Bangladesh Pharmaceutical Journal ***15****(1): 53-57, 2012*

Effect of Barium Chloride as A Cross Linking Agent on the Sodium Alginate Based Diclofenac Sodium Beads

Md Masud Morshed[1], Jewel Mallick[2], Aninda Kumar Nath[2], Md Zia Uddin[2], Mycal Dutta[2], Md Akbar Hossain[1] and Md Hassan Kawsar[1]

[1]Department of Pharmacy, Dhaka International University, Dhaka-1213, Bangladesh
[2]Department of Pharmacy, BGC Trust University Bangladesh, Chittagong, Bangladesh

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, $BaCl_2$ 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 percent entrapment was highest when beads were prepared with 5 % electrolyte solution. In case of $BaCl_2$ solution the highest entrapment efficiency was 73.70 % when the amount of polymer was 2.5 gram. The swelling study revealed that, up to sixth hours, the formulations swelled high, with few exceptions. In case of loss on drying of beads after formation showed that, the rate of solvent loss upto three hours eventually remained increasing but then decreased. *In vitro* dissolution data showed that drug release was increased with decreasing concentration of $BaCl_2$. The high amount of $BaCl_2$ ensures the maximum cross linking sodium alginate with $BaCl_2$ which augment the conversion of sodium alginate to barium alginate. With increasing drug, polymer and electrolyte amount the Diclofenac release percentage also decreased. Thus, by modification of the polymer amount and selection of cross linking agent play vital role in efficiency and sustained-release characteristics.

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

Introduction

Sodium alginate has been used as a matrix material to achieve a 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 incorporated 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).

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.

Correspondence to: Md Hassan Kawsar; E-mail: hassankawsar@yahoo.com

Materials and Methods

Diclofenac sodium was obtained from Hugestone Enterprise Co. Ltd, China. Sodium alginate was procured from Loba Chemie, India. Calcium chloride and Aluminium sulphate was 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 amount of 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, % weight gain by the beads was calculated by the following formula (Yeole *et al*., 2006):

$$\text{Swelling Index (SI)} = \{\frac{Wt - Wo}{Wo}\} \times 100$$

Here, 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 $\lambda_{max\ of}$ 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:

$$\text{LogC} = \text{Log}C_o - kt/2.303 \quad \text{…… (3)}$$

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 percentages of entrapment are given in in figure 1 and table 1 from which it can be concluded that in case of $BaCl_2$ with the increment of Drug-Polymer ratio the entrapment efficiency of drug decreased when the concentration was

5%. In case of F-1 the % entrapment was 73.38% when the drug and alginate ratio was 1:1 and the $BaCl_2$ concentration was 5%. But it was only 65.28% in F-5 where the drug and sodium alginate ratio was 1:3.5 and the concentration of $BaCl_2$ was same. Whereas, with the increment of $BaCl_2$ concentration the entrapment efficiency of drug become increased when the drug-polymer ratio was same. i.e. in case of F-6,F-7 and F-8 the % entrapment was 42.03%,54.1% and 71.1% and the $BaCl_2$ concentration was 5%,10% and 15% respectively, where the corresponding drug and alginate ratio was 2 : 2.

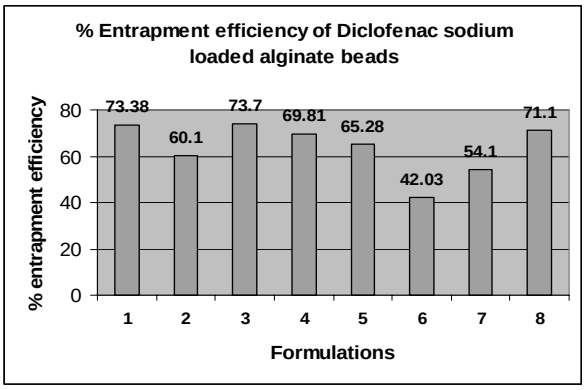

Figure 1. Percent entrapment efficiency of Diclofenac sodium loaded alginate beads.

Table 1. Correlation coefficient and release rate of Diclofenac sodium loaded alginate beads using $BaCl_2$

Batch No.	Alginate: Drug	% electrolyte	Correlation coefficient (r^2)			Release rate		
			Zero order	Higuch	First order	Zero order	Higuchi	First order
F-1	1.0 : 1.0	5	0.982	0.9529	0.8996	0.275	5.52	0.003
F-2	2.0 : 1.0	5	0.955	0.953	0.993	0.222	4.519	0.001
F-3	2.5 : 1.0	5	0.986	0.928	0.993	0.130	2.575	0.000
F-4	3.0 : 1.0	5	0.978	0.957	0.987	0.078	1.578	0.000
F-5	3.5 : 1.0	5	0.959	0.970	0.970	0.059	1.217	0.000
F-6	2.0 : 2.0	5	0.890	0.902	0.890	0.027	0.553	0.000
F-7	2.0 : 2.0	10	0.996	0.9275	0.9724	0.164	3.230	0.0011
F-8	2.0 : 2.0	15	0.983	0.884	0.9623	0.124	2.4059	0.0007

Here, F-1 to F-8 have $BaCl_2$ as electrolyte solution.

According to Lannuccelli *et al*. (1998), 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).

Loss on drying study: According to table 2 and figure 2 weight losses is greater for F-3, where the drug-polymer ratio is 1: 2.5 and the concentration of $BaCl_2$ is 5 %. On the other hand, the rate of weight loss is decreased in F-5 & F-7 when the drug-polymer ratios are 1:3.5 and 2:2 & the concentration of $BaCl_2$ are 5% and 10% respectively. When the drug: polymer ratio is 1:2.5 highest amount of weight is lost i.e. 8.33 gm. When the $BaCl_2$ concentration is 10 %, then the weight loss of F-7 is about 5.51 gm. F-5 and F-7 shows lowest amount of weight loss i.e. 5.51gm , whereas F-3 shows highest amount of weight loss i.e. 8.33 gm. But, weight loss gradually decreases with increasing electrolyte concentration.

Table 2. Loss on Drying of beads (in gm) when $BaCl_2$ was used

Time (min)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
0	10g	10 g	10 g	10 g	10 g	10 g	10 g	10 g
30	8.56g	9.00g	8.51g	9.24g	9.20g	9.33g	9.37g	9.42g
60	7.82g	8.36g	7.41g	8.58g	8.64g	8.56g	8.64g	8.71g
90	7.13g	7.67g	6.26g	7.75g	8.13g	7.93g	8.13g	8.19g
120	6.41g	6.69g	5.20g	7.08g	7.53g	6.67g	7.53g	7.45g
150	5.78g	6.05g	4.21g	6.45g	7.04g	5.68g	7.04g	6.84g
180	5.08g	5.41g	3.61g	5.70g	6.33g	4.52g	6.33g	6.16g
210	4.68g	4.84g	2.77g	5.05g	5.81g	3.83g	5.81g	5.39g
240	4.01g	4.33g	1.97g	4.37g	5.19g	3.29g	5.19g	4.61g
270	3.52g	3.81g	1.67g	3.62g	4.49g	2.71g	4.49g	4.06g
Total weight loss	**6.48**	**6.19**	**8.33**	**6.38**	**5.51**	**7.29**	**5.51**	**5.94**

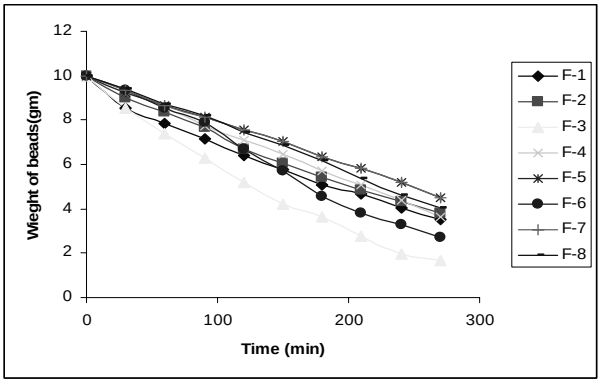

Figure 2. Loss on drying of alginate based Diclofenac beads in $BaCl_2$ solution

Swelling Study: The formulation F-2 to F-5 swelled up to 6 hour. On the other hand, considering varying $BaCl_2$ concentration in F-6, F-7 and F-8, F-6 swelled lowest at 3rd hour (SI of 470 %), then F-7 (445 %) at 5th

hour and F-8 (150 %) at 6th hour. Thus, when the electrolyte concentration is 15 %, then swelling gradually increases up to 6th hour (table 3, figure 3). Here, Alginate based F-2 swelled high up to 6 hour. Thus F-2 showed the highest swelling where the $BaCl_2$ concentration was 5 %, when the drug-polymer ratio was 1:2. On the other hand, Alginate based F-8 having swelling capacity less in comparison to other formulations within 6 hour. Thus, F-8 showed the lowest swelling where the $BaCl_2$ concentration was 15 %, when the drug-polymer ratio was 2:2.

Table 3. Swelling index (%) of alginate based Diclofenac beads in 5% $BaCl_2$ solution

Time (min)	Swelling index (%) of formulations							
	F 1	F 2	F 3	F 4	F 5	F 6	F7	F8
0	0	0	0	0	0	0	0	0
1	45	40	25	75	25	110	30	15
2	215	175	125	165	120	310	140	50
3	**340**	390	265	290	235	**470**	300	85
4	200	460	285	325	240	370	320	100
5	145	675	520	385	425	310	**445**	130
6	50	**830**	**675**	**580**	**610**	500	405	**150**

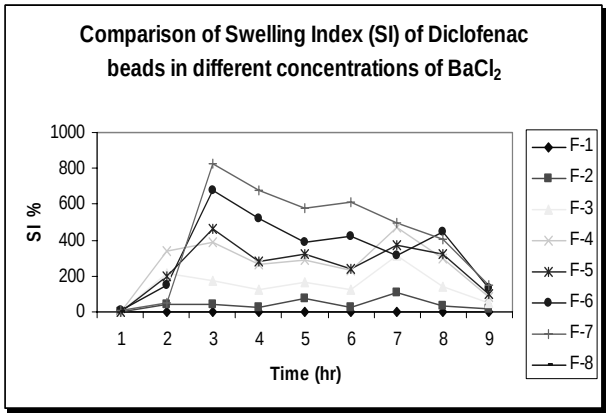

Figure 3. Comparison of swelling index of alginate based Diclofenac beads in 5%, 10% and 15% $BaCl_2$ solution.

In vitro release kinetics

Evaluation of diclofenac sodium beads in $BaCl_2$ solution: The release of drug decreased with increasing drug loading. After six hours the percent of drug release for eight formulations were 96.58 % (F-1), 75.68 % (F-2), 44.95 % (F-3), 27.59 % (F-4), 21.60 % (F-5), 12.57 % (F-6), 62.00 % (F-7), 47.30 % (F-8). *In-vitro* release data to see the effect of polymer load on the release of Diclofenac sodium from alginate beads using $BaCl_2$ solution (Table 4; Figure 4) and *in vitro* release data of DS beads to see the effect of $BaCl_2$ concentration (Table 5; Figure 5) are studied separately. 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 barium chloride thus more drug remained entrapped and release decreased.

Table 4. Effect of polymer concentration on *in vitro* release kinetics of Diclofenac sodium from alginate beads using $BaCl_2$ solution

Time (min)	F 1	F 2	F 3	F 4	F 5	F 6
0	0.00	0.00	0.00	0.00	0.00	0.00
30	7.45	6.71	4.15	3.56	3.01	2.48
60	18.60	15.70	5.94	5.21	5.00	4.76
120	42.46	36.33	15.66	12.35	11.35	5.64
180	59.70	54.63	27.51	18.00	14.40	6.64
240	73.36	63.13	33.74	21.20	17.35	7.00
300	84.53	70.15	38.97	25.00	18.83	8.11
360	96.58	75.68	44.95	27.59	21.60	12.57

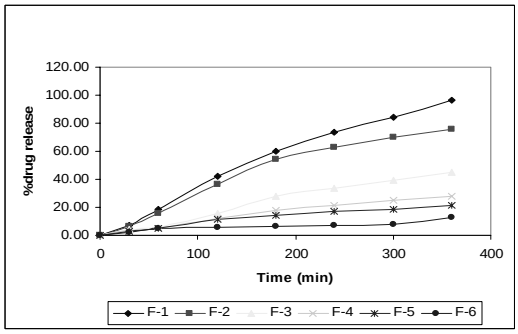

Figure 4. Effect of polymer concentration on the drug release pattern from Diclofenac sodium beads

Table 5. Effect of $BaCl_2$ concentration on *in vitro* release kinetics of DS beads

Time (min)	**F 1**	**F 7**	**F 8**
0	0.00	0.00	0.00
30	7.45	7.55	6.70
60	18.60	11.30	8.70
120	42.46	22.82	12.25
180	59.70	30.00	20.70
240	73.36	39.30	28.00
300	84.53	50.00	38.28
360	96.58	62.00	47.30

Alderman reported that when the hydrophilic matrix tablet enters to 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).

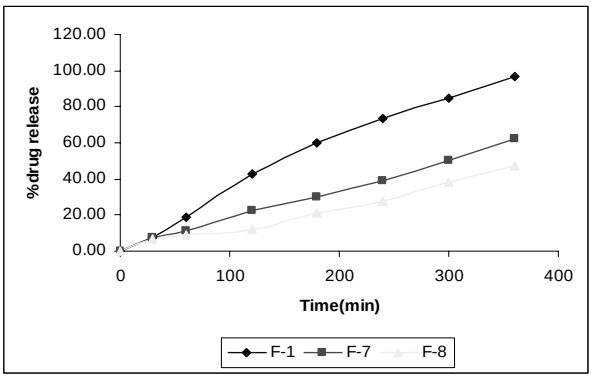

Figure 5. Percentage of release versus time curve to see the effect of $BaCl_2$ concentration.

It is observed from correlation coefficient table that, among F-1 to F-8, F-2 to F-5 follows First order release because the correlation coefficient (r^2) value indicates linearity. But, F-1, F-7, F-8 follows zero order release and F-6 follows Higuchi release.

References

Alderman, D.A. 1984. A review of cellulose ethers in hydrophilic matrices for oral controlled release dosage forms. *Int. J. Pharm. Techol. Prod. Manuf.* **5**, 1-9.

Chien, Y.W. 1991. Controlled and modulated-release drug delivery systems (New York: Marcel Decker Inc), 3rd edition.

Dhanaraju, M.D., Sundar, V.D., NandhaKumar, S. and Bhaskar, K. 2009. Development and evaluation of sustained delivery of diclofenac sodium from hydrophilic polymeric beads. *J. Young Pharmaceutics.* **1**, 301-304.

Donbrow, M. and Samuelov, Y. 1980. Zero order drug delivery from double-layered porous films: release rate profiles from ethylcellulose, hydroxypropylcellulose and polyethylene glycol mixtures. *J. Pharm. Pharmacol*. **32**, 463-470.

Higuchi, T. 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci*. **50**, 874-875.

Higuchi, T. 1963. Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.* **52**, 1145 -1149.

Kikuchi, A., Kawabuchi, M., Sungihara, M. and Okano, T.S. 1997. Pulsed dextran release from calcium alginate beads. *J. Control. Release*. **47**, 21-9.

Kikuchi, A. and Okano, T. 2002. Pulsatile drug release control using hydrogels. *Adv. Drug Delivery Rev.* **54**, 53-77.

Lannuccelli, V., Coppi, G., Bernabel, M.T. and Cameroni, R. 1998. Air compartment multiple-unit system for prolonged gastric residence. Part I: Formulation study. *Int. J. Pharm*. **174**, 47-54.

Lin, S.Y. and Kao, Y.H. 1991. Tablet formulation study of spray-dried sodium diclofenac enteric-coated micro-capsules. *Pharm. Res*. **8**, 919-24.

Okada, M., Suzuki, M., Ono, K., Kasai, S. and Iwasa, A. 1996. Dissolution mechanism and optimization of enteric coated long acting diclofenac sodium preparation. *Proc. Int. Symp. Control Rel. Bioact. Mater*. **23**, 559-60.

Ojantakanen, S., Hannula, A.M., Marvola, M., Klinge, E. and Makioaa, M. 1993. Bioavailability of ibuprofen from hard gelatin capsules containing sucralfate or sodium alginate. *Eur. J. Pharm. Biopharm.* **39**, 197-201.

Pawar, P.A., Gadhe, A.R., Venkatachalam, P., Sher, P. and Mahadik, K.R. 2008. Effect of core and surface cross-linking on the entrapment of metronidazole in pectin beads. *Acta Pharm*. **58**, 75–85.

Sankalia, M.G., Mashru, R.C., Sankalia, J.M. and Vijay, B.S. 2005. Papain entrapment in alginate beads for stability improvement and site-specific delivery: physicochemical characterization and factorial optimization using neural network modeling. *AAPS Pharm. Sci. Tech.* **6**, 31.

Scholer, D.W. Ku, E.C. Boettacher, I. and Schweizer, A. 1986. Pharmacology of diclofenac sodium. *Am J Med.* **80**, 34-8.

Stockwell, A.F., Davis, S.S. and Walker, S.E. 1986. *In vitro* evaluation of alginate gel systems as sustained release drug delivery systems. *J. Control Release.* **3**, 167-175.

Torres, D., Garcia-Encina, G., Seijo, B. and Vila-Jato, JL. 1995. Biopharmaceutical evaluation of microencapsulate ion-exchange resins containing diclofenac. *Eur. J. Pharm. Biopharm.* **41**, 127-31.

Tripathi, K.D. 1998. Delhi: Essential of medical pharmacology (Jaypee Brothers Medical Publishers Ltd.) 4th edition.

Veski, P. and Marvola, M. 1993. Sodium alginate as diluents in hard gelatin capsules containing ibuprofen as a model drug. *Pharmazie*. **48**, 757-760.

Veski, P., Marvola, M., Smal, J., Heiskanen, I. and Jurjenson, H. 1994. Biopharmaceutical evaluation of pseudoephedrine hydrochloride capsules containing different grades of sodium alginate. *Int. J. Pharm.* **111**, 171-179.

Vilivalam, V.D. and Adeyeye, C.M. 1994. Development and evaluation of controlled-release diclofenac microspheres and tabletted microspheres. *J. Microencapsul.* **11**,455-70.

Yeole, P.G., Galgatee, U.C., Babla, I.B. and Nakhat, P.D. 2006. Design and evaluation of xanthan gum based sustained release matrix tablets of Diclofenac Na. *Indian J. Pharm. Sci.* **68**, 185-189.