calcium chloride. This could be attributed due to the increase in the viscosity of polymer solution that in turn increases the droplet size during addition of the polymer solution to the cross-linking solution. The entrapment efficiency of the beads formed with increasing concentration of Na CMC and Na alginate

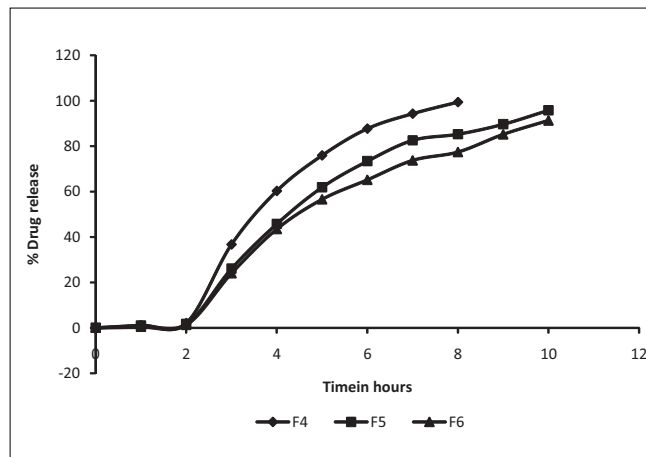


Figure 2: Drug release profile of diclofenac sodium from Na alginate beads

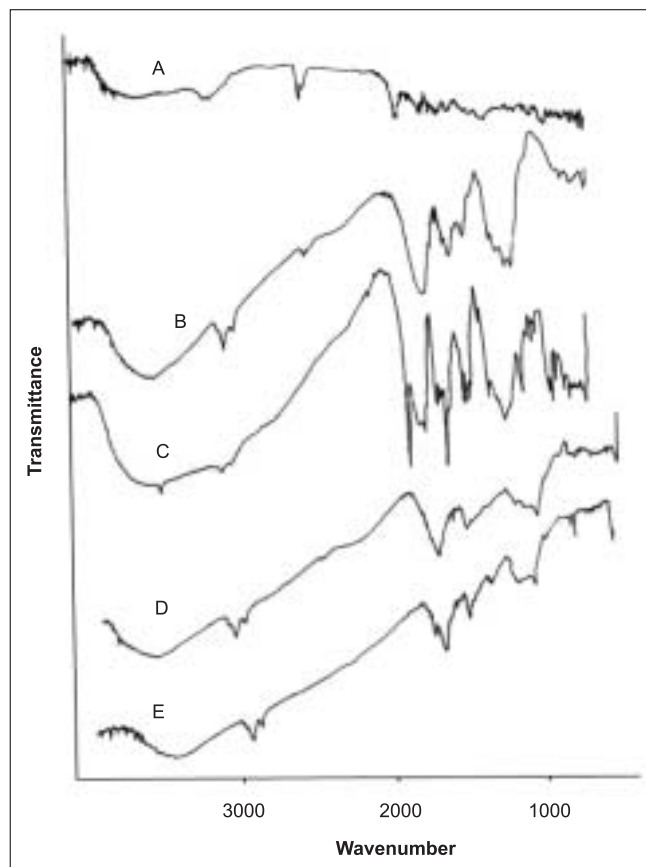


Figure 4: IR spectra of pure drug (A), Na CMC (B), formulation F 3 (C), Na alginate (D), formulation F 6 (E)

was found to be decreasing, which is in accordance with the results previously reported on diclofenac sodium beads.<sup>[16]</sup> The reason for decreased entrapment could be due to the difficulty in the formation of microspheres due to the high concentration of hydrophilic polymer.<sup>[17]</sup> The cross-linking or apparent gelation of calcium matrices of the hydrophilic polymers occur rapidly enclosing the drug, increasing the entrapment efficiency but further rearrangement of gel structure continued for a long period.<sup>[18]</sup>

The *in vitro* release studies were carried out for all the beads in the HCl medium (pH 1.2) for first 2 h and then in phosphate buffer (pH 7.4) for next 8 h. The Na alginate beads were found to release negligible amounts (<3%) of the drug in the HCl medium, due to the poor solubility of alginate in a pH less than 3. The trace amounts of release could probably be due to the surface-adhered drug. In contrast, Na CMC beads showed slightly higher release (<20%) in the acidic medium, which could be attributed to its free aqueous solubility. Among the formulations F1, F2, F3 with increasing concentrations of Na CMC, F3 (1:2) showed better sustainability by releasing 82.69% of the drug from the beads at the end of 10 h [Figure 1]. Similarly, among F4, F5, and F6 prepared with increasing concentrations of Na alginate, F6 (1:2) prolonged the 91.33% of the drug release at the end of 10 h in phosphate buffer pH 7.4 [Figure 2]. The slow release of the drug from beads with a higher concentration polymer may be due to the greater viscosity of the gel matrix in dissolution media. By comparison of the formulations F3 and F6, the sustaining ability of Na CMC and Na alginate can be inferred. It could be observed that for the same concentration, Na CMC beads delivers the drug in a more prolonged and uniform manner than alginate beads. This may be due to the fact that the higher porosity of alginate beads results in faster release of lower molecular weight drugs such as diclofenac sodium.<sup>[19]</sup> The drug release profiles are as shown in Figure 3.

The infrared spectra (FTIR) of diclofenac sodium and drug-loaded beads of Na CMC and Na alginate are shown in Figure 4. The FTIR spectra did not reveal any significant shifting of peaks, indicating the stability of the drug during the encapsulation process and the absence of the drug-polymer interaction.

## CONCLUSION

The ionotropic gelation technique can be successfully used for the preparation of diclofenac sodium beads of sodium alginate and sodium carboxymethyl cellulose. The methods of preparation of diclofenac sodium beads for SR characteristics were found to be simple and reproducible.

The carriers and polymers used were non-toxic, relatively less expensive and are easily available. The developed formulations were found to be effective in providing a SR of drug with high entrapment efficiency. A further study of Na CMC and Na alginate with varying concentration of calcium chloride is required to be carried out so that a more therapeutically effective dosage form with sustained and controlled drug release can be developed.

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