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Effect of manufacturing conditions on physico-chemical characteristics of Aceclofenac Sodium Microbeads for oral modified drug delivery

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Abstract

Aceclofenac, a novel NSAID used in the treatment of rheumatoid arthritis, frequency of administration may cause certain GI-adverse effects. The objective of the present research work to formulate the aceclofenac sodium microbeads by ionotropic external gelation technique by using sodium alginate and calcium chloride as cross-linking agent. The effects of different variables such as drug-polymer ratios, concentration of cross-linking agent, stirring speed, cross-linking time were evaluated on mean particle size, drug content, swelling properties, drug entrapment efficiency and drug release potential .The shape and surface characteristics were determined by scanning electron microscopy (SEM). While increasing in the concentration of sodium alginate dispersion increased size distribution, flow properties, mean particle size, swelling ratio and drug entrapment efficiency. The mean particle sizes of drug-loaded microbeads were found to be in the range 596.45±1.04 to 880.10±0.13. Increase in the stirring rate and cross-linking time tremendous decrease in mean particle size. The drug entrapment efficiency was obtained in the range of 63.24-98.90%w/v. No significant drug-polymer interactions were observed in FT-IR studies. There is no physical change of the drug in the formulations were observed by differential scanning calorimetry (DSC) and X-ray diffraction (XRD). The release of drug from the microbeads was pH dependent, showed negligible drug release in pH1.2. Under neutral conditions the beads will swell and the drug release depend on swelling and erosion process resulting optimum level of drug released in a sustained manner and exhibited zero-order kinetics and ultimately improves the compliance in the pharmacotherapy of arthritis. The entire process is feasible in an industrial scale and demands pilot study.

Key Words; Sodium alginate, Aceclofenac sodium, pH dependent, Ionotropic external gelation, Sustained release, Zero-order kinetics.

INTRODUCTION

Most of the conventional NSAIDs are used in the treatment of arthritis but have short biological half-lives and hence require for repeated administration 3 to 4 times a day. This leads patient non-compliance and also fluctuation in blood level drug concentration. A oral modified 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. The design of effective drug delivery systems has recently become an integral part of the development of new medicines. Hence, research continuously keeps on searching for ways to deliver drugs over an extended period of time, with a well-controlled release profile.[1] Most available drug delivery systems use biodegradable, biocompatible and natural biopolymers and are capable of rate and/or time controlled drug release. Alginate is a naturally occurring biopolymer that is finding increasing applications in the pharmaceutical technology and also has several unique properties that have enabled it to be used as a matrix for the entrapment and/or delivery of a variety of drugs and cells.[2] 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 β (1-4) mannuronic acid (M) and α (1-4) guluronic acid (G) residue in varying proportions and arrangements. It has been shown that the G and M units are joined together in blocks, and as such, the following 3 types of blocks may be found: homo-polymeric G blocks (GG), homo-polymeric M blocks (MM), and hetero-polymeric sequentially alternating blocks (MG). The reactivity with calcium and the subsequent gel formation capacity is a direct function of the average chain length of the G-blocks. Hence, alginates containing the highest GG fractions possess the strongest ability to form gels. This initially arises from the ability of the divalent calcium cation to fit into the guluronate structures like eggs in an “egg box junction”. Consequently, this binds the alginate chains together by forming junction zones, sequentially leading to gelling of the solution mixture and bead formation. When aqueous solution of sodium alginate is added to drop wise to an aqueous solution of calcium chloride, it forms a spherical gel with regular shape and size, also known as an “alginate bead”. Alginate microbeads have the advantages of being nontoxic orally, high biocompatibility, and inability to reswell in acidic environment, whereas they easily reswell in an alkaline environment. So acid sensitive drugs incorporated into the beads would be protected from gastric juice [3-4]

Aceclofenac sodium is non-steroidal anti-inflammatory drug used extensively in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after oral dose. The plasma elimination half-life of the drug is approximately 4h and dosing frequency 2-3 times daily with dose range 100-200mg.[5] An adverse gastrointestinal reaction has been observed and due to its short biological half-life requires multiple dosing. It leads to fluctuation in the drug blood levels and dose related adverse effects, multiple dosing also fail to release the drug at the desired rate and in the desired amount which often results in poor patient compliance and inefficient therapy[6]. Microencapsulation is well accepted technique for development of homogeneous, monolithic particles in the range of about 0.1-1000µm and employed to sustain the drug release. Since among the micropaticulate systems, microbeads have a special interest as carriers for NSAIDs, mainly to reduce or/ eliminate gastrointestinal irritation, dose intake and ultimately improve the compliance in the pharmacotherapy of arthritis, inflammation and pain. In the proposed method ionotropic gelation we drop the mixture of drug and polymer dispersion into aqueous calcium chloride solution gelation occurs instantaneously resulting to the formation of spherical micro-scale sized beads, with narrow particle size. Calcium induced alginate beads

have been developed in recent years as a unique vehicle for modified drug delivery systems. Their preparation is quite easy and is usually based on the gelling properties of the polysaccharide in the presence several divalent ions [7]. The aim of the present study was to develop sustained oral microbeads of aceclofenac sodium using sodium alginate as the hydrophilic carrier and calcium chloride as cross-linking agent and examine the effects of various process parameters on the physicochemical properties and drug release potential of the product.

MATERIALS AND METHODS

Materials

Aceclofenac sodium was obtained as a gift sample from Microlabs, Bangalore. Karnataka. India. Sodium alginate was a gift sample from F.M.C.International biopolymers, willingtown, Ireland, through Signet Chemical Corporation Pvt. Ltd, Mumbai, India. Calcium chloride (Fused) was purchased from S.B. Fine chemicals Ltd, Mumbai. India. All other reagents and solvents used were of analytical grade satisfying pharmacopoeias specifications

Preformulation studies

Saturation solubility study:

The saturation solubility of aceclofenac sodium was determined with various concentration of surfactants i.e. 0.5, 1.0, 1.5, and 2%w/v of sodium lauryl sulfate [SLS] in double distilled water, 0.1N HCl, pH 4.5 acetate buffer, pH 6.8 and pH7.2 phosphate buffers at 37^0 C. Excess quantity of aceclofenac sodium was added to 100ml of dissolution medium in a conical flask and agitated continuously at room temperature at 8h on a shaker. The solutions were kept aside for 6h until equilibrium was achieved. The solutions were then filtered through No-41 Whatman filer paper, and the filtrate suitably diluted and analyzed spectrophotometrically at 275nm. The results of the solubility study are summarized in table 1[8].

Solubility of aceclofenac sodium in calcium chloride solution;

The Solubility of drug in a calcium chloride (1%w/v) was determined by adding excess of drug into the medium containing vials and shaking at constant temperature 37^0C in a water bath for 12h. The sample were filtered diluted with distilled water and assayed spectrophotometrically at 275nm.The results summarized in table 1. [9]

Drug-polymer compatibility studies

Thin layer chromatography (TLC)

Silica gel 60g plates activated by heating at 105^0 C for 1h were used. The mixture of methanol: acetonitrile: buffer solution [pH6.8] in the ratio of 45:45:10 was used as solvent system. The drug extracted from different microbeads was spotted on the plate. The RF values were determined for the comparison of pure drug and extracted drug by examining of spot under UV-light.

Fourier transform- infrared spectroscopic analysis (FT-IR)

Drug polymer interactions were studied by FT-IR spectroscopy. One to 2mg of aceclofenac sodium alone, mixture of drug and polymer were weighed and mixed properly with potassium bromide uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR- spectrum of the pellet from 450-4000cm^{-1} was recorded taking air as the reference and compared to study any interference

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) was performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behaviors of drug alone and mixture of drug and polymer. The instrument comprised of calorimeter (DSC-60), flow controller (FCL-60), thermal analyzer (TA-60) and operating software (TA-60). The samples were heated in sealed aluminum pans under nitrogen flow (30ml/min) at a scanning rate of 5 ^{0} C/min from 24±1 to 250°C. Empty aluminum pan was used as reference. The heat flow as a function of temperature was measured for the drug and drug -polymer mixture. (10)

X-Ray powder diffractometry (X-RD)

The X-ray diffraction patterns of pure drug and the optimized drug loaded formulations were recorded using Philips X-ray diffract meter (model;PW 1710)with copper target to investigate the effect of microencapsulation on crystallinity of drug. Powder X-RD patterns were recorded using a radiation at 30kv and 25mA, scanning speed 20/min^{-1}, over the 4^0 to 40^0 diffraction angle (2θ) range. [10]

Preparation of Drug-Loaded Alginate Microbeads

The microbeads were prepared by ionotropic external gelation technique. Sodium alginate (1-3%w/v) was dissolved in deionized water by gentle heat at 40^0C on a magnetic stirrer. An accurately weighed 200mg of aceclofenac sodium was added and dispersed uniformly. The dispersion was sonicated for 30 min to remove any air bubbles The bubble free sodium alginate-drug dispersion (50ml) were added drop wise via a 20-guage hypodermic needle fitted with a 10ml glass- syringe into 50ml of calcium chloride solution (1-5%w/v) and stirred at 200rpm for 30min. The droplets from the dispersion instantaneously formed into discrete spherical beads upon contact with the solution of gelling agent. The drug loaded microbeads were further stirred in the solution of gelling agent for an additional 500- 2500rpm up to 0.5-3.h. After specified stirring time and stirring speed gelled beads were separated by filtration, washed with deionized water finally dried at 80^0c for 2h in a hot air oven. [10] The detailed composition of the various formulations stated in Table2.

Charecterization and evaluation of microbeads

Granulometric study

The particle size has significant effect on the release profile of microbeads. Size and size distribution was determined by sieve analysis was carried out on mechanical sieve shaker. The drug loaded microbeads were separated into different size fractions by sieving for 5 min using standard sieves having nominal mesh apertures of 1.4mm, 1.2mm, 1.0mm, 0.85mm and 0.71mm (sieve no 12, 14, 16, 18 and 22, respectively). Particles that passed through one sieve but were retained on the other were collected and weighed and the distribution was analyzed based on the weight fraction on each sieve. The particle size distribution and mean particle size of microbeads were calculated using the following formula [11]:

Mean particle size =Σ (particle size of the fraction x weight fraction) /Σ (weight fraction)

Measurement of Micromeritic properties of microbeads:-

The flow properties were investigated by measuring the angle of repose of drug loaded microbeads using fixed-base cone method. Microbeads were allowed to fall freely through a funnel fixed at 1cm above the horizontal flat surface until the apex of the conical pile just touches to the tip of the funnel. The height and diameter of the cone was measured and angle of repose was calculated by using the following formula. [11] Each experiment was carried out in triplicate [n=3].

$$Angle\ of\ repose\ (\theta) = \tan^{-1}(h/r)$$

h=cone height, r= radius of circular base formed by the microbeads on the ground.

The bulk and tapped densities were measured in a 10ml graduated cylinder as a measure of packability of the microbeads. The sample contained in the measuring cylinder was tapped mechanically by means of constant velocity rotating cam. The initial bulk volume and final tapped volume were noted from which, their respective densities were calculated. [11]
Compressibility index or Carr's index value of microbeads was computed according to the following equation:

$$Carr's\ index\ (\%) = [(Tapped\ density - Bulk\ density) / Tapped\ density] \times 100$$

Hausner's ratio of microbeads was determined by comparing the tapped density to the bulk density by using the equation:

$$Hausner's\ ratio = Tapped\ density / Bulk\ density$$

Mechanical strength study
To precisely measure mechanical strength of the alginate gel beads, large beads were prepared with sodium alginate polymer dispersion dropped through 1ml pipette into calcium chloride solution. The fully formed beads were collected, washed with distilled water and subsequently dried at 80^0C for 2hrs. Compression testing was performed with an Instron (4460). Ten beads of identical size were selected, crosshead speed and probe diameter were set at 1mm/min and 3.5cm respectively. [12]

Water Uptake determination
Weighed drug loaded microbeads were placed in a small basket, soaked in pH6.8 phosphate buffer or distilled water and shaken occasionally at room temperature. After a predetermined time to remove excess water and immediately weighed on an analytical balance. The water uptake can be calculated from the following equation [13]

$$Water\ uptake\ (\%) = [W_t - W_0 / W0] \times 100$$

Wt and W_0 are the wet and initial mass of beads, respectively.

Determination of calcium content in the beads
Alginate drug loaded microbeads (250mg) was dissolved in 10ml concentrated nitric acid by boiling. The samples were diluted with 1%w/v of nitric acid solution and calcium content was determined by spectrophotometrically. [14]

Disintegration test of drug-loaded microbeads
Disintegration studies were carried out in 50ml of buffer media pH1.2 and pH7.2 taken in 100ml conical flasks. A maximum of 5 pellets were taken in each trial and stirred using magnetic stirrer maintained at 37^0C, 25 rpm. Each batch of the microbeads was run in triplicate and the time taken for all the 5 pellets to disintegrate leaving behind polymer in the soluble form and drug in the insoluble form was noted as the disintegration time.

Particle size analysis

The particle sizes of both placebo and drug loaded formulations were measured by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. The Olympus model (SZX-12) having resolution of 30 Xs was used for this purpose. The instrument was calibrated at 1unit of eyepiece micrometer was equal to 1/30mm (33.33µm). In all measurements at least 100 particles in five different fields were examined [15] each experiment was carried out in triplicate.

Scanning electron microscopy analysis (SEM)

The shape and surface characteristics were determined by scanning electron microscopy (model-JSM, 35CF, jeol, Japan) using gold sputter technique. The particles were vacuum dried, coated to 200 A^o thicknesses with gold palladium using prior to microscopy. A working distance of 20nm, a tilt of zero-degree and accelerating voltage of 3kv, 4kv 5kv and 15kv were the operating parameters. Photographs were taken within a range of 50-500 magnifications.

Determination of entrapment efficiency

Aceclofenac sodium content in the microbeads was estimated by a UV-spectrophotometric method. Accurately weighed 50mg of microbeads were suspended in 100ml of phosphate buffer pH 7.2±0.1. The resulting solution was kept for 24hrs. Next day it was stirred for 15min. The solution was filtered, after suitable dilution, Aceclofenac sodium content in the filtrate was analyzed at 275nm using Shimadzu 1201 UV-Visible spectrophotometer. The obtained absorbance was plotted on the standard curve to get the exact concentration of the entrapped drug. Calculating this concentration with dilution factor we get the percentage of actual drug encapsulated in microbeads [16]. The drug entrapment efficiency was determined using following relationship;

% Drug Entrapment Efficiency = [Actual drug content /Theoretical drug content] x 100

Swelling Properties

The swelling properties of the drug loaded microbeads were determined in various pH ranges (i.e. 1.2, 4.8, and 6.8 buffer solutions) thirty dried microbeads were placed in a small beaker to which 100ml of buffer solutions was added and then allowed to swell at 37^0C. After 2h interval, the equilibrium swollen beads were observed and measured by Optical microscopy (Olympus model SZX-12). The magnitude of swelling was presented by the ratio of the mean diameter of swelling beads to the mean diameter of the dried beads before the test. [17] Swelling ratio was determined from the following relation.

Swelling ratio= [(Mean diameter at time t-initial diameter) / initial diameter of beads)] X100

***In-vitro* drug release studies**

The release profiles of Aceclofenac sodium from microbeads were examined in three different buffer solutions to mimic the various physiological GI-tracts. The media of pH 1.2 was representing the gastric condition; pH 6.8 was a compromise condition between pH of the gastric and small intestine and pH 7.2, which is simulated intestinal fluid. The dissolution process was carried out by using USP XIII rotating basket apparatus (Microlabs, Mumbai, India). The drug loaded microbeads (equivalent to 200mg of aceclofenac sodium) filled in empty capsule shells were put into the basket rotated at a constant speed at 75rpm and maintained temperature 37^0C.The 900ml of the dissolution medium, pH1.2 containing 2%w/v sodium lauryl sulfate (SLS) and the test was done for 2h. At the end of 2h continued the test with changing the dissolution media with pH6.8 buffer solution up to 6h and pH 7.2 phosphate buffers up to the

end of 12h.At scheduled time intervals, the sample (5ml) was withdrawn and replaced with same volume of fresh medium. The withdraw sample were filtered through a 0.45µm membrane filter and after appropriate dilution, then estimated for aceclofenac sodium concentration 275nm spectrophotometrically (Shimadzu 1201, Japan). Finally, corresponding drug content in the samples was calculated from the calibration curve of aceclofenac sodium to determine the drug release pattern [18]

Kinetics of drug release

In order to understand the mechanism and kinetics of drug release, the drug release data of the *in-vitro* dissolution study was analyzed with various kinetic equations like zero-order (% release v/s time), First- order (Log % retained v/s time) and korsmeyer and peppas equation. Coefficient of correlation (r) values were calculated for the linear curves obtained by regression analysis of the above plots.

Stability studies of microbeads

After determining the drug content, the optimized drug- loaded microbeads were charged for the accelerated stability studies according to ICH guidelines. To assess long-term stability, accurately weighed drug loaded microbeads equivalent to 200mg of Aceclofenac sodium were filled into a hard gelatin capsules manually and sealed in a aluminum packaging coated inside with polyethylene. The studies were performed at25^0C/60%RH, 40^0C/ 75% relative humidity (RH) in the desiccators with saturated salt solution for up to 6 months [19]. A visual inspection, drug content was conducted every 15 days for the entire period of stability study.

RESULTS AND DISCUSSION

Preformulation Studies

The available data on solubility profile of aceclofenac sodium indicated that the drug is freely soluble in acetone and practically insoluble in water. The results of the solubility study and the influence of sink conditions are summarized in Table 1.The results showed, that there was a significant increase in solubility with increasing pH. The addition of different concentrations of SLS in 0.1N HCl significantly increased up to 0.487mg/ml. The solubility of aceclofenac sodium in calcium chloride was found to be 0.96±1.54mg/ml. A dissolution study of dosage forms necessitates modifications in the dissolution medium to increase the solubility of practically insoluble drugs. Aceclofenac sodium is a lipophilic compound and is practically insoluble in water. It is a weak acid; the solubility of aceclofenac sodium in HCl was very less compared with distilled water. However, the addition of surfactant is a reasonable approach for solubilizing such drugs, because various surfactants are present in the GI-fluid. Saturation solubility of aceclofenac sodium in different media increased with an increase in buffer pH as well as with an increase in surfactant concentration. The significant increase is attributed to the micellar solubilization by SLS. Aceclofenac sodium showed sufficient solubility in 0.1N Hcl with 2%w/v of SLS which was adequate to maintain sink condition and was selected as the dissolution medium for *in-vitro* drug release studies. The solubility of aceclofenac sodium was more in 1%w/v of calcium chloride solution than in double-distilled water, which induces certain amount of drug release, when prolonged exposés of the beads in curing medium during the manufacturing process.

Drug-Polymer Compatibility Studies

Purity of pure drug of aceclofenac was determined by TLC method and detects the clear spots on the plate, and determined the RF value of aceclofenac, was 22, linearity was in between 700-2400 ng/zone. The RF value of extracted drug from microbeads was 21.40, linearity obtained in the range between 680- 2350ng/zone. The images of spots observed on the TLC plates, there is

no overlapping of the spots; it indicates the drug not containing any extraneous matter. Moreover, that the obtained RF values of extracted drug from microbeads are almost equal to that of the standard drug. It indicates there is no deformation during the process.

IR-spectra of pure aceclofenac sodium, sodium alginate and physical mixture of drug and polymer are shown in Figure 1.The characteristic absorption peaks obtained at 2966.36, 2915.5, 1716.5, 1589.3. 1479.6 and 665.4cm^{-1} for pure aceclofenac sodium, 2814.98, 1603.34, 1519.3, 1359.60 and 674.05 cm^{-1} for sodium alginate, 2820.28, 1591.72, 1384.91, 1102.03 and 666.4cm^{-1} for physical mixture of drug and polymer. The compatibility of aceclofenac sodium with polymer was investigated by IR-spectroscopy study. The IR spectra of the drug and polymer combination were compared with the spectra of the pure drug and individual polymer spectra. In which no considerable changes in the IR peaks of aceclofenac in the physical mixture thereby indicating the absence of any interaction.

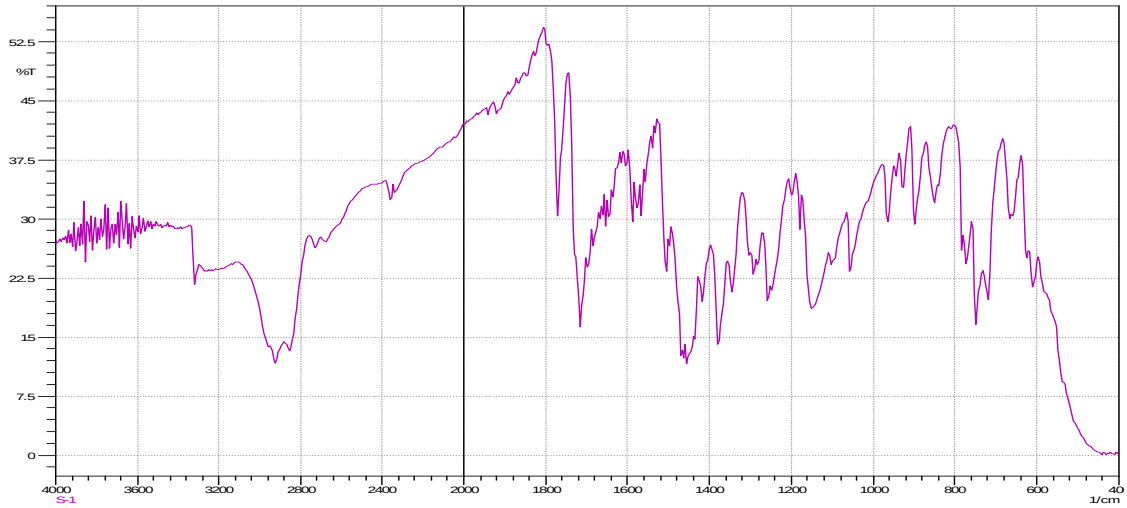
Table 1. Saturation solubility of aceclofenac sodium in different dissolution medium

Dissolution media	Concentration of SLS (%w/v)	Solubility (mg/ml)
Double-Distilled water	--	0.067±0.12
	0.5	0.126±0.56
	1.0	0.455±0.23
	1.5	0.643±0.55
	2.0	0.924±0.68
0.1N HCl	--	0.016±0.87
	0.5	0.098±0.77
	1.0	0.208±0.87
	1.5	0.389±0.65
	2.0	0.487±0.08
Acetate buffer pH 4.5	--	0.996±0.76
Phosphate buffer pH 6.8	--	3.963±1.06
Phosphate buffer pH 7.4	--	5.567±0.98
Calcium chloride solution (1%w/v)	--	0.096±1.54

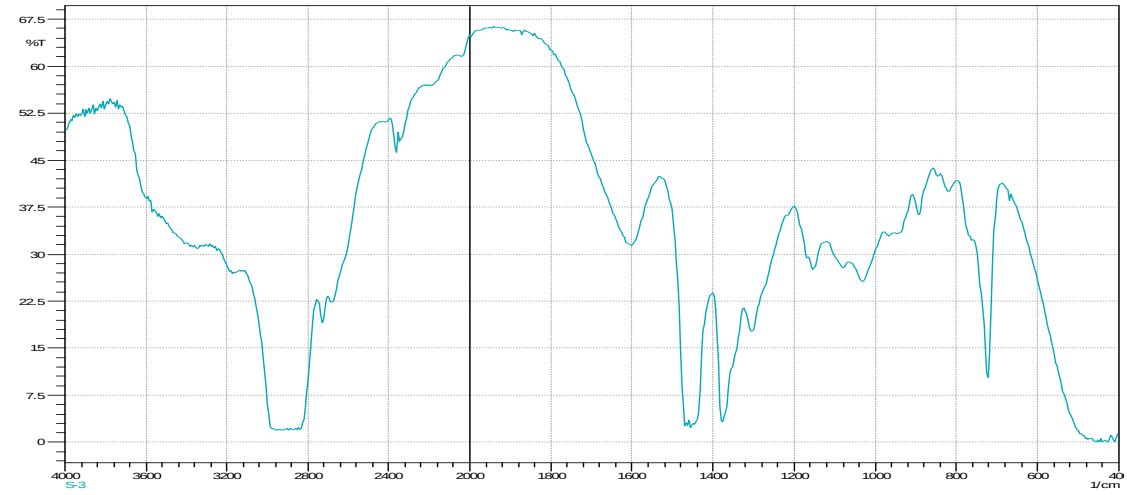
Data are expressed as mean ±SD of at least triplica te

Differential scanning calorimetry thermogram of pure drug and drug loaded sodium alginate microbeads was observed, calcium chloride shows two endotherm peaks in the temperature range 180-200^{0}C with broad exotherm. Pure drug of aceclofenac sodium showed a sharp endotherm at 154.50^{0}C corresponding its meting point. There was no appreciable change in the melting point of the physical mixture as compared to pure drug. No extra peak of the drug in the thermogram of the drug loaded microbeads. It may indicate that the drug was uniformly dispersed at the molecular level of the polymer.

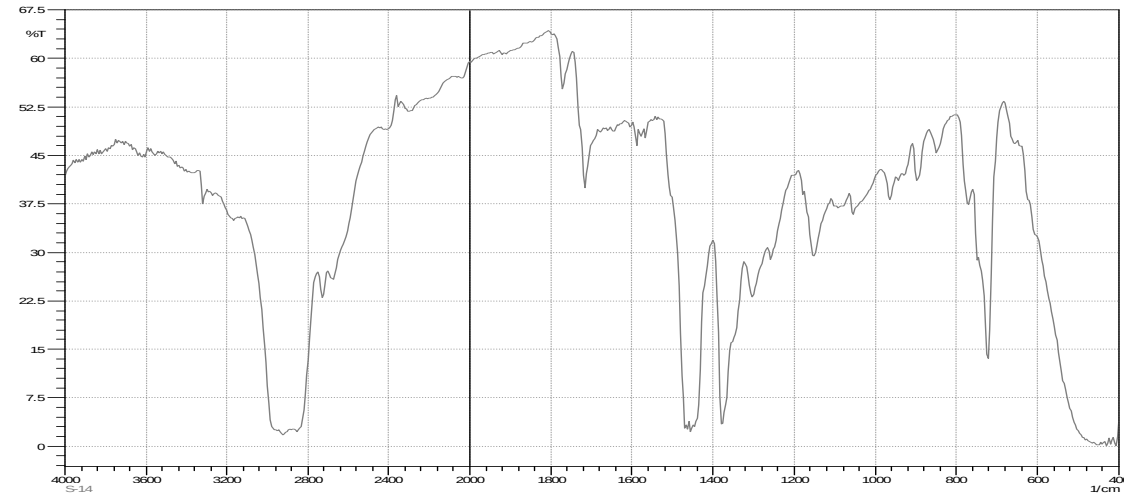
The X-ray powder diffraction patterns of pure drug and drug-loaded microbeads are compared and found that the intensity of the peaks of pure drug is sharper than that of the drug in polymer matrix. The loss of sharpness is due to decreased crystallinity of the drug in the formulation.



(a)

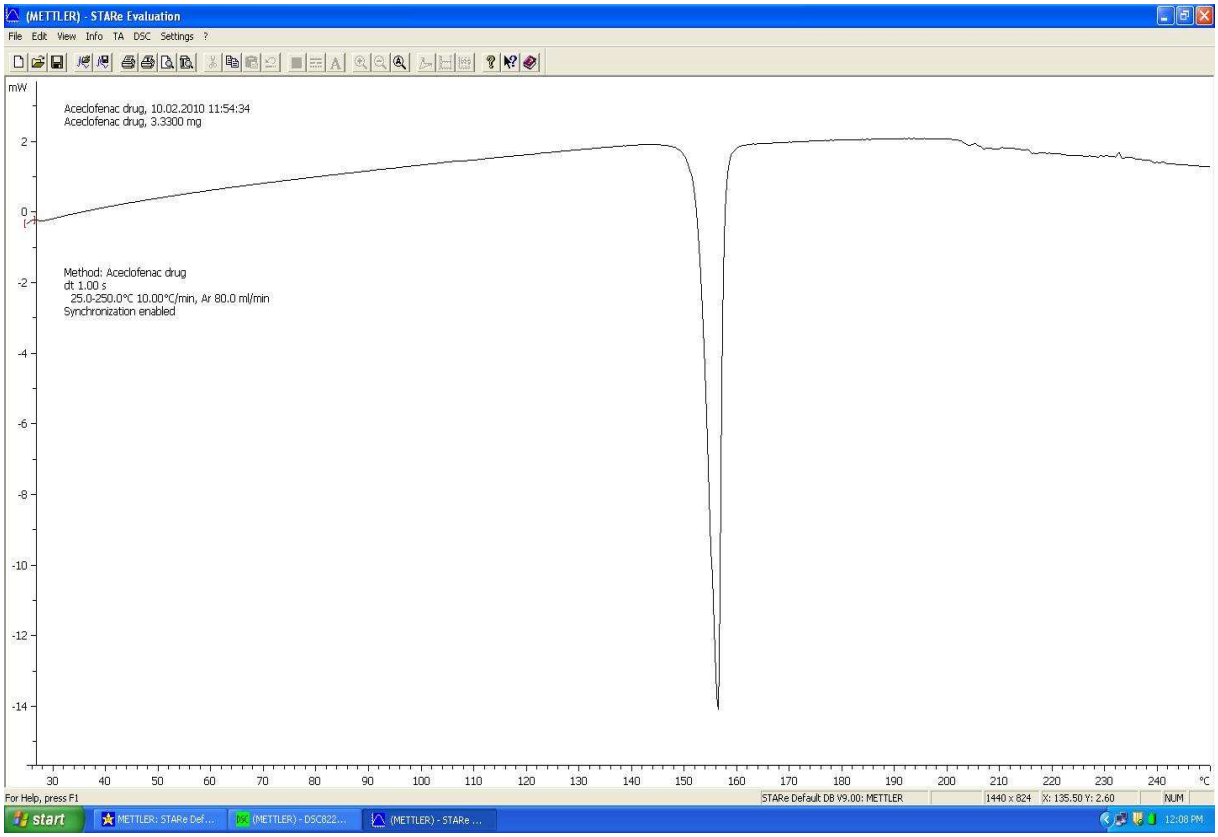


(b)



(c)

Figure 1.IR-spectra (a) aceclofenac sodium pure drug (b) sodium alginate (c) physical mixture



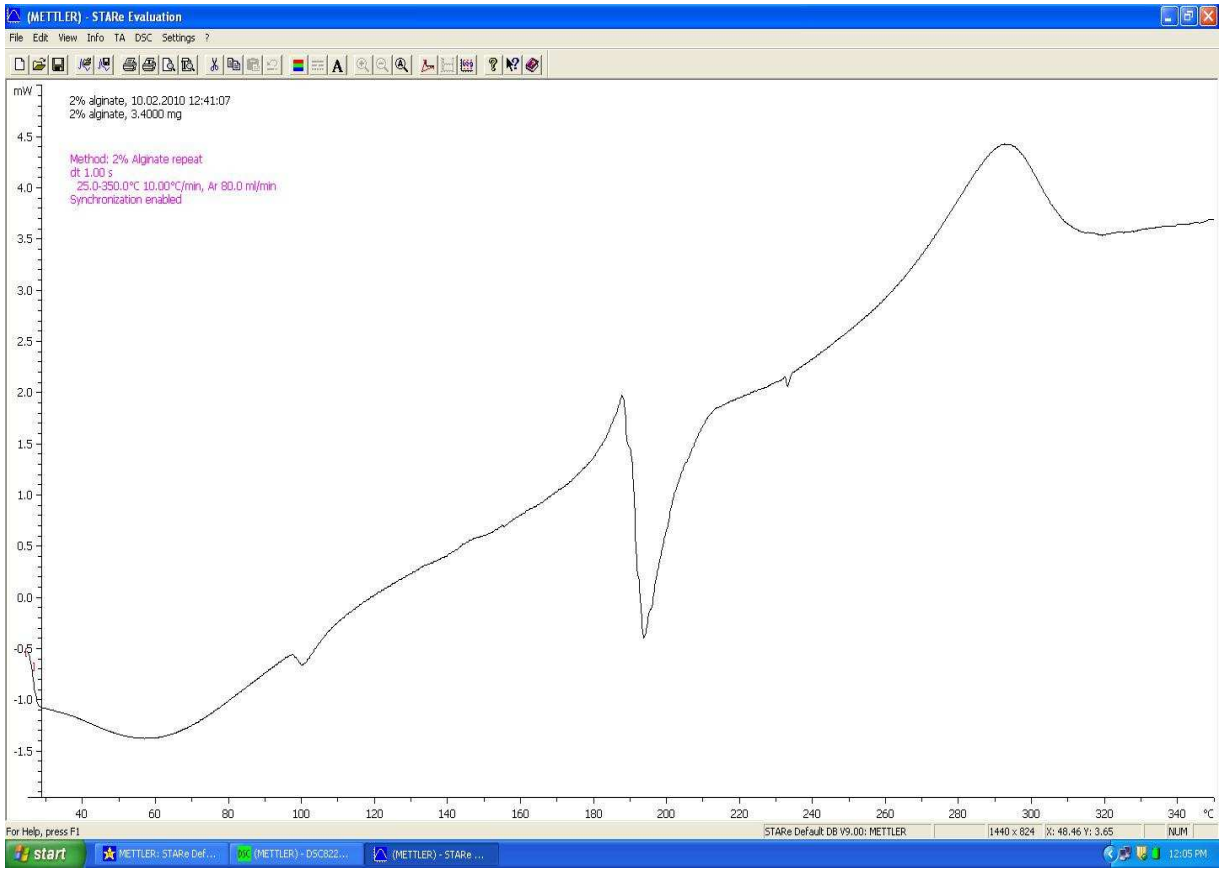


Figure 2. DSC thermo-grams (a) Aceclofenac sodium pure drug (b) Formulation containing 2%w/v of sodium alginate

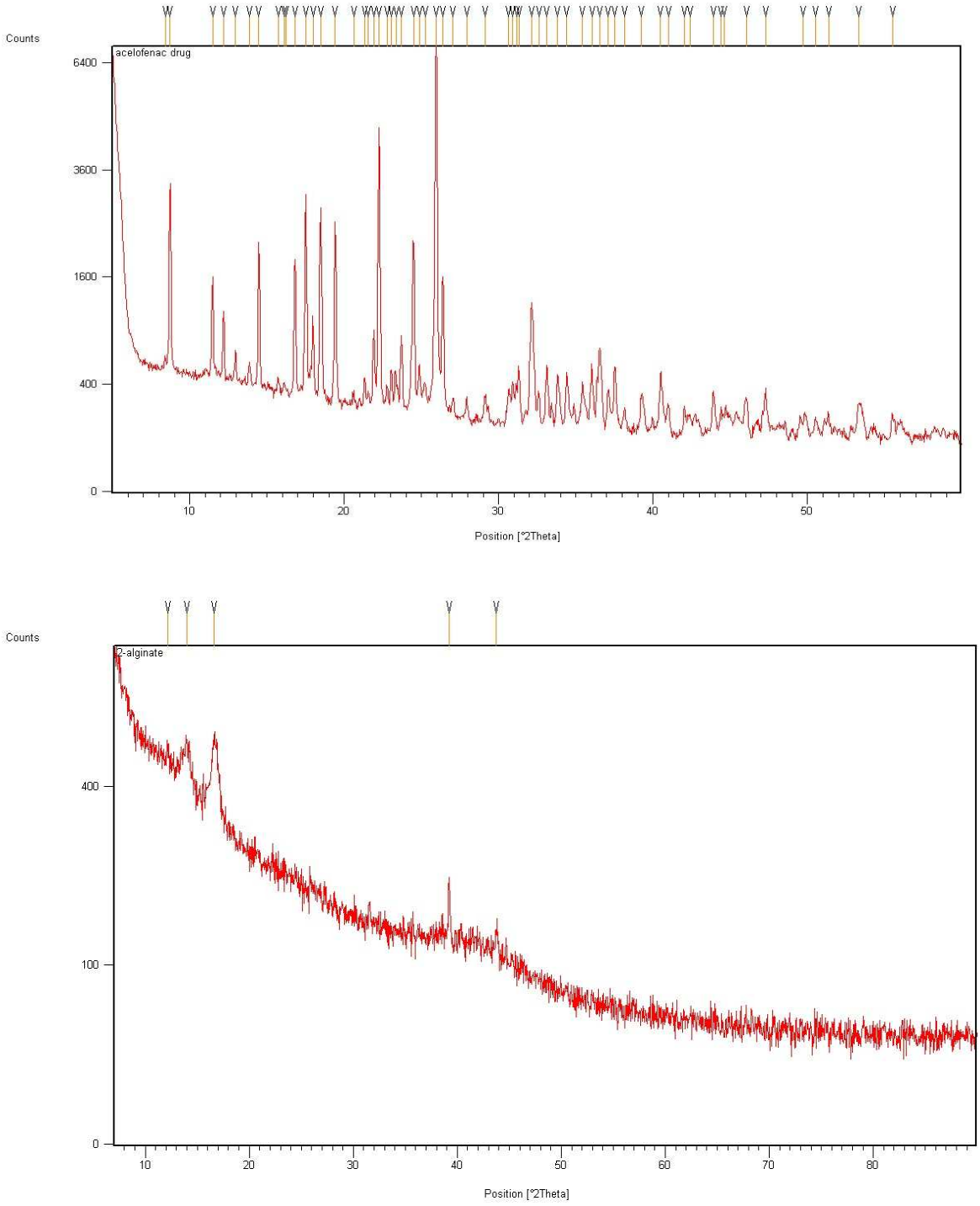
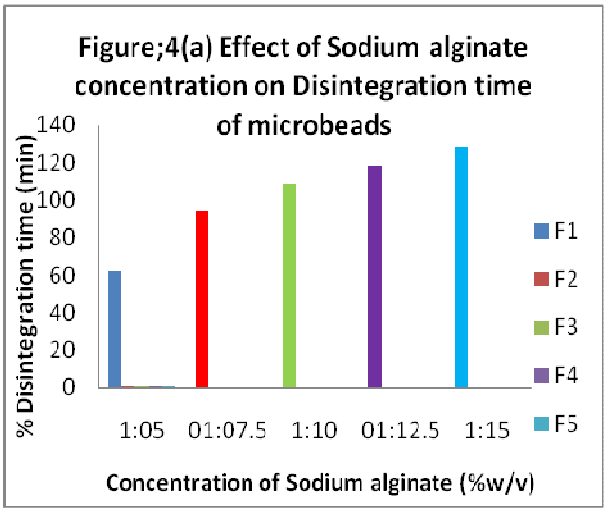


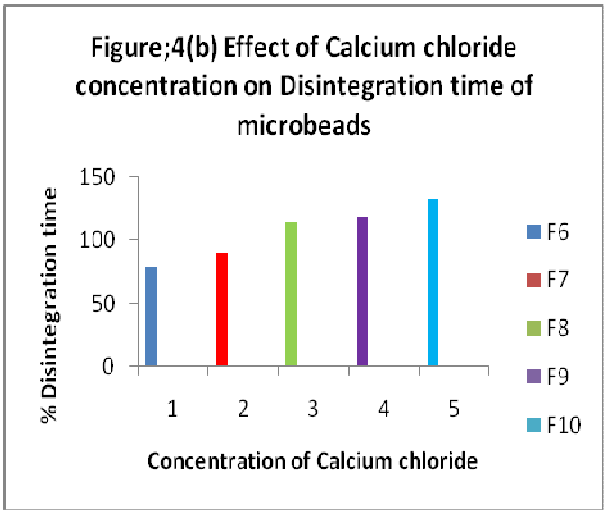
Figure. 3; X-ray powder diffraction patterns (a) Pure drug of Aceclofenac sodium (b) Formulation containing 2%w/v of sodium alginate

Characterizations and Evaluation of Microbeads

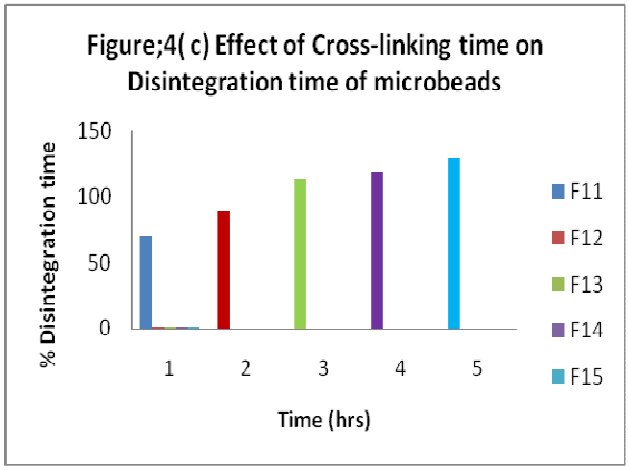
As shown in Table 2, the total percentage yields of drug-loaded microbeads obtained were in the range between 73.40 to 88.30%w/w. It was observed that increasing the polymer ratio in the formulation significantly lower the product yield, due to the formation of high viscous polymer dispersion which may be lost during manufacturing process. Further observation, when the drug polymer ratio was constant, an increase in the concentration of calcium chloride and curing time

slightly increased the percent of yield. Percentage of actual drug concentration in microbeads was evaluated and found to be in the range 56.92±0.39 to 72.80±0.5. The polymer concentration increases consequently the actual drug loading high due to increase in hydrophobicity, leading to better precipitation of polymer at the boundary phase of the droplets. Mechanical testing was performed in order to study the effect of concentration of calcium chloride and cross-linking time. As the results, increasing the concentration of calcium chloride and cross-linking time significantly increases the mechanical strength due to formation of dense matrix between sodium and Ca^{+2}divalent ions. The % water uptake of the aceclofenac sodium loaded microbeads in distilled water was significantly lower than that in pH6.8 phosphate buffer.





The equilibrium time of water uptake in distilled water of the beads was around 0.5-2 h. In case of phosphate buffer pH6.8 the equilibrium time of water uptake reaches within 1h because calcium ions were rapidly exchanged with sodium ions in phosphate buffer with prolonged cross-linking time. Moreover, calcium alginate gels could be solubilized by the addition of phosphate ion, which acted as calcium ions complexing agent at a pH above 5.5. [20] The sodium alginate concentration increased water uptake of the beads will increases, ultimately the swelling behavior of the beads increased in higher pH levels which would significantly delayed the drug release. Determination of calcium content in the all drug loaded microbeads, as the results known that calcium chloride concentration affects the amount of Ca^{+2} ions in alginate beads.



The formulation were prepared with 5%w/v, have high Ca^{+2} contents than those of the formulations prepared with low concentration calcium chloride. On other hand increases the sodium alginate concentration and cross-linking time increases the calcium content in the beads. The disintegration times of the drug loaded microbeads increased with increase the sodium alginate concentration because it leads to increased viscosity of the polymeric matrix. Increasing the concentration of calcium chloride turn to form stronger beads takes longer time for disintegration as shown in Figure 4a, 4b & 4(c).

The effect of various process and formulation parameters on the drug entrapment efficiency of microbeads were investigated, keeping the concentration of calcium chloride, stirring speed and cross-linking time fixed at 4%w/v, 2000rpm and 2h respectively. By increasing the drug-polymer ratio concentration from 1:5 to 1:15 w/w, the drug entrapment efficiencies were found to in the range 63.24±0.66 to 98.90±0.86%w/w. It was observed that the drug entrapment efficiencies increased progressively with increasing the concentration of sodium alginate resulting in the formation of larger beads entrapping the greater amount of the drug This may be attributed to the greater availability of active calcium binding sites in the polymeric chains and, consequently, the greater degree of cross-linking as the amount of sodium alginate increased. Alginate concentration increases may also reduced loss of drug in the curing medium due to the formation of dense matrix structure.

While keeping the concentration of drug polymer ratio, stirring speed and cross-linking time fixed at, 1:10, 2000rpm and 2h respectively. Increasing calcium chloride concentration from 1-5%w/v the drug entrapment efficiencies were found to be in the range 83.30±0.75 to 93.30±0.2.%w/w. From the results, it is obvious that increasing calcium chloride concentration produced beads with higher levels of Ca^{2+}ions. Consequently, the cross-linking of the polymer and compactness of the formed insoluble dense matrices also increased, resulting in more drug entrapment in the microbeads.(Table2) On other hand further increase in the concentration of calcium chloride above (5%w/v) did not enhance the drug loading. This could be due to possible saturation of calcium binding sites in the guluronic acid chain, preventing further Ca^{2+}ions entrapment and, hence, cross-linking was not altered with higher concentration of calcium chloride solution.

Evaluate the drug entrapment efficiencies while keeping the drug: polymer ratio, concentration of calcium chloride, and stirring speed constant at 1:10w/w, 4%w/v, and 2000rpm respectively. Increasing cross-linking time from 0.5 to 2.5h the drug entrapment efficiencies were found to be

found in the range 85.40±0.55 to 96.77±0.30%w/w. The cross-linking time also effects the drug entrapment efficiencies of formulated drug loaded microbeads. Increasing the cross-linking time resulted decrease in the drug entrapment efficiencies [Table 2], since the solubility of aceclofenac sodium was slightly higher in calcium chloride than in distilled water. Prolonged exposure in the curing medium caused greater loss of drug through weakly cross-linked alginate beads. However, constant drug loading was achieved at 2h, with no further decrease after 4 and 5h of curing time. This could be due to the formation of tight junction between calcium ions and the active sites on the guluronic acid chain. Consequently, the drug was entrapped in highly bound calcium alginate matrix resulting in no further diffusion of drug in the curing medium. Increasing the stirring speed 500 to 2500rpm the drug entrapment efficiencies were found to be in the range 87.44±0.90 to 90.56±0.35.[Table2] There was no significant change on encapsulation efficiency of drug with increase in the speed of agitation.

Table 2: Composition and physical characteristics of various formulations

Batch code	D : P Ratio (%w/w)	Calcium chloride (%w/v)	Stirring rate (rpm)	Stirring Time (h)	Yield (%)	Actual drug content (%)	Drug entrapment efficiency (%)
F1	1:5	4	2000	2	88.30	56.92± 0.39	63.24±0.66
F2	1:7.5	4	2000	2	80.60	60.82±0.30	75.43±0.42
F3	1:10	4	2000	2	76.40	68.99±0.20	89.95±0.25
F4	1:12.5	4	2000	2	74.80	70.47±0.80	93.85±0.50
F5	1:15	4	2000	2	73.40	72.60±0.62	98.90±0.86
F6	1:10	4	500	2	74.10	64.90±0.78	87.44±0.90
F7	1:10	4	1000	2	76.30	66.20±0.75	87.96±0.98
F8	1:10	4	1500	2	75.80	67.87±0.86	88.35±0.93
F9	1:10	4	2000	2	76.40	68.99±0.20	89.95±0.25
F10	1:10	4	2500	2	76.30	69.54±0.64	90.56±0.35
F11	1:10	1	2000	2	72.40	60.45±0.68	83.30±0.75
F12	1:10	2	2000	2	74.60	64.53±0.45	86.05±0.96
F13	1:10	3	2000	2	75.10	66.76±0.57	88.94±0.84
F14	1:10	4	2000	2	76.40	68.99±0.20	89.95±0.25
F15	1:10	5	2000	2	77.60	72.33±0.40	93.30±0.23
F16	1:10	4	2000	0.5	75.65	73.44±0.47	96.23±0.30
F17	1:10	4	2000	1.0	76.15	70.84±0.93	92.15±0.48
F18	1:10	4	2000	1.5	76.30	69.54±0.96	91.08±0.87
F19	1:10	4	2000	2.0	76.40	68.99±0.20	89.95±0.25
F20	1:10	4	2000	2.5	77.30	66.40±0.75	85.40±0.55

D: P ratio:-Drug: Polymer ratio [Aceclofenac: Sodium alginate] Each formulation containing 200mg of Aceclofenac sodium. Data are expressed as mean ±SD, n=3

The effect of various process and formulation parameters on the Micromeritic properties of drug loaded microbeads were evaluated, the size distribution of the microbeads in different sieves were observed, and showed 32.46% to89.50% of microbeads retained ≠22 sieve. From the results of sieve analysis, the size distribution of microbeads was observed that by an increase in the concentration of sodium alginate and calcium chloride solution tends to form the particles more spherical and obtaining the uniform size spheres. On other hand increase in the cross-

linking time and stirring speed are also favorable to the formation of more spherical beads and the distribution of particle size slightly shifts to the lower pore size The rheological parameters like angle of repose, bulk density and tapped density of all microbeads confirms better flow and packaging properties. All the formulations showed excellent flowability represent in terms of angle of repose ($<40^0$)[20]. Here, too, the sodium alginate concentration has a significant positive effect on the angle of repose. Particle size increased with increase in the concentration of sodium alginate and resulted in a decrease angle. However, higher calcium chloride concentration, cross-linking time and high stirring speed influenced the formation of smaller beads because of shrinkage and showed an increased angle of repose. [Table3] Bulk and tapped density of beads showed good acceptable range indicates that have good packability. The density of the beads increases as the concentration of the polymer increases suggesting that the beads formed at high polymer concentration are more compact and less porous than those prepared at low polymer content. Carr's index, and Hausner's ratio explains the formulated microbeads had excellent compressibility and good flow properties. The improvement of flow properties suggest that the microbeads can be easily handled during processing. [Table 3] The mean particle sizes of drug loaded microbeads were performed by Optical microscopy, and mean particle sizes of the various formulations (F1-F15) of microbeads were obtained in the range between 596.45±1.04 to 880±1.23 [Table 3]. It was found that the particle size distribution of each formulation was within a narrow size but the mean particle size was different among the formulations. The results indicated that the proportional increase in the mean particle size of microbeads increased with the amount of sodium alginate in the formulations. This could be attributed to an increase in relative viscosity at higher concentration of sodium alginate and formation of large droplets during addition of polymer solution to the gelling agent. On the other hand the mean particle size of microbeads was found to decrease with an increase in the concentration of calcium chloride. It has been stated that when a drop of alginate solution comes in contact with calcium ions, gelation occurs instantaneously. As Ca^{+2} ions, penetrates into interior of droplets, water is squeezed out of the interior of droplets resulting in contraction of beads.[Table 3] The size of the spherical matrix could easily be controlled by varying the stirring speed of the system. The mean particle sizes of microbeads were tremendous decreased with increasing the rotational speed. At a stirring speed of 500rpm, the mean particle diameter and the size distribution of the beads increased significantly. This low stirring speed might have decreased the uniformity of the mixing force throughout the emulsion mixture, and the particles were found to settle at the bottom of vessel hence resulting in a wider diameter of the final beads. Consequently at higher stirring speed, a vigorous, uniform, increased mechanical shear might have been influenced in the formation of lesser diameter beads. A higher mixing rate did not further reduce the mean diameter, because high turbulence caused frothing and adhesion to container wall. The effect of cross-linking time at a particular stirring speed was also observed, and it was recorded that cross-linking time influenced the shape as well as the size distribution of microbeads, possibly because of variable shear force experienced by particulate system. All the observed data suggest that the stirring speed 2000rpm and stirring time 2h were found to be optimal for the drug loaded microbeads.

Table 3: Micromeritic properties of drug-loaded microbeads

Formulation code	Mean Particle size [µm]	Angle of Repose [θ]	Bulk Density [g/ml]	Tapped Density [g/ml]	Carr's Index (ci) %	Hausner's ratio
F1	596.45±1.04	32.20±1.96	0.475±0.07	0.593±0.03	19.89	1.24±0.20
F2	624.86±0.98	28.16±0.62	0.566±0.92	0.675±0.06	16.14	1.19±0.30
F3	703.55±0.75	22.65±0.55	0.665±0.75	0.782±0.05	14.96	1.17±0.58
F4	844.75±1.10	20.55±1.07	0.695±0.05	0.807±0.87	13.87	1.16±0.15
F5	880.10±1.23	19.85±0.54	0.745±0.08	0.855±0.16	12.86	1.14±0.78
F6	784.60±1.08	23.65±1.65	0.585±0.85	0.727±0.15	19.55	1.24±0.08
F7	764.55±1.06	25.15±0.93	0.595±0.96	0.735±0.80	19.05	1.23±0.20
F8	743.20±1.44	26.78±0.75	0.622±1.10	0.755±0.36	17.64	1.21±0.40
F9	703.55±0.75	28.65±0.55	0.665±0.73	0.782±0.05	14.96	1.17±0.58
F10	716.80±0.96	20.15±0.05	0.685±0.09	0.790±0.18	13.30	1.15±0.32
F11	746.60±0.73	30.65±0.85	0.515±0.16	0.665±0.22	22.55	1.29±0.12
F12	734.10±0.54	27.75±0.96	0.565±0.25	0.697±0.45	18.95	1.23±0.45
F13	724.40±0.34	26.25±0.55	0.635±0.35	0.753±0.96	15.70	1.18±0.68
F14	703.55±0.75	22.65±0.55	0.665±0.75	0.782±0.05	14.96	1.17±0.58
F15	688.56±1.25	19.10±1.23	0.712±0.15	0.810±0.46	12.10	1.13±0.77
F16	804.35±1.43	25.75±0.64	0.555±o.77	0.695±0.55	20.14	1.25±0.84
F17	764.45±1.05	24.66±0.77	0.588±0.93	0.724±0.15	18.80	1.24±0.56
F18	724.64±1.54	23.15±0.87	0.625±0.66	0.758±0.35	17.62	1.20±0.34
F19	703.55±0.75	22.65±0.55	0.665±0.75	0.782±0.05	14.96	1.17±0.58
F20	708.10±0.86	18.85±1.15	0.695±0.82	0.805±0.77	13.65	1.15±0.55

Data are expressed as mean ±SD of at least triplicate

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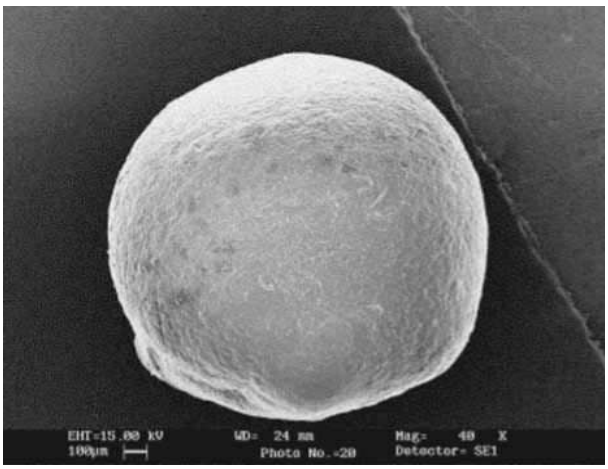
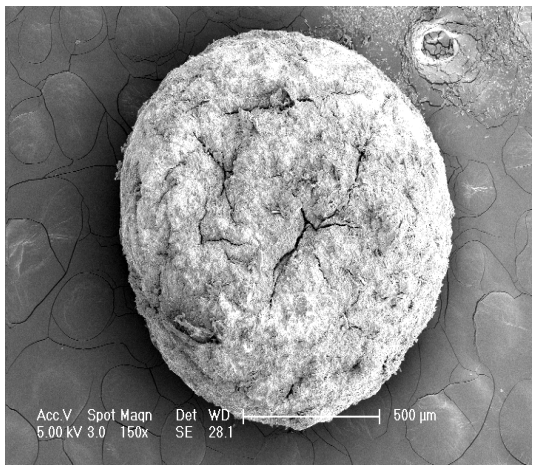


(a)



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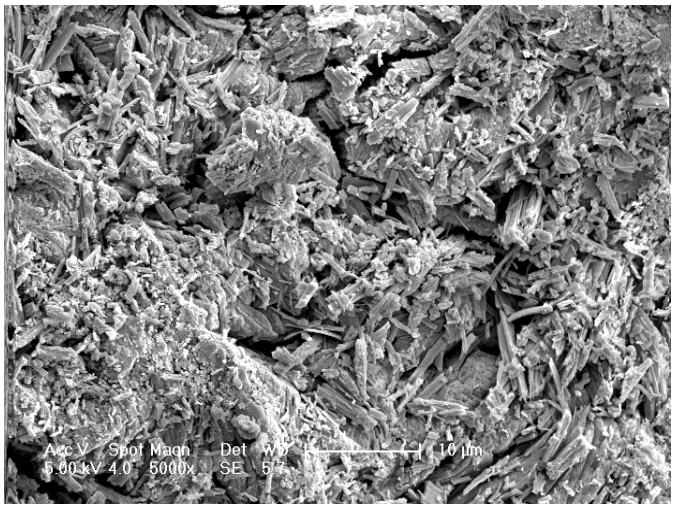

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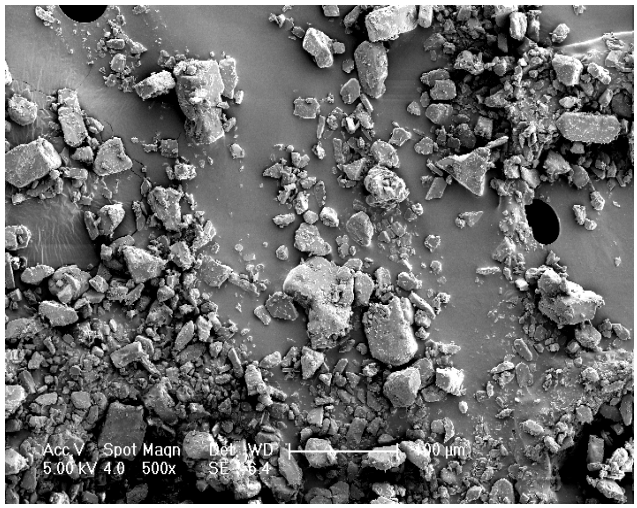


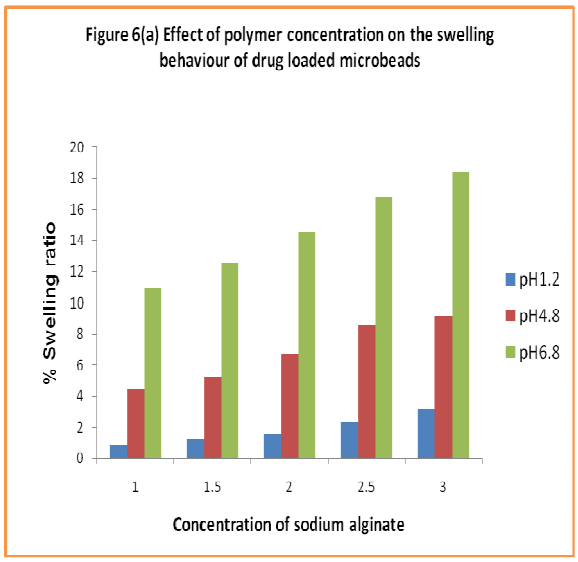
(d)

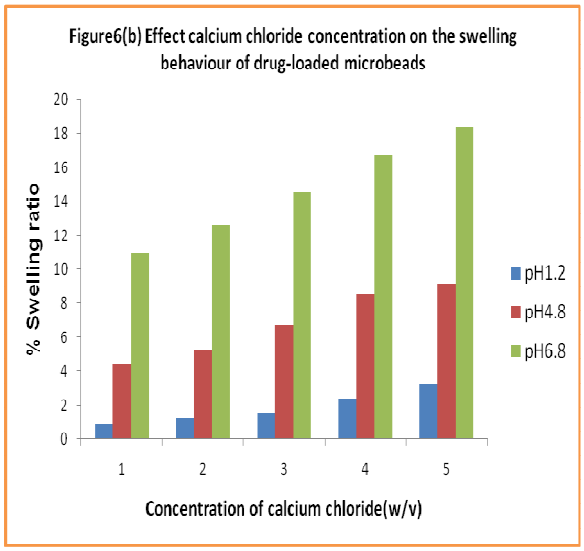
Figure;5. Scanning Electron Microphotographs [SEM] of aceclofenac sodium microbeads (a) at 15kv magnification 40X (b) at 3kv magnification 150X (c) overall surface at 5kv magnification 500X (d) Aceclofenac sodium pure drug at 5kv magnification 500X

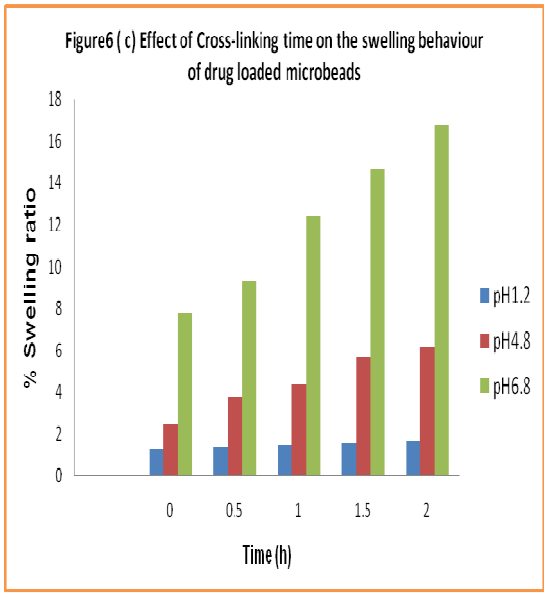
The SEM photomicrographs of the dried drug-loaded microbeads and their surface morphology are shown Figure 5. Morphology of the formulation containing 2%w/v of sodium alginate drug loaded microbeads were discrete and spherical in shape[Figure 5a] The large visible wrinkles and small cracks have a sandy appearance has observed because of the surface-associated crystals of drug. The drug crystals observed on the surface were probably formed as a result of their migration along with water to the surface during drying [Figure 5b]. The overall surface morphology was observed the aceclofenac pure drug crystals covered by polymer matrix to controlled diffusion of drug in the dissolution media and ultimately prolong the drug release

The swelling ratio of the beads was dependent on the pH of the solution. Under acidic conditions swelling of calcium alginate beads occurs scarcely. Under neutral conditions the beads will swell and the drug release depends on the swelling and erosion process. Being a polyelectrolyte, alginate can exhibit swelling properties that are sensitive to the pH, ionic strength and ionic composition of the medium.[20] Optical microscopy was used to investigate the hydration and swelling of microbeads at pH1.2, 4.8 and 6.8 up to 4hrs. The equilibrium swelling studies showed, with increase in the polymer concentration, swelling of beads was significantly increased. The low swelling in acidic media pH1.2 was probably due to proton-calcium ion exchange forming insoluble alginic acid regions and followed by solvent penetration into the gel net work. The swelling of beads was ultimately increased in pH 4.8 and pH6.8 at the end of 4h. This was due to increased solubility of the polymer in basic pH leading to relaxation of the cross-linked polymeric network. It has been reported that the swelling can be enhanced by the presence of phosphate ions in higher pH which displaces the Ca^{2+} ions within the beads.[Figure 6(a)] Increasing the concentration of calcium chloride produces the beads with higher levels of Ca^{2+} ions that could reduce the swelling of the beads in acidic medium. However, the amount of calcium in swollen gel films after 4h in the medium was about 10-30%, which has apparently to prevent total breakdown of the gel structures. The swelling behavior of beads in pH4.8 and 6.8 were observed as a result the swelling ratio slightly increases due to ionic exchange between the phosphate ions in the buffer and higher level of Ca^{2+} ions within the beads. [Figure 6(b)] When we compared the swelling ratio with prolonged cross-linking time maintaining same drug-polymer ratio and concentration of calcium chloride in the system showed appreciably maximum

swelling with increased pH level. These results may be because of the maximum extent of cross-linking that yielded compact beads, which might have rehydrated to a greater extent. The sequestering action of phosphate ions in higher pH media on Ca^{2+} ions may have contributed to the swelling of cross-linked beads. The lower rehydration of beads that were prepared at shorter cross-linking time may be correlated to incomplete cross-linking of sodium alginate. [Figure6(c)]We further observed the swelling ratio of microbeads prepared by various stirring speed could not much effect on the swelling equilibrium of the beads. When we compared the overall results of the swelling ratio of all formulations, the slowest swelling ratio was obtained at pH 1.2, whereas the highest at increased pH level of the medium initially, further they were broken after 2h. The overall results suggest that the dried beads swell slightly in the stomach. When they are subsequently transferred to upper intestine, the particles are begin to swell and they behave as matrices for sustained release of incorporated drug but they are subjected to erosion in the lower intestine.







***In-Vitro* drug release**

Generally, when microbeads formulated with hydrophilic polymer are immersed in water, they swell and form a gel diffusion layer that hinders the outward transport of the drug, hence

producing a sustained release effect. However, the drug release from alginate beads was pH dependent, all the formulations showed negligible drug release in acidic pH 1.2 (<5%w/w)in the range between 2.030±0.12 to 4.03±1.12 may be due to the stability of alginate at lower pHs and conversion of Ca-alginate to the insoluble alginic acid to formed tightening of the gel mesh work. In other hand, the polymer is eroded at alkaline pH and the contents are released in a sustained manner by both diffusion and slow erosion of polymer matrix. However, the swelling behavior of drug-loaded Ca-alginate beads at higher pH could be explained by the ionotropy that occurs between Ca^{2+} ion of alginate and Na^{+} ions present in phosphate buffer and consequently, capturing of the Ca^{2+} by phosphate ions. The ion exchange with phosphate buffer which resulted in swelling and erosion of the beads and formation of the solute Ca-phosphate all have influence on increase in the drug release rate at higher pH that might be the lower number of Na^{+} ions present in that buffer and consequently slower rate of ion exchange and swelling of the polymer at this pH. Based on these results we reported that the swelling is the main parameter controlling the release rate of aceclofenac sodium from alginate matrices is modulated by a swelling-dissolution-erosion process.

The effect of drug-polymer ratio on aceclofenac sodium release from different batches of microbeads is shown in Figure7 (a). Formulations F1 to F5 were showed the percentage of drug release in pH6.8 buffer media at the end of 6h was 80.74, 76.38, 69.28, 68.01, and 63.23. Moreover, at the end of 12hr in pH7.2 phosphate buffer solution the percentage of drug released in the range 98.54, 94.61, 90.63, 88.04, and 85.06 respectively. As the drug-polymer ratio increased, the release rate of aceclofenac sodium from the microbeads decreased. The slower in the release rate can be explained by the increase in the extent for swelling and the gel layer thickness that acted as a barrier for the penetration medium thereby retarding the diffusion of drug from the swollen alginate beads. However, the steady state release was achieved after an initial lag time and it was directly proportional to the concentration of sodium alginate. The first phase might be for the negligible dissociation of alginate beads in phosphate buffer mainly based on drug diffusion through the small pores and cracks. The second phase exhibited a burst-like release pattern, which was accompanied by alginate disintegration. The sodium alginate concentration in the formulation greatly influenced the steady state release of drug from the microbeads.

Effect of variation in the stirring speed on drug release profile were also been studied and observed aceclofenac sodium release from different batches of microbeads is shown in Figure 7(b). The percentage of drug release from the formulations F6 to F10 in pH 6.8 buffer media at the end of 6hr were showed 64.17, 69.68, 72.76, 78.58, and 84.14. The drug released at the end of 12hr in pH7.2 was observed 83.91, 87.20, 90.55, and 92.94. When the stirring rate was increased, the drug release was found to be faster. This may be due to the reduction in the size of microbeads, which are able to provide a large surface area for increasing in the drug release.

The effect of cross-linking agent on aceclofenac sodium release from different batches of microbeads is shown in Figure 7 (c). The percentage of drug release from the formulations F11 to F15 was observed in pH6.8 buffer solution at the end 6hr 76.15, 72.37, 64.66, 60.80, 57.72 and at the end of 12hr in pH7.2 phosphate buffer media was 94.20, 91.84, 88.44, 84.26, and 81.25 respectively. The results indicate that rate and extent of drug release decreased significantly with increase of concentration of calcium chloride, because sodium alginate as a linear copolymer consisting of β (1→4) mannuronic acid and α (1→4) L-guluronic acid residues; a tight junction is formed between the residues of alginate with calcium ions. However, in case of higher calcium chloride concentration due to increased surface roughness and porosity

[Figure4 (b)] and also poor entry of dissolution medium into the polymer matrix may be delayed drug release.

The effect of cross-linking time on aceclofenac sodium release from different batches of microbeads is shown in Figure 7(d). The percentage of drug release form the formulations F16 to F20 at the end of 6hr in pH6.8 buffer solution and at the end of 12hr in pH 7.2 phosphate buffer were observed in the range 80.25, 75.65, 71.80,66.24, 60.48 and 96.76, 94.45, 90.62, 86.60, and 82.15 respectively. An increase in the cross-linking time from 0.5-2.5h significantly decreased the drug release due to penetration of calcium to the interior of the beads. Faster drug release was observed with 0.5-1h which can be attributed to the poor binding of drug into the polymer matrix and also incomplete gelling of sodium alginate. Increasing the cross-linking time more than 2h, however, there is no significant change in the amount of drug release

Table 4: Study of various kinetic models on In-vitro drug release

Formulation code	Various Kinetic Models on drug release					
	Zero-Order	First-Order	Huguchi Matrix	Korsmeyer-Peppas	Korsmeyer-Peppas	
					n-values	k-values
F1	0.9117	0.9814	0.9124	0.9162	1.6448	3.0689
F2	0.9209	0.9774	0.9113	0.9201	1.6756	2.7783
F3	0.9392	0.9821	0.9108	0.9240	1.7315	2.3240
F4	0.9474	0.9829	0.9103	0.9250	1.7711	2.0693
F5	0.9521	0.9830	0.9097	0.9257	1.7764	1.9066
F6	0.9399	0.9803	0.9082	0.9291	1.7535	2.0130
F7	0.9372	0.9811	0.9088	0.9262	1.7449	2.1643
F8	0.9278	0.9801	0.9076	0.9217	1.7523	2.2625
F9	0.9129	0.9775	0.9602	0.9148	1.7482	2.4075
F10	0.9007	0.9768	0.9020	0.9115	1.7361	2.6019
F11	0.9224	0.9826	0.9142	0.9162	1.6704	2.8220
F12	0.9300	0.9846	0.9168	0.9153	1.6788	2.6173
F13	0.9410	0.9860	0.9156	0.9186	1.6988	2.3596
F14	0.9468	0.9857	0.9154	0.9276	1.6838	2.29.8
F15	0.9551	0.9854	0.9131	0.9347	1.6920	2.1173
F16	0.9104	0.9816	0.9114	0.9074	1.6874	2.8213
F17	0.9277	0.9826	0.9134	0.9154	1.7078	2.5682
F18	0.9432	0.9832	0.9126	0.9197	1.7203	2.3581
F19	0.9425	0.9828	0.9120	0.9777	1.7070	2.2797
F20	0.9518	0.9815	0.9079	0.9772	1.7552	1.8920

All the results shows S.D. n=3, n=Diffusion exponent related to mechanism of drug release, according to equation Mt/M_=Ktn , r-Correlation Coefficient

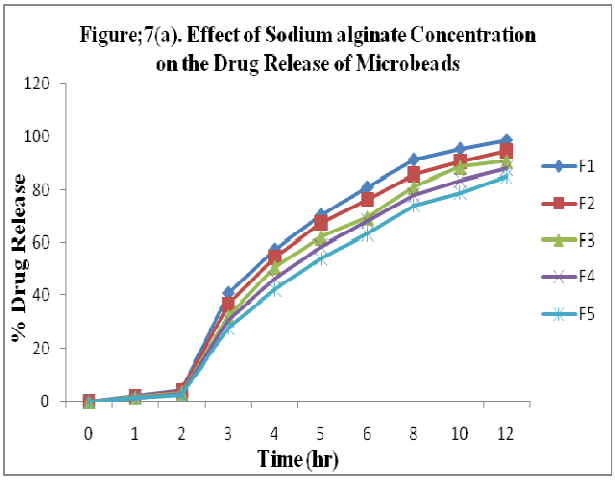
The *in-vitro* dissolution data were analyzed by different kinetic models in order to find out the n-value, which describes the drug release mechanism (Table; 4). The values of correlation (r) were calculated and were found to be more linear for first-order release as compared to zero order. Cumulative % drug release was analyzed using PCP-DISSOv2.08 Software. The kinetic data was best fitted to Korsmeyer and Peppa's model and good regression co-efficient was observed. The values of diffusion co-efficient ranged between n=1.6448 and 1.7764 indicating the drug release

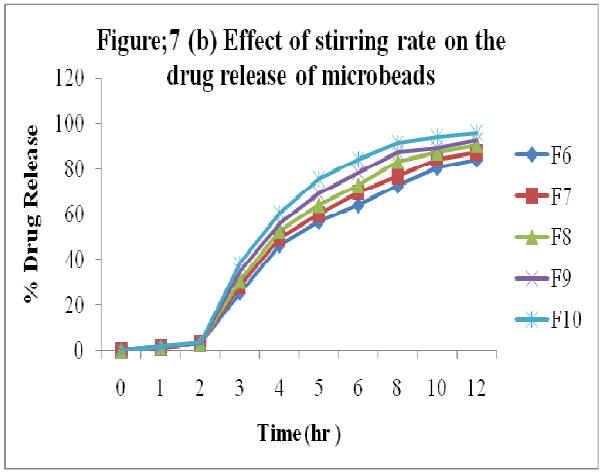
from the microbeads followed by Zero-order controlled by swelling and relaxation of polymer chains. For the developed optimum formulations were subjected to stability studies at25^{0}C/60%RH, 40^{0}C/ 75% RH up to 6 months. Overall, results from the stability studies indicated that capsules were physically stable but the drug content at 40^{0}C/75%RH was slightly reduced to 92.64%w/w after 6 months.[Table;5] Good stability was observed at low temperature for more than 6 months. More than 6 months drug-loaded microbeads inside the capsule at room temperature changes the sphericity and also decreases flow properties

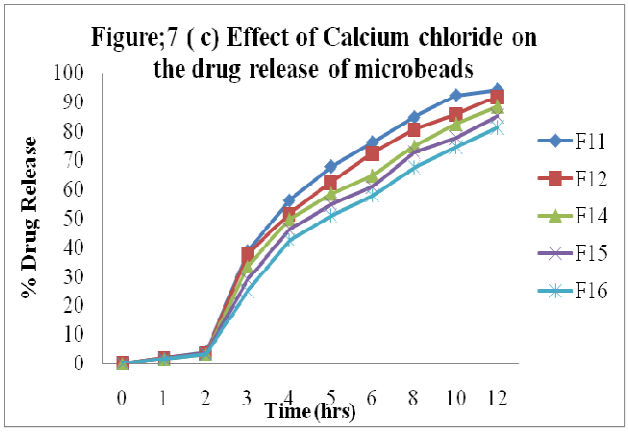
Table: 5 Stability Data for Aceclofenac Sodium Drug Loaded Microbeads

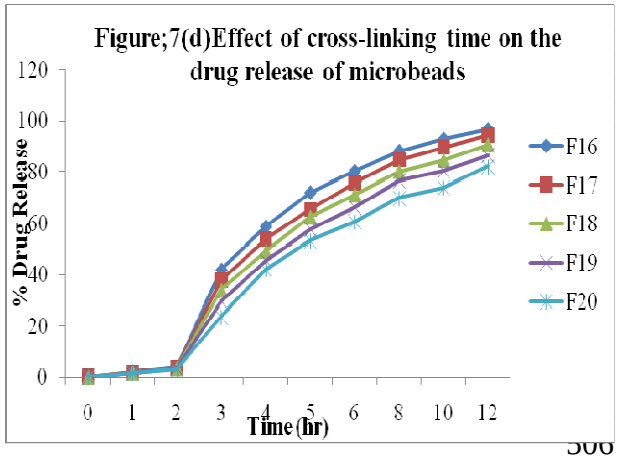
Serial No.	Sampling Interval (months)	Drug-content of microbeads			Physical characteristics		
		5^{0}C %w/w	25^{0}C/60%RH %w/w	40^{0}C/75%RH %w/w	5^{0}C	25^{0}C/60% RH	40^{0}C/75%RH
0	0	100	100	100	*	*	◙
1	1	100	100	99.56	*	*	◙
2	2	100	99.89	98.67	*	*	◙
3	3	100	98.76	97.45	*	*	◙
4	4	100	97.90	96.16	*	*	◙
5	5	100	97.32	94.55	*	*	◙
6	6	100	96.87	92.64	*	*	◙

**No change* ◙ *Small changes*









CONCLUSION

Ionotropic gelation technique is very easy to prepare, free from any organic solvents and low manufacturing cost can be successfully used for preparation of aceclofenac sodium microbeads using sodium alginate as drug release modifier. We can conclude from the above investigation that the proper selection of optimized formulation conditions is very important to achieve high encapsulation efficiency and to control the release of aceclofenac sodium from the alginate microbeads. The alginate drug loaded microbeads swelled at pH 1.2 predominantly very slow but underwent increases at pH 6.8. The drug release from the microbeads was affected by the pH of the dissolution medium initially at acidic buffer [pH1.2] very less of drug release but at pH 6.8 and pH7.2 all formulations showed burst release initially and then tend to release at sustained manner. Therefore, the aceclofenac sodium microbeads are promising pharmaceutical dosage forms by providing modified drug release. However, the formulated microbeads not stable in higher temperature more than 6 months. Therefore, further coating will need to maintain the stability.

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