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Research Article

ORAL CONTROL RELEASE MICROPARTICULATE DRUG DELIVERY STUDY OF ACECLOFENAC USING NATURAL POLYMER

SUNIL KUMAR SHAH*, CHANDRA KISHORE TYAGI, DEENANATH JHADE, PRIYANKA PANDEY

Department of Pharmaceutics, College of Pharmacy, Sri Satya Sai University of Technology & Medical Sciences, Sehore, Madhya Pradesh, India. Email-sunilph86@gmail.com

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ABSTRACT

Objective: The present study was to prepare controlled release microsphere of aceclofenac using sodium alginate as a natural polymer.

Methods: Microspheres of the Aceclofenac sodium by ionotropic gelation technique using sodium alginate as hydrophilic carrier and three different cross-linking agent in various proportions and different condition drying, and examines the influences of various process such as drugs polymer ratio, different concentration of cross linkage agents, drying condition, and cross-linking time on physicochemical properties of drug loaded microbeads.

Results: Formulated drug loaded microbeads were investigated for physicochemical properties and drug release potential. All investigated properties showed satisfactory results. While increasing in the concentration of sodium alginate, and barium chloride cross-linking time increased sphericity, size distribution, flow properties, mean particle size, swelling ratio, and drug entrapment efficiency. No significant effect of drug polymer interactions was observed in Fourier transform infrared studies. The drug entrapment efficiency obtained in the range of 97.59-99.88. The particle size of drug loaded formulations was measured by an optical microscope. The mean particle size of drug-loaded microbeads was found to be in the range 948.555±1.673 to 998.41±0.428. The shape and surface characteristics were determined by scanning electron microscopy using gold sputter technique. *In-vitro* drug release profile of aceclofenac sodium from microbeads was examined in simulated gastric fluid pH 1.2 for initial 2 hrs mixed phosphate buffer pH 6.8 up to 6 hrs and simulated intestinal pH 7.4 at the end of 24 hrs studies. The release of drug from the microbeads was pH dependent, showed negligible drug release in pH 1.2. Under pH 7.4 conditions the beads will swell, and the drug release depends on the swelling and erosion process resulting the optimum level of drug released in a sustained manner and exhibited zero-order kinetics.

Conclusion: Result of studies this system was able to prolong the drug release, minimizing the drug-related adverse effects and improve bioavailability in different GI-tract conditions.

Keywords: Controlled drug delivery, Aceclofenac sodium, Sodium alginate, Ionotropic gelation.

INTRODUCTION

For many decades treatment of an acute diseases or illness has been mostly accomplished by delivery of drugs to the patients by various conventional delivery system which is known to provide a prompt release of drugs, to achieve as well as maintain drug concentration within the therapeutic effective range, it is often necessary to take several times a day which result in significant fluctuation in drug level. The therapeutic nature of the drugs dictates the methods of administration, for, e.g., oral drug delivery may be the most logical choice for gastrointestinal disease. If the drug release is systemic, and then the choice of method often relies on the physiological and the therapeutic properties of the drug molecules. Transdermal drug delivery although having the advantages of being noninvasive, it has to meet several criteria such as high potency, ready permeability through stratum cornea and non-irritation [1]. The drug delivery method is chosen drug, the desired site of action, the biological barrier including drug metabolism that must be overcome to deliver the drug. The most common based on the physiochemical properties of parental, transdermal, ophthalmic, nasal, rectal and anal each delivery route involves special challenges and requirements for proper and safe administration of drugs. Recently several technical advancements have been made which resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, and or targeting the delivery of drug to tissues.

The current trend points to an increasing interest in the use of natural substances in food, drugs and cosmetics. The naturally occurring alginate polymers have a great potential in drug formulation due to their extensive application as food additives and their recognized lack of toxicity. Alginate is a nostalgic term for dietetic, biotechnology, cosmetic, and pharmaceutical industries. As this group of polymers possesses a number of characteristics that makes it useful as a formulation aid, both as conventional excipients and more specifically as a tool in polymeric controlled drug delivery [1].

an oral sustained/controlled release drug delivery system should be able to achieve optimum therapeutic drug concentration in the blood with minimum fluctuation, to predict and reproduce release rates for extended duration, to enhance pharmacotherapy of short half-life drugs, to reduce frequent dosing, minimize/or eliminate dose related adverse effects, improving therapy, safety, efficacy, and better patient compliance [2]. The use of microbeads systems for controlling the release of drugs has increasingly well-known respond to surrounding conditions such as pH, ionic strength, temperature and frequent changes of environment in the gastrointestinal-tract, which has a variation of pH from the stomach to intestine. Microbeads from natural polymers, especially polysaccharides have been widely used of their advantageous properties over biocompatibility, biodegradability ability to modify the properties of the aqueous environment, the capacity to thicken, emulsify, stabilize, encapsulate, and swell to form gels, films. Alginate is one the natural polysaccharide that has been widely used in numerous biomedical applications. Sodium alginate is a salt of alginic acid; a natural polysaccharide found in all species of brown algae and certain species of bacteria. It is a linear polymer of ß (1-4) mannuronic acid (M) and a (1-4) guluronic acid (G) residues in varying proportions and arrangements. It has been shown that the G and M units are joined together [3].

MATERIALS AND METHODS

Aceclofenac sodium was a gift sample from gift sample from Cipla Ltd., Indore. Sodium alginate gift sample from Loba Chemie Pvt. Ltd., India, All other reagents and calcium chloride (Qualigens Fine Chemical, Glaxo Smithkline Pharmaceutical) Barium chloride (Qualigens Fine Chemical, Glaxo Smithkline Pharmaceutical) aluminum sulfate (Oxford Laboratories Ltd., solvents used were of analytical grade satisfying pharmacopoeial specifications.

Preparation of aceclofenac sodium-alginate microbeads

The microbeads were prepared by inotropic external gelation using the formulation as shown in Table 1. Sodium Alginate was dissolved in deionized water at a concentration 1-2% w/v. using gentle heat and magnetic stirring on complete solution, an accurately weighed quantity of Aceclofenac sodium was added dispersion uniformly [4]. The dispersion was sonicated for 30 minutes to remove any air bubbles that may have been formed during the stirring process. The bubble free sodium alginate drug dispersion (50 ml) were added dropwise via a 18-guage hypodermic needle fitted with 10 ml glass syringe into 50 ml of 2, 4, 6, 8% w/v of cross-linking agents being stirred at 200 rpm, respectively. The cross-linking agents were used $CaCl_2$, $Al_2(SO_4)_3$ and $BaCl_2$. The formed gel beads were harvested for 12 hrs, an excess of cross-linking agent was washed out with deionized water. Then, alginate beads were separated by filtration and air-dried for 48 hrs. Like that beads containing drug polymer ratio 1:1 cross linked with 4% $CaCl_2$, $Al_2(SO_4)_3$ and $BaCl_2$, respectively, dried at 50°C for 12 hrs in a hot-air oven. All batches were in triplicates [6-8].

F_{12}, F_{13}, and F_{14} were the codes given to the formulations prepared in the same way as that of F_2, F_6, F_9 formulation, respectively, but contained polymer to drug ratio 32:1. Like that formulations exposed to oven drying were assigned as $F_3O(1)$, $F_3O(2)$, $F_3O(3)$ using 4% cross-linking agent $BaCl_2$, $Al_2(SO_4)_3$, $CaCl_2$, respectively with drug polymer ratio 1:1 [7-9].

Measurement of micromeritic properties

Determination of bulk density and tapped density

An accuracy weighed quantity of drug crystals and prepared microspheres were carefully poured into the graduated cylinder (10 ml). The initial volume was measured. The graduated cylinder was tapped for 100 times. After that, the volume was measured [10].

Bulk density = W/V_o

Tapped density = W/W_F

Where W = Weight of the formulation:

V_0 = Bulk volume

Table 1: Formulation of alginate beads

Formulation code	Sodium alginate (g)	Drug (g)	Cross-linking agents (%)
F_1	1	1	2 $BaCl_2$
F_2	1	1	4 $BaCl_2$
F_4	1	1	6 $BaCl_2$
F_5	1	1	2 $Al_2(SO_4)_3$
F_6	1	1	4 $Al_2(SO_4)_3$
F_7	1	1	6 $Al_2(SO_4)_3$
F_8	1	1	2 $CaCl_2$
F_9	1	1	4 $CaCl_2$
F_{10}	1	1	6 $CaCl_2$
F_{11}	1	1	8 $CaCl_2$

W_F = Tapped volume

Bulk and Tapped density expressed in gm/ml.

Carr's index or compressibility index:

Carr's index = (Tapped density-bulk density/tapped Density) × 100.

Grading of the powders for their flow properties according to the Carr's index.

Packing Factor/Hausner Ratio: It indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density.

Hausner ratio = Tapped density/bulk density.

Particle size determination of beads

Beads were separated into different size fractions by sieving for 5 minutes using standard sieves having nominal mesh apertures of 1.0 mm, 0.71 mm, and 0. 5 mm (sieve no. 16, 22 and 30, respectively). The particle size distributions of the beads were determined and mean particle sizes of beads were calculated [11-13].

Swelling study of individual beads

Swelling property of the beads was studied by the measurement of the percentage of water uptake at the end of 24 hrs. The pre-weighed dry beads were immersed in H_2O, 0.1N HCl (pH-1.2) and in phosphate buffer pH 7.4. At room temperature and weighed changed were mentioned after 24 hrs. The % of water uptake was calculated by the formula:

Percentage of water uptake = (Wet weight-dry weight/dry weight) × 100

Drug entrapment efficiency

About 25 mg of accurately weighed drug-loaded alginate beads were added to 50 ml of phosphate buffer of pH 7.4. The resulting mixture was kept shaking on mechanical shaker for 24 hrs. Then after the solution was filtered, the drug content was estimated at 274 nm spectrophotometrically after appropriate dilution with phosphate buffer pH 7.4. The drug entrapment efficiency was determined using the relationship

Drug entrapment efficiency = (Experimental drug content/theoretical drug content) × 100.

Results were based on the triplicate determination [5].

In-vitro drug release study

The *in-vitro* release of Aceclofenac from the alginate beads was monitored in phosphate buffer pH 7.4 at 37°C±1°C using USP basket type dissolution rate test apparatus (Rolex Laboratories). An accurately weighed amount of alginate beads were stirred in 900 ml dissolution medium at 100 rpm. Samples were withdrawn at a predetermined time interval and were replenished immediately with the same volume of fresh medium. Aliquot's, following suitable dilution, were analyzed spectrophotometrically at 274 nm. The concentrations of Aceclofenac in test samples were corrected for sampling effect [15,17].

Release Kinetics

Data obtained from *in vitro* release studies were fitted to various kinetic equations to find out the mechanism of drug release from alginate beads. The kinetic models used were Korsemeyer–Peppas model and modified Korsemeyer–Peppas model, Zero order model

Korsmeyer–Peppas Model

Korsemeyer developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time(t), which can be described as:

$M_t/M_\infty = kt^n$

Where M_t/M_∞ is the fraction of the drug released at time 't' and 'k' is the rate constant and 'n' is the release exponent. To determination the exponent 'n', the portion of the release curve, where $M_t/M_\infty < 0.6$, should only be used. Peppas used this 'n' value to characterize different release mechanisms, This model can be used to analyze the release of drug from pharmaceutical dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved.

Modified Korsemeyer–Peppas model

A modified form of the above equation was developed by Korsmeyer and Peppas to accommodate the lag time (t_{lag}) in the beginning of the drug release from the pharmaceutical dosage form:

$M_t/M_\infty = k(t-t_{lag})^n$

or, it's logarithm version:

$\log M_t/M_\infty = \log k_1 + n \log(t-t_{lag})$

Where, is the constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of drug release mechanism.

Classically, in both the above cases (korsmeyer-Peppas model and the modified form this model), the 'n' value depicted in table is indicative of release kinetics.

Infrared (IR) study

IR spectra of aceclofenac, blank alginate beads and drug loaded alginate beads cross-linked with different metals ions were obtained at room temperature in KBr pellets using a Varian Resolution spectrophotometer between the ranges of 500-6500 cm^{-1} sampling effect [18].

Scanning electron microscopy (SEM)

JEOL, JSM-6360, SEM was used to characterize surface topography of the alginate beads. The beads were placed on a metallic support with a thin adhesive tape, and the samples were coated with gold under vacuum (fine coat, ion sputter, JFC-1100) to render them electrically conductive. The surface was screened, and photomicrographs were taken at 15 kV and 20 kV for the drug-loaded beads cross-linked with different metal ions [19,20].

RESULTS AND DISCUSSION

Flow property of beads

Compressibility index, the packing factor of various formulations was compared with the pure drug. The higher the percentage of compressibility index lesser the flow property [22]. Among the various formulations $F_3(O)2$ has the highest compressibility index and F_1 has low compressibility than other formulations. Hence, drug exhibit high compressibility index and $F_3(O)2$ exhibit low flow property as compared to other formulations but F_1 show excellent flow property. In comparison to drug the various formulations shows the excellent flow property, i.e., lies between 1 and 15 as shown in Table 2.

In the case of packing factor, all the formulations compared with pure drug. The pure drug has more packing factor as compared to other formulations. All the formulations have shown the free flowing nature. Among all the formulations F_1 shows the lowest packing factor that it indicates this formulation exhibit free flow property. But formulation containing $F_3(O)2$ shows the more packing factor as compared to other formulations. So it shows less free-flowing property [21].

Mean particle size

The formed beads of all formulation were more or less spherical in nature. The mean particle size of the formulation was between 948.555±0.1673 mm and 998.41±0.428 as shown in Table 2. It was found that with increase in sodium alginate conc. the mean particle size of beads increases [16]. This may be due to increase in viscosity which in turn increases droplet size during addition of the polymer solution to the cross-linking agent solution. The nature of drying also influences the particle size of the beads. When size of oven dried beads cross-linked with 4% $BaCl_2$(F_3) was compared with that of air dried beads (F_2), it was found that over drying produced small beads as compared to air drying. This may be due to the fact that air drying leaves water particle inside the beads as a result of partial dehydration, which may increase its size.

Swelling characteristics of dried beads

Being a polyelectrolyte, alginate exhibits swelling properties that are sensitive to pH, ionic strength and ionic composition of the medium. The percentage of swelling was found to be depending on the nature of cross-linking agents and pH of the solution as shown in Table 3.

When the percentage of swelling of the various formulations were compared, it was found that the lowest percentage of swelling was

Table 2: Determination of bulk density, tapped density, compressibility index, packing factor

Formulation code	Polymer drug ratio	Bulk density	Tapped density	Compressibility index (%)	Packing factor	Mean particle size in (μ)
F_1	1:1	0.705±0.012	0.715±0.011	1.3±0.006	1.0141±0.006	992.51±0.829
F_2	1:1	0.567±0.004	0.607±0.005	6.58±0.004	1.0705±0.006	996.26±0.367
$F_3(O)$	1:1	0.783±0.007	0.829±0.014	5.5±0.008	1.058±0.004	949.28±0.680
F_4	1:1	0.782±0.011	0.8255±0.011	5.21±0.011	1.054±0.06	992.63±0.526
F_5	1:1	0.603±0.012	0.644±0.012	6.3±0.012	1.067±0.005	996.26±0.300
F_6	1:1	0.658±0.010	0.705±0.007	6.6±0.011	1.0714±0.008	995.46±0.293
$F_3(O)2$	1:1	0.500±0.007	0.576±0.008	13.1±0.011	1.152±0.011	948.555±1.673
F_7	1:1	0.646±0.008	0.689±0.006	6.24±0.006	1.066±0.007	998.41±0.428
F_8	1:1	0.560±0.012	0.570±0.008	1.7±0.006	1.017±0.011	997.20±1.865
F_9	1:1	0.671±0.006	0.716±0.009	6.2±0.007	1.067±0.010	993.93±0.400
$F_3(O)3$	1:1	0.576±0.012	0.625±0.010	7.8±0.008	1.085±0.012	995.166±0.966
F_{10}	1:1	0.635±0.011	0.683±0.011	7.0±0.014	1.075±0.008	996.28±0.367
F_{11}	1:1	0.636±0.012	0.678±0.012	6.1±0.012	1.066±0.006	997.72±0.289
F_{12}	2:1	0.632±0.011	0.674±0.013	6.2±0.010	1.066±0.014	998.28±0.573
F_{13}	2:1	0.618±0.012	0.660±0.014	6.3±0.011	1.067±0.011	997.60±0.567
F_{14}	2:1	0.620±0.006	0.661±0.010	6.2±0.014	1.066±0.008	997.26±0.734
Pure drug	-	0.500 0.001	0.714±0.002	29.9±0.009	1.428±0.001	

obtained in water and whereas highest was obtained in pH-7.4. It was also noted that the beads started to erode at this particular pH. These results suggest that the dried gel particles swells slightly in the stomach but when they were transferred into intestine the particles began swell rapidly and released the drug in a controlled manner and in lower part the swelling of intestine they swells up to maximum value and start to erode. Water uptake rate was found to be dependent on the nature of pH, i.e., pH-7.4> pH-6.6>pH-1.2>water. The above study also depicts that the equilibrium water uptake value follows the order Ca^{++}>Al^{+++}> Ba^{++}.

Table 3: Swelling characteristics of dried beads

Formulation code	% of Swelling after 24 hrs	Erosion time (hr)
In H_2O		
F_1	12	X
F_2	8	X
F_5	50	X
F_6	46	X
F_8	54	X
F_9	48	X
F_6	46	X
In pH-1.2		
F_1	56	X
F_2	52	X
F_5	46	X
F_6	40	X
F_8	72	X
F_9	46	X
In pH-6.6		
F_1	2000	X
F_2	1900	X
F_5	2550	X
F_6	2400	X
F_8	3100	X
F_9	2900	X
In pH-7.4 (just before erosion time)		
F_1	2200	6
F_2	1950	18
F_5	2600	3
F_6	2460	5
F_8	3174	2
F_9	2952	2½

Table 4: Percentage drug entrapment efficiency

Formulation code	Mean±SD	
	Percentage of drug content with	Percentage of drug entrapment with
F_1	48.79±0.834	97.184±1.345
F_2	48.796±0.287	97.592±0.574
F_3(O)1	48.796±0.287	97.592±0.574
F_4	49.94±0.020	99.882±0.041
F_5	48.11±0.189	96.226±0.378
F_6	44.469±0.205	88.936±0.410
F_3(O)2	35.022±0.116	70.043±1.80
F_7	40.865±0.116	81.730±0.233
F_8	23.404±0.211	70.327±0.635
F_9	39.546±0.012	79.093±0.410
F_3(O)3	37.613±0.929	75.227±1.858
F_{10}	43.814±0.703	87.629±1.407
F_{11}	39.525±0.012	79.05±0.025
F_{12}	32.74±0.082	98.23±0.246
F_{13}	30.028±0.082	92.84±0.246
F_{14}	39.04±0.251	87.14±0.759

SD: Standard deviation

Percentage drug entrapment efficiency

Drug entrapment efficiency of all the formulation was found to be between 70% and 99% as shown in Table 4. The high entrapment efficiency with minimum standard deviation suggests better drug content uniformity [14]. This high drug content was due to the practically insoluble nature of aceclofenac in the processing medium. In the case of barium and aluminum cross-linked beads, better drug entrapment efficiency as compared to calcium cross-linked beads was noticed. This may be due to increase in extent of cross-linking so that aceclofenac could not easily diffuse to the aqueous medium during curing. The loading efficiency was also found to be more when the concentration of alginate was further increased (Keeping the cross-linking amount constant, i.e. 4%)which may be due to a greater degree of cross-linking as the quantity of sodium alginate increased.

***In vitro* release behavior of drug**

Effect of cross-linking agent

The effect of different cross-linking agents such as $BaCl_2$, $Al_2(SO_4)_3$, and $CaCl_2$ in three different concentration(2%, 4%, 6%) was used to investigate the influence on release pattern while keeping drug to polymer ratio (1:1).The effect of cross-linking agent concentration, on the release of aceclofenac is very pronounced.

It was found that in the case of $CaCl_2$, as the concentration of $CaCl_2$ increases the release of aceclofenac from the formulations becomes more sustained and the release rate was found to be in the order of 2%>4%>6%>8%>. The higher release rate at lower $CaCl_2$ concentration, i.e., 2% (98% in 2 hrs) may be due to the fact that this small concentration of $cacl_2$ is not enough to form an insoluble hydrogel. Thus, this gel is not strong enough to delay the penetration of dissolution medium into the matrix. But as the concentration of $CaCl_2$ increases, a strong and rigid gel is formed around the matrix and this strong gel does not allow the dissolution medium to penetrate into the matrix at high speed resulting in a reduction in release rate. The water swellability study shown in Table 6 may be considered as a sole proof of the above fact.

With formulations containing $BaCl_2$ and $Al_2(SO_4)_3$ at lower concentration are capable of forming a more rigid gel. In both $Al_2(SO_4)_3$ and $BaCl_2$, the release rate was found to be more sustained when they were used at the concentration of 4%. But when the concentration of the above two was increased up to 6% the release rate was found to be more faster as compared to 4%. This may be due to complete saturation of the alginates with positive charges from the above two cations respectively.

The release profile from the beads was found to be in a pulsatile manner except formulation F_{12}. Pulse or pulsatile release is defined as the rapid release of certain amount of drug within a short time period after a long time. The pulse release pattern is due to the swelling controlled

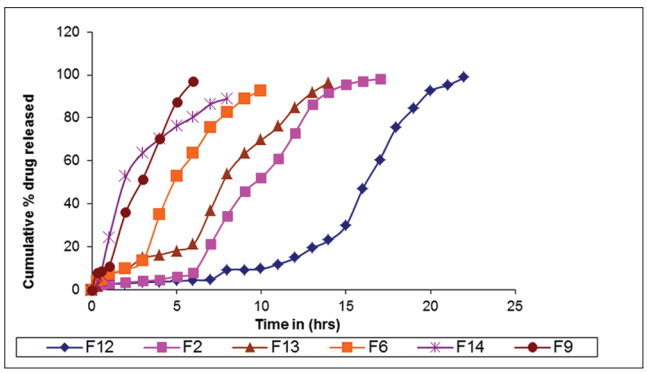

Fig. 1: Effect of polymer concentration on drug release from formulations F_{12}, F_2, F_{13}, F_6, F_{14}, and F_9

Table 5: Comparative dissolution study

Time in (hrs)	% drug released									
	F_1	F_2	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}
0	0	0	0	0	0	0	0	0	0	0
0.25	8.188776	1.811224	3.852041	9.464286	4.362245	3.086735	18.90306	7.678571	3.852041	4.362245
0.5	8.76449	2.335918	4.903265	12.27532	4.652245	4.362245	34.10531	9.525714	6.68898	5.672653
1	10.80939	2.595102	6.697143	26.31154	7.205306	6.658163	68.66449	11.83592	12.32367	7.978776
2	36.20735	3.36449	8.762449	37.03011	9.521633	29.87245	97.91959	36.20735	18.25633	10.81143
3	51.64	3.880816	14.14	62.04011	13.36653	48.75		51.64	38.96449	17.9951
4	70.16041	4.652245	22.08898	80.41481	35.08082	59.97449		70.16041	58.06857	53.90735
5	87.64612	6.186939	43.62776	96.23746	52.60122	72.47449		87.64612	72.74	66.06653
6		7.99102	59.37265		63.19918	86.25			88.43388	81.48694
7		21.0502	74.5298		75.27265	96.70918				94.34408
8		34.63184	81.74		82.51143					
9		45.70939	90.21551		88.94612					
10		52.17598	96.1502		92.82367					
11		60.8849								
12		73.21347								
13		86.06653								
14		92.03592								
15		95.39918								
16		97.21143								
17		97.99102								

Table 6: Various parameters model equations of the *in vitro* release kinetics

Formulation code	Korsmeyer-Peppas			Modified Korsmeyer-Peppas		
	r^2	n	k_1	r^2	n	k_2
F_1	0.98727	0.839	0.239	0.997	0.496	0.364
F_2	0.82	0.82	0.0255	0.992	0.859	0.0864
F_3(O)1	0.834	1.03	0.0421	0.984	0.372	0.360
F_4	0.91	0.84	0.0769	0.988	0.640	0.326
F_5	0.98	0.75	0.244	0.993	0.618	0.392
F_6	0.953	0.85	0.090	0.997	0.537	0.353
F_3(O)2	0.970	1.566	0.102	0.995	0.287	0.483
F_7	0.972	1.17	0.113	0.996	0.642	0.302
F_8	0.993	0.927	0.671	x	x	X
F_9	0.970	0.846	0.1856	0.990	0.504	0.365
F_3(O)3	0.982	1.466	0.195	1	0.720	0.598
F_{10}	0.930	0.930	0.122	0.950	0.776	0.271
F_{11}	0.933	0.871	0.0957	0.992	0.403	0.519
F_{12}	0.870	0.79	0.0209	0.999	0.653	0.297
F_{13}	0.970	0.873	0.0613	0.997	0.809	0.211
F_{14}	0.976	1.564	0.162	0.944	0.691	0.431

r^2=Is the correlation coefficient, k_1 and k_2 are the release rate constant of Korsmeyer-Peppas, modified Korsmeyer-Peppas model and n is the release exponent of Korsmeyer-Peppas and modified Korsmeyer-Peppas mode

release behavior aceclofenac beads in the dissolution medium. When the dissolution was completed, the beads were dissociated into gel type matrix. The dissociation of alginate beads is due to the exchange of chelated divalent or trivalent cations with the sodium ion in the phosphate buffer medium. The initial log time was found to be increase with increase in the concentration of cross-linking agent in case of $CaCl_2$. But in $BaCl_2$ and $Al_2(SO_4)$, the lag time increases up to 4% and then decreases.

The size and the charge of the cross-linking agent had a pronounced effect on the rate of drug release from the loaded beads, the sustaining effect was found to be in the order of $Bacl_2$> Al_2 (SO_4) >$CaCl_2$. Since Ba^{++} and Ca^{++} ions are divalent their bonding to alginate is expected to occur in a two-dimensional planner inside the beads. But since Ba^{++} ions have largest have largest radius, i.e., 1.74A° as compared to other two, i.e., 1.14 A° for Ca^{++} and 0.68A°Al^{+++}, it is supposed to be fill a large space between

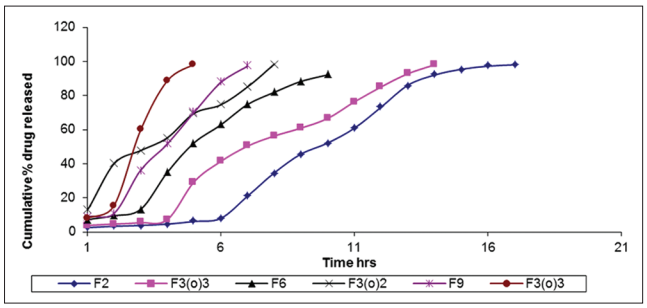

Fig. 2: Effect of nature of drying on drug release

the alginate molecules leading to a tight arrangement with smaller voids. Therefore, the exchange of large barium (Ba^{++}) ions in the beads with Na^+ ions and also their removal in the form of insoluble $BaSO_4$ is hindered which ultimately affects the drug diffusion across the beads.

In the case of Calcium (Ca^{++}), the relatively smaller size as compared to barium (Ba^{++}) makes it more diffusible. Although the aluminum has a small size as compared to calcium the release of aceclofenac from the beads cross-linked with aluminum $Al_2(SO_4)_3$ was found to be more sustained as compared to the beads cross linked with calcium chloride. The reason is that aluminum carries an extra change. The trivalent Al^{3+} forms a three dimensional valent bonding with sodium alginate. This three dimensional bonding results in extended cross-linking through whole beads. Hence, it releases the drug at a slow manner as compared to calcium.

Effect of sodium alginate concentration

The comparative dissolution study profile of various formulations containing drug to polymer ratio 1:1 and 1:2 cross-linked with 4% divalent and trivalent cations, respectively, shows that with increase in concentration of alginate the release becomes more sustained [14]. It is so because of increase of viscosity of the system as well as greater availability of active binding sites in the polymeric chain and consequently the greater degree of cross-linking as the quantity of sodium alginate increased show in Fig. 1 and Table 5.

Effect of drying

When the release of Aceclofenac from oven dried beads cross-linked with 4% cross-linking agent [$BaCl_2$,(Al_2SO_4)$_3$,$CaCl_2$] with 1:1 drug

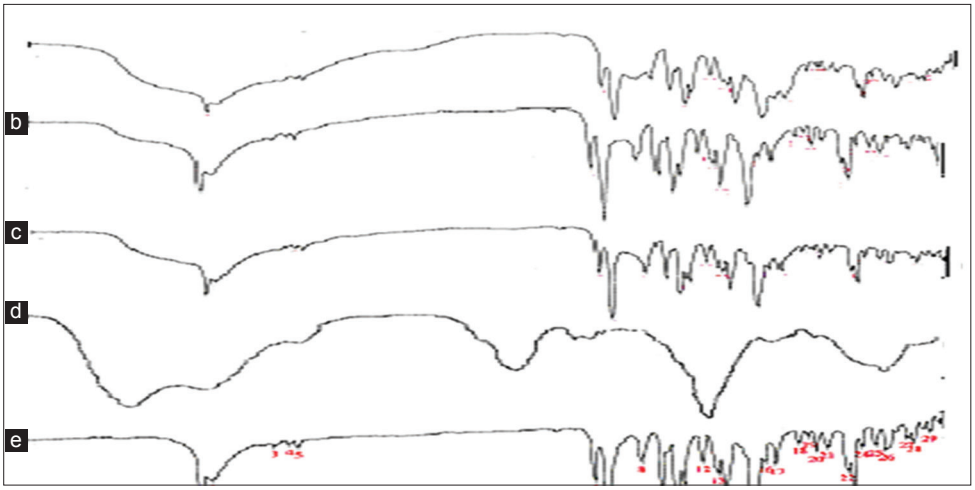

Fig. 3: Infrared spectra of curves of beads cross-linked with $Al_2(SO_4)_3$ (a), Beads cross-linked with $BaCl_2$ (b), beads cross linked with $CaCl_2$ (c), blank alginate (d), pure drug (e)

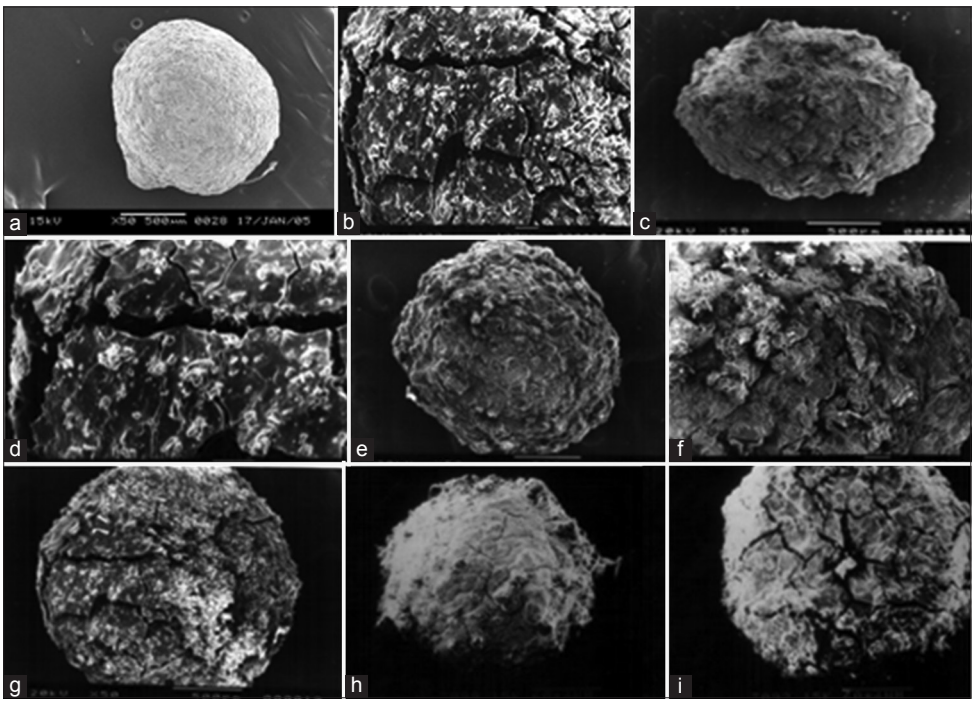

Fig. 4: Scanning electron microscopy of various formulations: (a) $CaCl_2$ air dried alginate beads, (b) $CaCl_2$ oven dried alginate beads with high magnification, (c) $BaCl_2$ air dried alginate beads, (d) $BaCl_2$ oven dried alginate beads with high magnification, (e) $Al_2(SO_4)_3$ air dried alginate beads, (f) $Al_2(SO_4)_3$ oven dried alginate beads with high magnification, (g) $CaCl_2$ oven dried alginate beads, (h) $BaCl_2$ oven dried alginate beads, (i) $Al_2(SO_4)_3$ oven dried alginate beads

polymer ratio respectively was compared with that of the same formulation which was subjected to air drying. It was found that both of them released the drug in the same pattern but the release rate was faster in the case of oven dried beads. It is so because air drying results partial drying of the beads which ultimately minimizes the porosity of alginate beads and alginate beads reswell only slightly upon rehydration resulting in increased alginate conc. of beads reduce pore size. Hence, sustains the release of drug for a longer period of time. Oven drying leads to complete dehydration of alginate beads and results in surface cracking as shown in Fig. 2 facilitate surface erosion of beads upon rehydration.

Evaluation of Drug Release mechanism by various kinetic Model

The (n') values from Korsemeyer–Peppas model for formulation F_1, F_4, F_5, F_6, F_8, F_9, F_{10}, F_{11}, F_{12}, F_{13} were between 0.5 and 1 indicating the mechanism of drug release to be non-fickian type (Table 6). The 'n' value of formulation $F_{3(0)1}$, $F_{3(0)2}$, $F_{3(0)3}$, F_7 and F_{14} was found to be greater than one indicating super Class II transport. When the release rate constant 'K_1' values of various formulations were compared it was found that the 'K_1' value is depended upon the nature of the cross-linking agent, amount of sodium alginate and nature of drying.

The low 'K_1' value in Korsemer and Peppas model for most of the formulation suggest a slow drug release rate for initial period of drug release and high 'K2' value in modified Korsemery–Peppas model shows a high drug release rate after the lag time.

From release kinetic study of above formulations, it is found that the formulation containing polymer drug ratio i.e. 2:1 and cross-linked with $BaCl_2$ 4% gives the highest sustaining effect i.e. 22 hrs. but in case of

1:1 ratio it was 17 hrs. In case of oven dried ratio 1:1, formulation of Aceclofenac beads, the release of drugs from beads is faster than the air dried beads. In comparison the cross-linked agent like $BaCl_2$, $Al_2(SO_4)_3$, $CaCl_2$ the formulation cross-linked with 4% $BaCl_2$ shows the maximum sustaining effect than other formulations. Increase in sodium alginate concentration the release becomes more sustained. In case of oven drying the rate of release of drugs from alginate beads was found to be faster than air drying beads.

Fourier transform IR analysis

The IR spectra of pure drug Aceclofenac and sodium alginate beads of formulations cross-linked with calcium chloride, barium chloride, and aluminum sulfate of aceclofenac were shown in Fig. 3. Drug spectrum shows prominent peaks at 2419.54, 2415.97, 2411.41, 2419.54, cm^{-1} corresponding to OH stretching, NH stretching of secondary amine, -C–H stretching(–C=CH), C–H stretching ($–CH_2$ asymmetric), C–H stretching (symmetric) and C=O stretching.

The characteristic peak of OH stretching, NH stretching, –C–H stretching (–C=CH), C–H stretching ($–CH_2$ asymmetric), C–H stretching (symmetric) and C=O stretching remains intact in the various formulations. This indicates the stable nature of drug during the encapsulation process.

SEM

SEM was used to investigate the physical appearance of alginate beads before dissolution study. The SEM photography revealed that the resulting microspheres were spherical in nature with rough surfaces containing cracks and holes over its surface. The various SEM photographs as shown in Fig. 4.

CONCLUSION

The present work describes a study on formulation and evaluation of sodium alginate beads of aceclofenac by using different cross-linking agent. It is a nonsteroidal anti-inflammatory drug used for the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.

In this present work attempt is being made for various formulations, i.e., drug polymer ratio 1:1 and 1:2. For this purpose, different concentrations of cross-linking agent for the controlled release formulation of aceclofenac were used. From the flow property study, it is found that all the formulation shows excellent flow property. The mean particle sizes of all the formulation were more or less spherical in nature. It was found that with increase in sodium alginate concentration the mean particle size of beads increases. In the case of air dried and oven dried beads, it was found that oven dried beads produced small size beads as compared to air drying.

From swelling study of various formulations in different pH media, it was concluded that the water uptake of alginate beads is maximum in case of pH-7.4 and in pH-1.2 is less as compared to pH-6.6 and 7.4. So it is proved that the dried beads were slightly swelled in the stomach but when they transferred into intestine the particles began to swell rapidly and release the drug in a controlled manner and in the lower part of intestine it swell maximum and erode. The loading efficiency was found more when the concentration of alginate increased.

From release kinetic study of above formulations, it is found that the formulation containing polymer-drug ratio, i.e., 2:1 and cross-linked with $BaCl_2$ 4% gives the highest sustaining effect, i.e., 22 hrs. But in the case of 1:1 ratio, it was 17 hrs. In the case of oven dried ratio 1:1, formulation of aceclofenac beads, the release of drugs from beads is faster than the air dried beads. In comparison, the cross-linked agents such as $BaCl_2$, $Al_2(SO_4)_3$, and $CaCl_2$ the formulation cross-linked with 4% $BaCl_2$ shows the maximum sustaining effect than other formulations. Increase in sodium alginate concentration the release becomes more sustained. In the case of oven drying the rate of release of drugs from alginate beads was found to be faster than air drying beads.

From IR analysis, it was concluded that there is no interaction between drug and polymer. It indicates the more stability of formulation.

It may also concluded that the changing in polymer drug ratio, i.e. increase in polymer ratio the formulations formed gives the more sustained effect than the 1:1 ratio formulation containing aceclofenac. Hence, these formulations were a more effective in the pain management for better Pharmacological response.

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