Development and Evaluation of Diclofenac Sodium Loaded Alginate Cross-Linking Beads

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Abstract

Sustained-release polymeric beads containing Diclofenac sodium fabricated with sodium alginate were prepared by the ionotropic gelation method. Drugs were blended with sodium alginate in 1:1, 1:2, 1:2.5, 1:3, 1:3.5 and 2:2 ratios. Here, calcium chloride and aluminium sulphate was used as a cross-linking agent. Beads of Diclofenac sodium were prepared with different concentrations of drug, polymers and electrolytes. Prepared beads were evaluated for their drug entrapment efficiency, loss on drying, swelling index and release behavior. The entrapment efficiency of drug in beads depended on the amount of drug and polymer ratio as well as electrolyte concentration. The percent entrapment was highest when beads were prepared with 5 % electrolyte solution. In case of calcium chloride solution with highest amount of polymer i.e.3.5 gram the entrapment efficiency was 75.12 %. But, in aluminium sulphate solution the entrapment efficiency was highest (99.06 %) when polymer amount was 2 gram. In most cases, the swelling study revealed that, up to third hour the formulations swelled high, but swelling started to decrease after fourth hour. In case of loss on drying of beads after formation showed that, the rate of solvent loss until three hours eventually continued to increasing but then decreased. *In vitro* dissolution data showed that, with increasing drug, polymer and electrolyte amount the Diclofenac release percentage also decreased. Among the sixteen formulations, nine of them followed Higuchi release kinetics. Thus, by modifying the polymer amount and the selection of cross linking agent plays a vital role in efficiency and sustained-release characteristics.

Key words: Diclofenac sodium, ionic cross-linking technique, sodium alginate, encapsulation efficiency, swelling index, release kinetics.

Introduction

Sodium alginate has been used as a matrix material to achieve controlled-release drug delivery due to its hydrogel-forming properties (Kikuchi *et al.,* 1997; Kikuchi and Okano, 2002). The ability of alginate sodium salt, to rapidly form viscous solutions and gels on contact with aqueous media has been exploited by the pharmaceutical industry in sodium alginate's wide application as a carrier in hydrophilic matrix controlled-release oral dosage forms. Matrices incorporating alginate salts have been employed to successfully prolong the release of many drugs (Stockwell *et al*., 1996; Veski and Marvola, 1993; Ojantakanen *et al*.; 1993; Veski *et al*., 1994).

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 hours, 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 (Scholer *et al*., 1986). In order to eliminate these adverse effects, enteric coated and/or SR forms have been developed and commercialized (Lin and Kao, 1991; Vilivalam and Adeyeye, 1994; Torres *et al*., 1995; Okada *et al*., 1996). Diclofenac sodium is poorly soluble in water and acidic pH but is rapidly soluble in alkaline pH (Tripathi, 1998).

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 (Chien, 1991).

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The beads were evaluated with respect to percent entrapment efficiency, loss on drying study, swelling index and *in vitro* drug release in phosphate buffer of pH 7.2.

Materials and Method

Diclofenac sodium was obtained from Hugestone Enterprise Co. Ltd, China. Sodium alginate was procured from Loba Chemie, India. Calcium chloride and Aluminium sulphate were obtained from Uni-chem (China) and Merck (India) respectively. All other reagents were of analytical grade satisfying pharmacopoeial specifications.

Preparation of core and surface cross-linked beads: Sodium alginate solutions of different concentrations were prepared by dissolving alginate in phosphate buffer of pH 7.2 under gentle agitation. Diclofenac sodium was dispersed in alginate solution under constant stirring for uniform distribution. The resultant dispersion was extruded dropwise through a needle into different concentrations of stirred calcium chloride solution at room temperature. Then the beads formed were allowed to remain in the stirred solution for 10 min curing time. The beads were filtered and washed with phosphate buffer and dried at room temperature for 24 hours. Such beads are named surface cross-linked beads (Pawar *et al*., 2008).

Estimation of encapsulation efficiency: For the assay procedure, we can easily get the concept of drug loading within the polymer and efficacy of that drug. Firstly, 100 mg of beads of any particular batch formulation was taken in a mortar and pestle. Then they were crushed to powder. Some extent of fresh phosphate buffer was added and the powder was dissolved using phosphate buffer (pH 7.2). After that, suitable dilution was done where necessary, and absorbance was measured at 277 nm. From the values of absorbance, the concentration of the corresponding sample solution was determined. Finally, entrapment efficiency was calculated. The ratio of the actual Diclofenac sodium content in the drug-loaded beads to the theoretical Diclofenac sodium content was termed encapsulation efficiency. The total mass of dried beads obtained from a batch was considered as practical yield of the process (Pawar *et al*., 2008).

$$\text{Entrapment efficiency} = \frac{\text{Diclofenac sodium loaded}}{\text{Theoretical Diclofenac sodium loading}} \times 100$$

Loss on drying study: When all the beads were prepared, decantation was done. Prepared beads were allowed for drying in open air. Weight of certain amount of beads was taken at 30 minutes interval for about five hours.

Swelling index study: The extent of swelling was measured in terms of % weight gain by the beads. The swelling behaviors of all the formulations were studied. In this test 20 mg of beads from each formulation was kept in petridish containing distilled water. At the end of 1 hour, the beads were withdrawn, soaked with tissue paper and weighed. Then for every 1 hour, weights of beads were noted and the process was continued till the end of 8 hours. The % weight gain by the beads was calculated by the following formula (Yeole *et al*., 2006):

$$\text{Swelling Index (SI)} = [\{W_t - W_0\}/ W_0)] \times 100$$

where, W_t= Mass of swollen beads at time t

W_0= Mass of dry beads at t=0

In vitro dissolution study: Dissolution study was carried out at 50 rpm at 37± 0.5^0 C in phosphate buffer of pH 7.2 media for 6 hours. The absorbance of the collected sample was analyzed for dissolution by using UV-VIS spectrophotometer at λ_{max} of 277 nm (Dhanaraju, 2009).

Kinetic models: The suitability of several equations that are reported in the literature to identify the mechanisms for the release of Diclofenac sodium was tested with respect to the release data. The data were evaluated according to the following equations (Donbrow and Samuelov, 1980; Higuchi, 1961; Higuchi, 1963):

Zero-order equation:

$$Q_t = K_0 t \quad \text{..... (1)}$$

Higuchi equation based on Fickian diffusion:

$$Q_t = K_H \sqrt{t} \quad \text{..... (2)}$$

where, Q is the amount of drug release in time t, k_0, and k_H are rate constant of zero order and Higuchi rate equations, respectively.

First order model:

$$\text{LogC} = \text{LogC}_o - kt/2.303 \quad \text{..... (3)}$$

where, C = cumulative percent of drug release, C_o = the initial concentration of drug and k = first order rate constant.

Results and Discussion

Entrapment efficiency estimation: The percentage of entrapment is given in figure 1 and table 1, from which it can be concluded that, with the increment of drug : polymer ratio the entrapment efficiency also increased. In case of F-1, the % entrapment was 56.13 % where the drug : alginate ratio was 1 : 1 in 5 % $CaCl_2$ solution. But, this was increased to 75.12 % in F-5 where drug : alginate ratio was 1 : 3.5. Whereas, with the increment of amount, the entrapment efficiency of drug decreased though the drug : alginate ratio was 2 : 2. In case of F-6, F-7 and F-8, the % entrapment was 55.02 %, 35.64 % and 32.91 % with formulations having 5 %, 10 % and 15 % of $CaCl_2$ concentration.

According to Lannuccelli *et al.,* (1998), with the addition of sodium alginate to a calcium chloride solution, instantaneous interfacial cross-linking takes place with precipitation of calcium alginate followed by a more gradual gelation of the interior which decreases the loss of surface drug as well as decrease the number of pores (Lannuccelli *et al*., 1998). Mayur *et al.,* (2005) reported that high level of calcium chloride concentration was affecting negatively on the entrapment efficiency because water soluble calcium chloride created significant number of pores on the surface of beads through which the drug molecules leached from the membrane into the medium (Sankalia *et al*., 2005).

Same phenomena occurred in $Al_2 (SO_4)_3$ solution when the drug : alginate ratio was changing i.e. F-9 has entrapment efficiency of 77.76 % and it was enhanced to 95.97 % in F-13. But, with the increment of $Al_2 (SO_4)_3$ concentration the entrapment efficiency beads also increased. In case of F-14, F-15 and F-16 the % entrapment was 43.04 %, 51.12% and 57%, respectively.

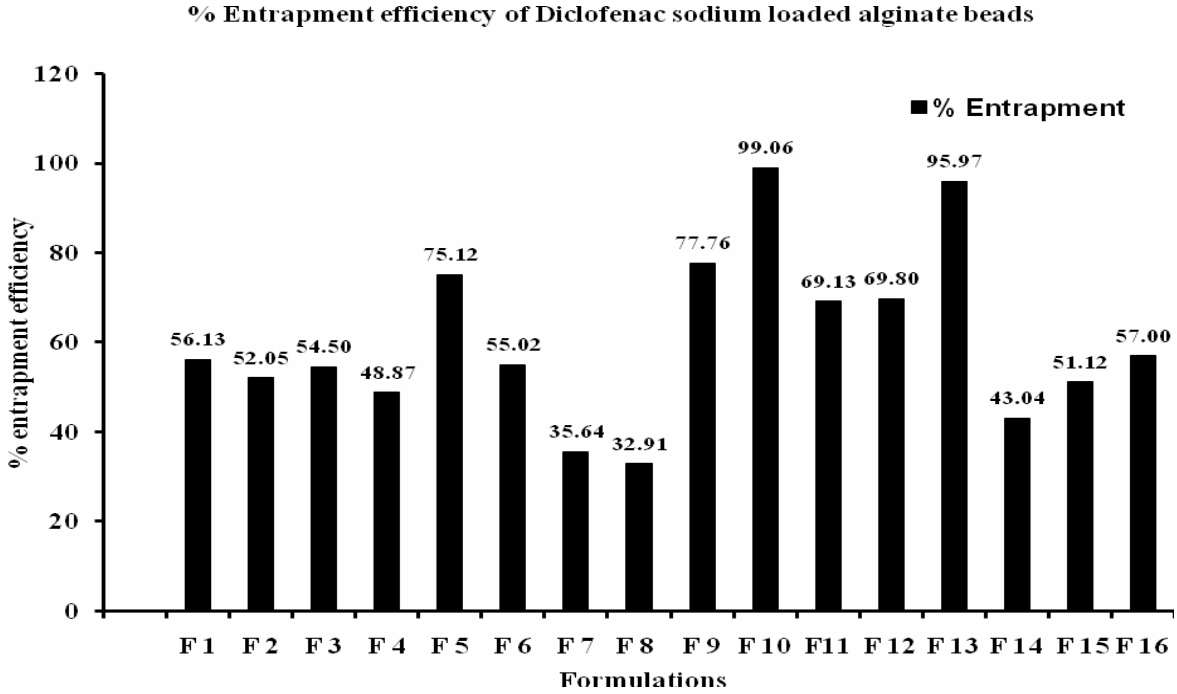

Figure 1. Percent entrapment efficiency of Diclofenac sodium loaded alginate beads

Table 1. Correlation coefficient and release rate of Diclofenac sodium loaded alginate beads

Batch No.	Alginate : Drug	% of electrolyte	Correlation coefficient (r^2)			Release Rate		
			Zero order	Higuchi	First order	Zero order	Higuchi	First order
F-1	1:1	5	0.83	0.94	0.89	0.18	3.87	0.0013
F-2	2:1	5	0.82	0.95	0.88	0.16	3.40	0.0011
F-3	2.5:1	5	0.83	0.96	0.88	0.14	3.02	0.0009
F-4	3:1	5	0.76	0.93	0.81	0.12	2.62	0.0007
F-5	3.5:1	5	0.84	0.95	0.87	0.11	2.45	0.0007
F-6	2:2	5	0.99	0.86	0.94	1.24	12.80	0.0079
F-7	2:2	10	0.84	0.94	0.88	0.16	3.42	0.0011
F-8	2:2	15	0.95	0.80	0.83	0.11	2.52	0.0007
F-9	1:1	5	0.95	0.80	0.83	0.31	5.16	0.0031
F-10	2:1	5	0.96	0.99	0.99	0.13	2.79	0.0008
F-11	2.5:1	5	0.97	0.92	0.98	0.13	2.57	0.0007
F-12	3:1	5	0.97	0.93	0.97	0.08	1.62	0.0004
F-13	3.5:1	5	0.96	0.86	0.94	0.07	1.39	0.0004
F-14	2:2	5	0.94	0.92	0.85	0.04	0.87	0.0002
F-15	2:2	10	0.53	0.75	0.56	0.03	0.74	0.0001
F-16	2:2	15	0.66	0.88	0.68	0.02	0.51	0.0001

***** F-1 to F-8 has $CaCl_2$ as electrolyte solution and F-9 to F-16 has $Al_2 (SO_4)_3$ as electrolyte solution

Loss on drying study: According to table 2 and figure 2, weight losses was greater for F-7, where the drug-polymer ratio was 2:2 and the concentration of $CaCl_2$ was 10 %. When the drug : polymer ratio was 1:3.5 highest amount of weight was lost i.e. 6.51 gm.

When the $CaCl_2$ concentration was 10 %, then the weight loss of F-7 was about 8.19 gm which was the highest. From figure 3 and table 2, F-9 showed lowest amount of weight loss, whereas F-13 showed highest amount of weight loss. But, weight loss gradually decreased with increasing electrolyte concentration.

Table 3 and figure 4 show that F-13 lost more media than the other formulations which was about 7.98 gm. and F-9 showed the lowest amount of media. Thus, beads formed in $Al_2 (SO_4)_3$ showed that, with increasing polymer amount the beads became more and more hard and less swellable.

Table 2. Data of weight of beads (in gm) when $CaCl_2$ is used

Time (min)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
0	10	10	10	10	10	10	10	10
30	9.52	9.72	9.70	9.06	8.60	8.81	8.50	8.77
60	8.93	8.96	8.82	8.38	7.82	7.21	8.23	8.00
90	8.03	8.36	8.36	7.73	7.14	6.75	6.21	6.13
120	7.71	7.80	7.78	7.14	6.41	6.42	5.40	5.46
150	6.84	6.77	6.91	6.25	5.72	5.88	4.19	4.84
180	6.24	6.30	6.47	5.78	5.09	5.09	3.39	4.04
210	5.75	5.71	6.08	5.45	4.63	3.62	2.65	3.61
240	4.75	4.92	5.64	4.98	4.00	3.43	2.04	3.31
270	4.32	4.27	5.21	4.61	3.49	3.15	1.81	2.81
Total weight loss	5.68	5.73	4.79	5.39	6.51	6.85	8.19	7.19

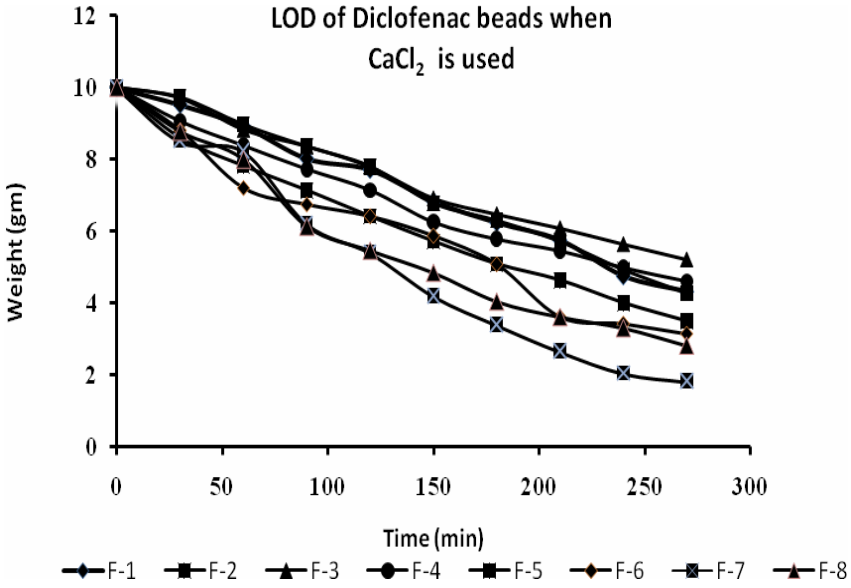

Figure 2. Data of loss on drying of alginate based Diclofenac beads in $CaCl_2$ solution

Table 3. Data of weight of beads (in gm) when $Al_2 (SO_4)_3$ is used

Time(min)	F-9	F-10	F-11	F-12	F-13	F-14	F-15	F-16
0	10	10	10	10	10	10	10	10
30	9.33	8.50	8.24	8.98	8.92	8.06	8.48	8.97
60	8.23	7.91	7.25	8.13	7.79	7.22	7.91	8.32
90	7.78	7.42	6.32	7.12	6.78	6.44	7.27	7.76
120	7.16	6.95	5.52	6.41	5.79	5.95	6.36	6.94
150	6.55	6.46	4.71	5.63	4.89	4.79	5.66	6.22
180	6.14	5.81	3.97	4.88	3.98	4.08	5.13	5.64
210	5.42	5.32	3.43	4.10	3.13	3.43	4.44	5.03
240	4.98	4.94	2.90	3.49	2.66	2.84	3.67	4.30
270	4.29	4.27	2.36	3.15	2.02	2.51	2.85	3.84
Total weight loss	5.71	5.73	7.64	6.85	7.98	7.49	7.15	6.16

Swelling study: Formulations F-1 to F-6 swelled up to 3 hour then eventually swelling decreased from 4th hour. On the other hand, considering varying $CaCl_2$ concentration in F-6, F-7 and F-8, F-6 swelled lowest at 3rd hour (SI of 130 %), then F-7 (155 %) and F-8 (235 %). Thus, when the electrolyte concentration was 15 %, then swelling gradually increased up to 3rd hour with sharp fall in SI after that hour (table 4, figure 4).

Beads formed in $Al_2 (SO_4)_3$ solution showed that F-9 to F-16 swelled up to 3 hour then from 4th hour swelling decreased (table 5 and figure 5). But, in 5th hour again swelling increased. Here, F-9 showed the highest swelling and then swelling eventually decreased with increasing alginate amount. Simultaneously, comparison of swelling index in various $Al_2 (SO_4)_3$ concentrations, F-14 showed lowest swelling index (105 %) at 3rd hour whereas, F-15 and F-16 showed swelling index of 130 % at 3rd hour. Thus, this result showed a similar trend of swelling index as beads formed in $CaCl_2$.

Table 4. Swelling index (%) of alginate based Diclofenac beads in 5 % $CaCl_2$ solution

Time (Min)	Swelling index (%) of formulations					
	F 1	F 2	F 3	F 4	F 5	F 6
0	0	0	0	0	0	0
1	230	290	330	295	245	230
2	255	470	545	590	560	270
3	260	450	525	570	530	260
4	95	175	235	290	250	170
5	65	85	125	205	215	105
6	60	70	130	60	40	15

Table 5. Data of swelling index of alginate based Diclofenac beads in 5 % $Al_2 (SO_4)_3$ solution

Time (Min)	Swelling index (%) of formulations					
	F 9	F 10	F 11	F 12	F 13	F 14
0	0	0	0	0	0	0
1	150	140	110	100	85	90
2	185	130	95	90	55	40
3	150	140	135	130	110	105
4	105	135	125	115	110	55
5	115	90	85	50	40	45
6	110	70	60	55	25	30

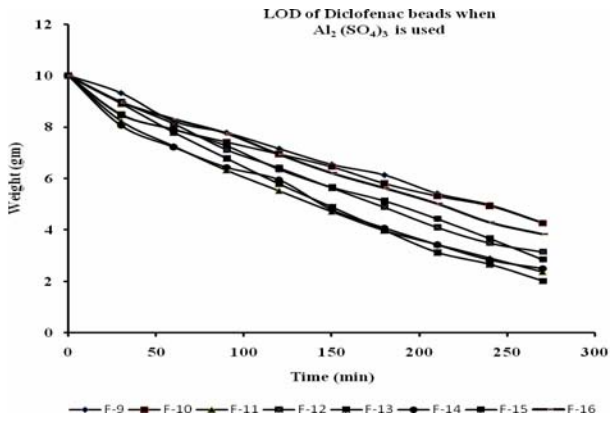

Figure 3. Data of loss on drying of alginate based Diclofenac beads in $Al_2 (SO_4)_3$ solution

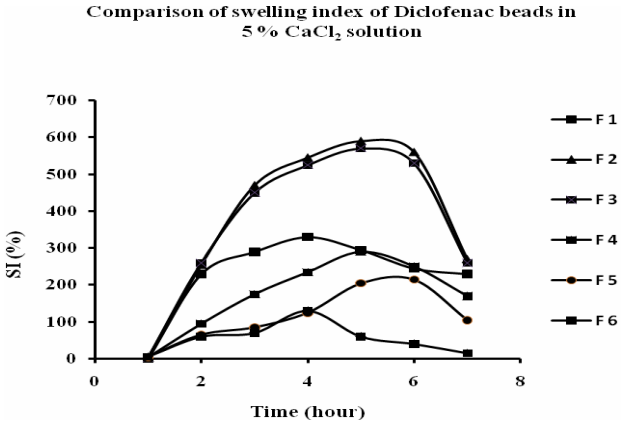

Figure 4. Comparison of swelling index of alginate based Diclofenac beads in 5 % $CaCl_2$ solution

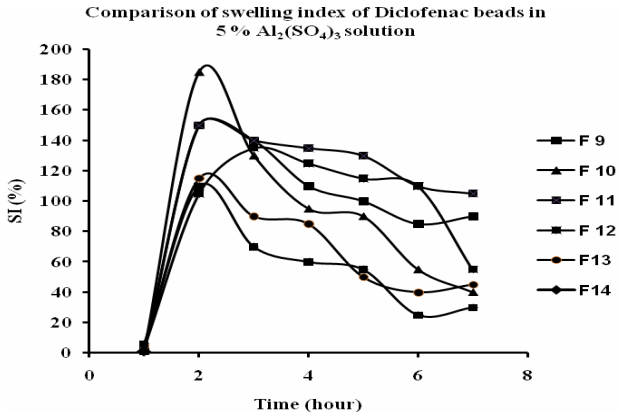

Figure 5. Comparison of swelling index of alginate based Diclofenac beads in 5 % $Al_2 (SO_4)_3$ solution

In vitro release kinetics

(a) Evaluation of diclofenac sodium beads in $CaCl_2$ solution: The release of drug decreased with increasing drug loading. After six hours the percent of drug release for six formulations were 64.90 % (F-1), 58.36 % (F-2), 52.13 % (F-3), 46.30 % (F-4), 41.25 % (F-5) and 226.06 % (F-6). The decrease in drug release was due to simultaneous increase in alginate amount. Because the more the amount of alginate, the more the cross-linking between sodium alginate and calcium chloride, thus more drug remained entrapped and release decreased. Alderman reported that when the hydrophilic matrix tablet enters an *in vitro* dissolution medium, drug particles initially pass into solution from the surface (immediate release). The solid matrix also begins to swell (polymer relaxation) as soon as hydration with solvent molecules, diffusion of the dissolved drug and erosion of gelatinous viscous polymer layer into aggregates of granules and these in turn

disaggregates into fine particles that release their drug content by dissolution (Alderman, 1984).

It is observed from table 1 that drug release was increased with decreasing the concentration of calcium chloride which was observed in F-1, F-6, F-7 and F- 8. When cross linking is properly occurred by the increasing amount of calcium chloride, calcium alginate entrapped much drug precisely. Among formulation 1 to 8, F-1 to F-5 and F-7 follows Higuchi release because the correlation coefficient (r^2) value indicates linearity. But, F-6 and F-8 follows zero order release kinetics.

(b) Evaluation of Diclofenac sodium beads in $Al_2(SO_4)_3$ solution: The formulations, F-9, F-15 and F-16 with 5 %, 10 % and 15 % $Al_2(SO_4)_3$ concentration shows percent release of 90.90 %, 15.66 % and 9.8 % respectively. The high amount of aluminium sulphate ensures the maximum cross-linking sodium alginate with aluminium sulphate which augments the conversion of sodium alginate to aluminium alginate. The effect of increasing alginate amount created the decrease in drug release in F-9 to F-13. Thus, both the electrolytes produce more or less same style regarding percent drug release and drug release rate. But, anomaly is in drug release pattern. Formulations with $Al_2(SO_4)_3$ follows zero order kinetics (F-9, F-12, F-13, F-14), higuchi kinetics (F-15, F-16) and first order kinetics (F-10, F-11).

Conclusion

The entrapment efficiency, swelling and release behaviors of Diclofenac sodium loaded alginate beads were investigated in this study. Cross linked alginate beads of Diclofenac sodium were prepared by changing concentration of calcium chloride and aluminium sulphate. Divalent calcium beads showed more drug release when compared to trivalent aluminium beads. Both the drug entrapment efficiency and release rate decreased with increasing drug and polymer amount. However, further studies should be carried out to check the reproducibility of beads by using *in-vitro-in-vivo* correlation. This will help to get information about the efficacy of sodium alginate beads of Diclofenac sodium.

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