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Effect ofDrying Techniques on Drug Release of Cross Linked Alginate Simvastatin Beads by using Hydrophilic Polymers.

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ABSTRACT

The aim to study of release kinetic, and to increase the bioavailability of simvastatin hydrogel beads and increase the residence time of dosage form in GI tractwith blend of sodium alginate as a coating material with hydrophilic polymers by ionic gelation method. The beads were characterized for swelling behavior and *in-vitro* release and other physical and analytical studies were done naming for surface morphology, entrapment efficiency, differential scanning calorimetry and XRD and FTIR studies and confirmed there will be no reaction among used excipients. Drying of beads was done by multiple techniques which shows influence on rate of drug release and on morphology of beads. The *in-vitro* release of the drug encapsulated beads in different media suggests that the release of the drug is governed mainly by the swelling and diffusion of drug molecules. Drying of beads confirmed its marked influence on rate of drug release. The optimized contains sodium alginate (3%) with carbopol 934 P was forms best one with zero order kinetics with non fickian mechanism on basis of korsemeyerpeppas equation. Prepared cross linked alginate-carbopolmicrobeads were best fitted higuchi model which indicated the drug release by diffusion in slow and sustained pattern.

Keywords: Gastro retentive**,** Simvastatin beads**,** Swelling behavior, Drying effects,

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INTRODUCTION

Though, the low bioavailability and short biological half-life of drug for the oral administration favors the development of a controlled release formulation [1].Multiparticulate system imparts its vital role in development of sustained release dosage forms. Now a day's many of research studies going for long days. Microbeads can improve the rate of bioavailability due to high surface to volume ratio and more contact time or residence time with mucous layer. The use of natural and thus biodegradable polymers to achieve desired release profile is widely accepted practice in pharmaceutical formulation. Among of all, particularly beadsposses and qualifies many of problems which will be common on fine powders.The parameters like high density, small particle size distribution, and regular shape. The concept of sustained dosage form calls many merits, of which mostly they maximize drug absorption, reduce peak plasma fluctuations [2-3] and minimize potential side effects Mucoadhesive preparations like microbeadshave been developed to increase the contact time of the dosage form, thus enhance drug absorption and its bioavailability[4-7].

Alginate is anionic linear polysaccharides, are linear polysaccharides extracted from brown seaweed. It composed of both D mannuronic (M) and L-guluronic (G) acids. Alginates are of pharmaceutical interest because of their non toxicity, biocompatibility and biodegradability. Alginate hydrogels have the potential to be used as either controlled release membrane or matrix systems for therapeutic drugs. The ability of sodium alginate to form gel in the presence of multivalent/divalent ions has been applied to prepare cross linked beads by ionotropic gelation method where the dispersion of alginate and drug material to be encapsulated is added drop wise into multivalent ion solution. The properties of the beads prepared by ionotropic gelation method are influenced by formulation and processing parameters. This statement is evidenced by several papers reporting that drug release and/or drug loading efficiency is dependent on type of drug and its physico chemical characteristics,[8-11]type and strength of polymer incorporation of various hydrophilic/hydrophobic additives[12-13],drug to polymer weight ratio as well as on process variables like curing time.

Simvastatin belong to category of anticholesterol, a crystalline compound, is a white, non hygroscopic fine powder, it is insoluble in water, and 0.1 N Hcl (30mg/ml and 60 mg/ml), and has gained the remark of getting low bioavailability due to not being soluble in water and its intestinal metabolism by CYP3 enzyme. Thus, simvastatin arrests a key step for cholesterol biosynthesis in the liver and is widely used in the case of hypercholesterolemia and dyslipidemia as an adjunct to diet. It belongs to BCS class II category drug having low solubility (1.45 µg/ml) and high permeability, hence, the dissolution rate becomes the governing parameter for bioavailability. These drugs exhibit variable bioavailability and need enhancement in the dissolution rate for improvement in bioavailability therefore it shows low oral bioavailability (5%) and it is well absorbed from GIT[14-15]. This drug exhibit variable bioavailability and need enhancement in the dissolution rate for improvement in bioavailability. Drug has biological half life3 h, but its bioavailability is only 5-7 % indicating extensive first pass metabolism in liver. Improvement of aqueous solubility in such a case is a valuable goal to improve therapeutic efficacy. Being a BCS Class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in bioavailability. The properties of the beads prepared by ionotropic gelation are influenced by formulation and processing parametersalong with coating materials along with other hydrophilic polymers ex.xanthan gum, carbopol 934 P, methyl cellulose and hydroxy propyl methyl cellulose (HPMC E15) were added to effective the rate of swelling and delay the rate of drug release of beads.

The rationale of the current work was to develop dosage form using gastro-retentive drug delivery technology.The characterization of these cross linked alginate gel beads and their swelling properties in different media and drying roleinconverting of wet beads into dry bead and their rate of drug release were discussed.

EXPERIMENTAL SECTION

Materials and methods

Simvastatin (Gift sample from Hetero lab, Hyderabad,India), Sodium alginate (SD Fine Chemicals) Aluminium chloride, Carbopol 934P (SD fine Chemicals Pvt. Ltd. Mumbai), Xanthan gum , Hydroxy propyl methyl cellulose , Methyl cellulose,Aluminium chloride, Potassium dihydrogen phosphate, Potassium

hydroxide pellets(E. Merck, India), Sodium lauryl sulphate, Methanol and Distilled water were also used. All other used reagents were of analytical grade.

Preparation of alginate beads

Accurately weighed amount of coating materials i.e. sodium alginate shown in table were transferred to a clean bowl. Sodium alginate with pure drug and hydrophilic polymers were dissolved in distilled water at a concentration of 3% (w/v) and 0.3 % w/v, and make it homogenization until it has to convert into smooth uniform viscous solution by using sigma blade mixture and agitated vigorously for 45 min. The solution forms foam solution, which was disappeared by keeping solution under sonicator for 1 hr. Beads were prepared by dropping polymer blend slowly into curing solution which contains 5% $Alcl^{+3}$ w/v through needle and formed beads by ionic gelation mechanism and keep wet and soft beads as such in curing solution for one hour to harden surface of wet beads. And make it sure the distance between the edge of the needle and the surface of the $Alcl^{+3}$ medium was about 10 cm. The beads were collected, washed with distilled water twice and dried by different techniques.

Table 1.Formulation of simvastatin alginate beads

Code No.	Polymers	Curing time (min.)	Curing agent	Conc. of curing agent(%w/v)
1	Sodium alginate + Carbopol 934P	60	$Alcl^{+3}$	5
2	Sodium alginate + Xanthan gum	60	$Alcl^{+3}$	5
3	Sodium alginate + Methyl cellulose	60	$Alcl^{+3}$	5
4	Sodium alginate + HPMC E15	60	$Alcl^{+3}$	5

Solubility

An excess amount of simvastatin was placed in contact with phosphate buffer of pH 1.2, 4.5, 6.8 and 7.4 to investigate drug solubility throughout the whole pH range of the gastrointestinal tract (GIT). The samples were shaken for 72 h at 37°C in a horizontal shaker. The supernatant was filtered through a Millipore filter (pore size 0.45 mm). The filtrate was immediately injected at a flow rate of 1.8 mL/min (Hypersil C18 column, Thermo Electron Corporation) and assayed using an HPLC with UV detector (SPD-10A, Shimadzu, Japan) at 240 nm. Acetonitrile: 0.05M ammonium acetate (60:40 v/v) was used as the mobile phase. All experiments were conducted in triplicate.

Determination of wavelength of maximum absorbance of simvastatin

Standard simvastatin solution 1 ml exactly was transferred to a 10 ml standard volumetric flask. The volume was adjusted to 10 ml with 6.8 phosphate buffer solution. The absorbance of the final solution (10 µg/ml) was scanned in the range 400-200 nm against 6.8 phosphate buffer (6.8) with 0.03% SLS as a blank.

Preparation of calibration curve of simvastatin

Standard solutions of simvastatin in the concentration range of 5 µg/ml to 65 µg/ml were prepared by transferring 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5 5.0, 5.5, 6.0, and 6.5 ml of simvastatin stock solution (100 ppm) to a series of 13 volumetric flasks of 10 ml. The volume in each volumetric flask was made up with the solvent. The absorbance of the solutions were measured at the wavelength (λmax) 238.0 nm against phosphate buffer pH 6.8 with 0.03%w/v SLS as blank and calibration curve was plotted solubility profile.

Determination of drug content

For determination of drug content, 10 mg of beads were crushed into fine powder and dissolved in 100 ml of 6.8 phosphate buffer for 12 h. The filtered solution was measured for simvastatin content using a UV spectrophotometer at 238 nm. Drug content was computed using a calibration curve (R^2 = 0.9998) prepared using solutions with concentrations of 1-6 µg/mL of drug.

Drug loading and entrapment efficiency

To determine the entrapment efficiency, specific amount of simvastatin microbeads were crushed and suspended in 100 ml of freshly prepared phosphate buffer of pH 6.8 with constant agitation at room temperature for 20 h. Finally, the solution was filtered through desired whatman filter paper, and drug content was determined by using UV absorption spectrophotometer at the wavelength of 238 nm. The entrapment efficiency was calculated by using the following equation. The drug loading capacity of the beads was then computed according to the following equation.

$$\textbf{Drug Loading (\%)} = \frac{\text{Total amount of drug in beads}}{\text{Weight of the beads}} \times 100$$

$$\textbf{\% Drug Entrapment} = \{\text{Calculated drug content} | \text{Theoriticaltical drug content}\} \times 100$$

Swelling study of individual beads[16-18]

Swelling property of the beads was studied by a measurement of percentage water uptake as a function of time. Three different beads exposed to aluminium chloride at different time intervals were selected and incubated with 6.8buffer medium in a watch glass. The mass of all the three beads was taken at different intervals of time and the average value was calculated. During this process, care should be exercised while handling of the swollen beads so as to avoid any weight loss due to breaking or erosion of the beads. All the mass measurements of the swollen beads were taken on single pan balance. The percentage uptake of water was calculated as by using following equation.

$$\%\,\text{water uptake} = \left(\frac{\text{wet weight} - \text{dry weight}}{\text{dry weight}} \right) 100$$

Differential Scanning Calorimetry (DSC)[19]

DSC studies were carried out by using Shimadzu thermal analyzer (TA-60WS). A few milligrams of beads sample, were hermetically sealed into aluminium pans and heated under nitrogen atmosphere with the heating rate of 10 °C/min.

Scanning Electron Microscopic studies (SEM)

Surface topography of the beads were evaluated by scanning electron microscopy.SEM photographs were taken with a scanning electron microscope model Bruker nano X flash detector 5010,Germany, at the required magnification at room temperature. Simvastain showed a solubility of 1.45 µg/mL in distilled water, 14.5 µg/mL in pH 1.2 buffer, and 24.4 µg/mL in pH 6.8 phosphate buffer. Simvastatin exhibits maximum solubility in phosphate buffer pH 6.8 (i.e. simvastatin solubility increaseswith an increase in medium pH). In short, it exhibits pH-dependent solubility.

***in-vitro* release studies**

In-vitro release of prepared microbeads were carried in triplicate by using united states pharmacopoeia (USP) dissolution type II apparatus (Basket type) at 37± 0.5º C under 60 rpm. Freshly prepared phosphate buffer of pH 6.8 (900 ml) was selected as dissolution medium. Microbeads containing 20 mg equivalent of drug was placed basket and which is placed in 900 ml of phosphate buffer pH 6.8 with methanol in 9:1ratio dissolution medium. The revolution speed of the basket was maintained at 60 rpm. At different time intervals, 5 ml of dissolution medium was collected and the dissolution media was always replenished with a fresh stock solution of 6.8 phosphate buffer solution. Suitable dilutions were done with the dissolution fluid; the samples were analyzed for the drug concentration by using UV-Visible spectrophotometer (Shimadzu, Japan) at 238 nm.

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Release kinetics

To study the data of release kinetics, statistical data was obtained from *in-vitro* dissolution study was fitted and make various kinetic models naming zero order as cumulative percent of drug released vs time, first order as log cumulative percentage of drug remaining vs time and higuchi's model as cumulative percent drug released vs square root of time, Hixon crowel describes the release from systems when there is a change in a surface area and diameter of particles. To determine the mechanism of drug release, the data was fitted into korsmeyer and peppas equation as log cumulative percentage of drug released vs. log time and the exponent n was calculated from slope of the straight line. The diffusional exponent, n, notifies the mechanism of release. For spheres, values of n between 0.43 and 0.85 are an indication of both diffusion controlled drug release and swelling controlled drug release (anomalous transport). Values above 0.85 indicate case-II transport which relate to polymer relaxation during gel swelling

RESULTS AND DISCUSSION

FTIR data for simvastatin

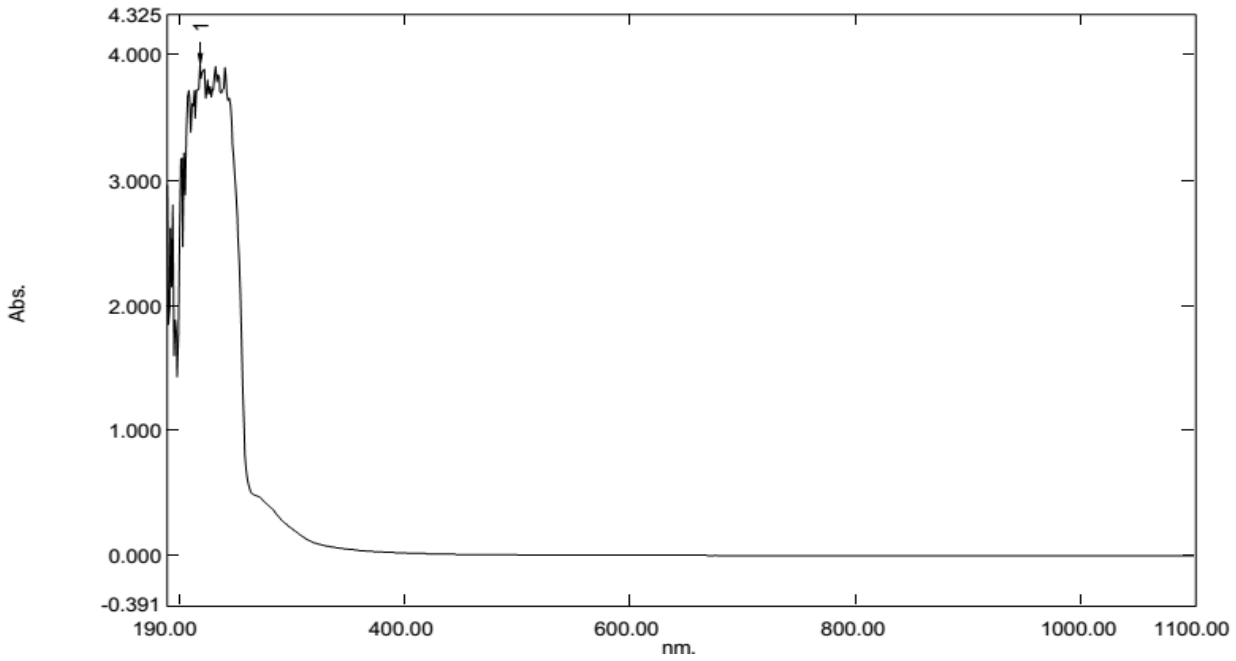
The spectrum of pure simvastatin presented characteristic peaks at various ranges mainly 3392.78 cm^{-1}(alcoholic O-H stretching vibration), 2926.8715 cm^{-1}(methyl and methylene C-H asymmetric and symmetric vibration)and 1697.35 cm^{-1}(lactone C=O and ester C=O stretching), 1390.67 cm^{-1}(methyl and methylene C-H bending vibration), and 1267.23 cm^{-1},1154.21 cm^{-1} and 1029.98 cm^{-1}(lactone C=O and ester C-O-C bending vibration).

On the other side the characteristic peaks of HPMC are at 3050–3750 cm-1 and are attributed to the –O–H stretching and the triple peak in the so-called fingerprint spectrum area of >C–O– at 960–1230 cm^{-1}.

UV spectrum of simvastatin

The absorbance of the final solution i.e.10 µg/ml was scanned in the range 400-200 nm against 6.8 phosphate buffer with 0.03% SLS as a blank. The spectrum was displayed in following figure 1.It gives maximum wavelength at 238 nm.

Figure 1: UV spectrum of Simvastatin in phosphate buffer pH 6.8 with 0.03% w/v SLS.



pH-dependent solubility studies[20-22]

Saturation solubility was conducted by shake-flask method plain simvastatin excess quantity was placed in separate glass-stoppered flasks containing 10 ml of distilled water. The samples were placed on a magnetic stirrer at 37 °C and at 120 rpm until equilibrium was achieved (20 hr). The aliquots were filtered through whatman No. 41 filter paper only. The filtrates were diluted appropriately with distilled water and assayed spectrophotometrically at 238 nm. 0.03% SLS was added to improve the solubility of simvastatin. Simvastatin was found to be freely soluble in methanol. The pH dependent solubility of simvastatinwas determined in pH 1.2 and pH 6.8 buffers. Solubility values of simvastatin at 37°C in aqueous buffers of pH 1.2, 4.5, 6.8, and 7.4 were 14.498, 8.261, 24.861 and 26.087 mg/mL, respectively. The solubility of simvastatin in other solvents and media has been studied previously [23].It was reported that simvastatin is virtually insoluble in water, with solubility of 1.5 mg/mL at 23°C[24-25].

Simvastatin showed a solubility of 1.45 µg/mL in distilled water, 14.5 µg/ml in pH 1.2 buffers, and 24.8µg/mL in pH 6.8 phosphate buffer.

Pre compression evaluation studies

All the formulations were evaluated forrheological studies which covers angle of repose, bulk density, tapped density, carr's index and Hausner's ratio. Their values were listed in following table 2.

Table No 2: Evaluation of pre compression parameters of formulations.

Formulation	Angle of Repose* (θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carrs Index* (%)	Hausners Index
1	17.99	0.32	0.321	17.98	1.13
2	21.32	0.29	0.297	18.12	1.09
3	24.23	0.32	0.413	20.32	1.43
4	21.89	0.32	0.342	19.23	1.96

***Results are given in mean of triplicate.**

Morphology of the beads

The selection of drying techniquehas influence the morphology i.e. size and shape of dry beads. Closed detailed examination by SEM studies,we can observed surface structure reveals cracks caused by partial collapsing of the polymer network during drying. In addition, appearance of pores with small diameter of micrometers and severe wrinkles are present, in contrast ethanol drying caused significant improvement on the maintenance of the spherical shape and led to the decrement of the cracks on the surface.

Ethanol treatment

During ethanol drying, a beads show extended dehydration of the alginate membrane which surrounding and coversthe entire bead surface, leading to corrugations and loss of the spherical shape i.e. contract like. On the other hand, ethanol treatment contributed substantially to the reduction of the roughness of the alginate layer and the elimination of the cracks observed on the surface and resulted in a smoother surface of beads in outer side.

In the current work it was demonstrated that drying conditions had great impact on shape and morphology of beads including outer surface as well as internal structure characteristics of the beads.

The freeze-dried beads were the largest as they remained almost of the same size as before drying i.e. no change in physical appearance.Their surface was almost rough.Their internal structure was almost porous and more porosity and less physical strength making them and offerseasy brittle to the touch. Such characteristics of freeze-dried beads are due to the rapid sublimation of frozen water from alginate matrix

resulting in formation of pores in areas of former ice crystals without having time to shrink. Over all the freeze-dried beads were found to be the largest and the most spherical shape.

Fluidized drying

Fluidized-bed-dried and air-dried beads substantially shrankand became smaller during drying. The first ones were folded and irregularly shaped (Figure 1:. 2c). It is supposed that fluidized-bed drying was very rapid resulting in immediate drying of the bead surface. As a consequence of liquid inner part, beads collapsed and particles of irregular shape were formed. The air-dried i.e. at room temperature beads were the smallest (Figure 1: 1d). They were more spherical than fluidized-bed-dried beads (Figure 1:. 2) owing to slower water removal during air-drying resulting in slower and more uniform shrinkage of beads.

Oven drying

The wet beads dried by hot air oven in order to dry it has proved that the rate of release of drug from cross linked alginate beads was faster than beads which dried by at room temperature. In case of drying done by oven the beads forms small size beads in comparison to air drying.

Effect of freeze drying

The freeze-drying method could reduce the roughness and eliminate cracks on the surface of dry beads, interest point is that there is a chance of that the drug molecules are more tightly bound within the gel matrix layer during the freeze-drying process.

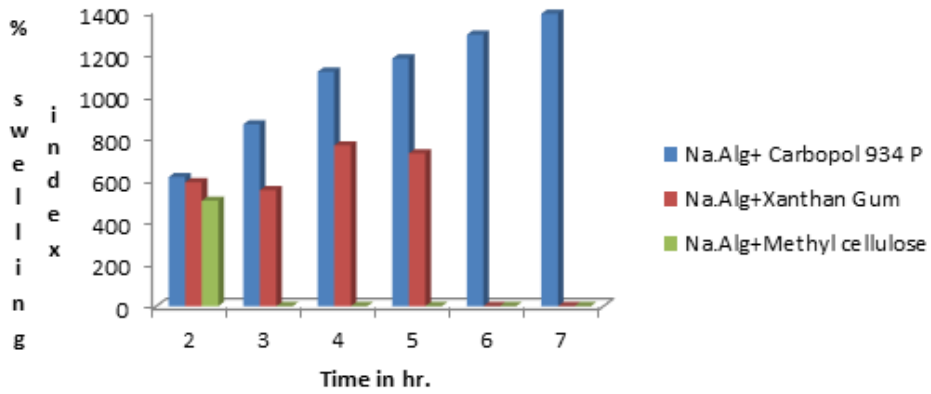
Overall, on basis of all drying techniques, it was reported that due to the porous structure and higher size offreeze-dried beads the water uptake into the bulk of beads was greater compared to vacuum-dried and air-dried beads[26]with dense network in interior surface of beads.

Such difference inwater absorption could have a tremendous impact on drug release kinetics. This indicates that and confirms owing to changes in bead morphology during drying conditions it surely affect drug release from the cross linked alginate beads.

Swelling atmosphere

The swelling mechanism in this case is related with the Al^{+3} and Na+ exchange process. The same cross linked alginate beads tend to shrink when exposed to the acidic environment of gastric fluid. Ouwerx and coauthors (1998) have studied that at acidicpH values (<4) the carboxylate groups of alginate are protonizedand hence the electrostatic repulsion among these groups weakensand shrinkage is favored. The swelling intensity in the basicenvironment of phosphate buffer solution begins to decline indicating dissolution ordegradation of beads.

Figure 2: Percentage swelling index of formulations.



***Results are given in mean of triplicate.**

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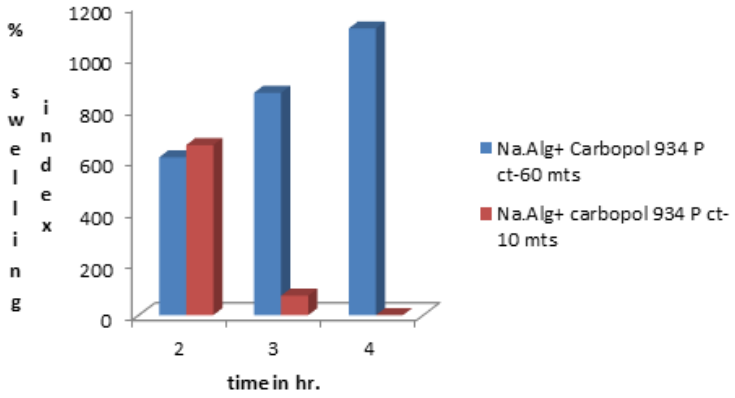
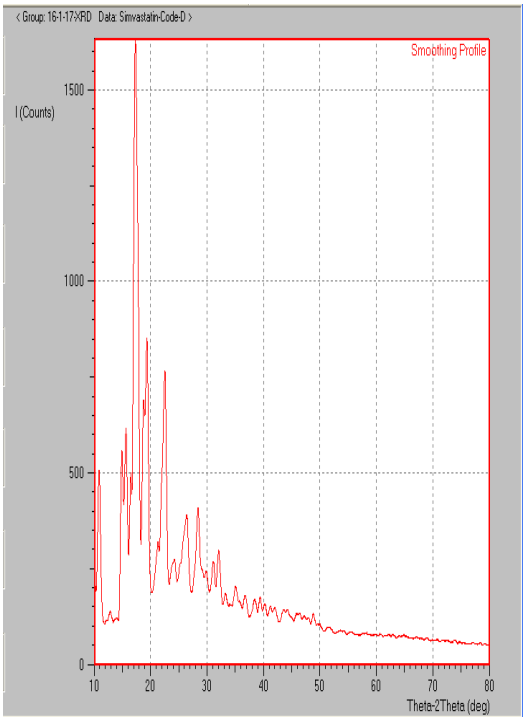
Figure 3: Percentage swelling index of formulations containing sodium alginate and carbopol 934 P at different curing time only. (Ethanol drying technique).



***Results are given in mean of triplicate.**



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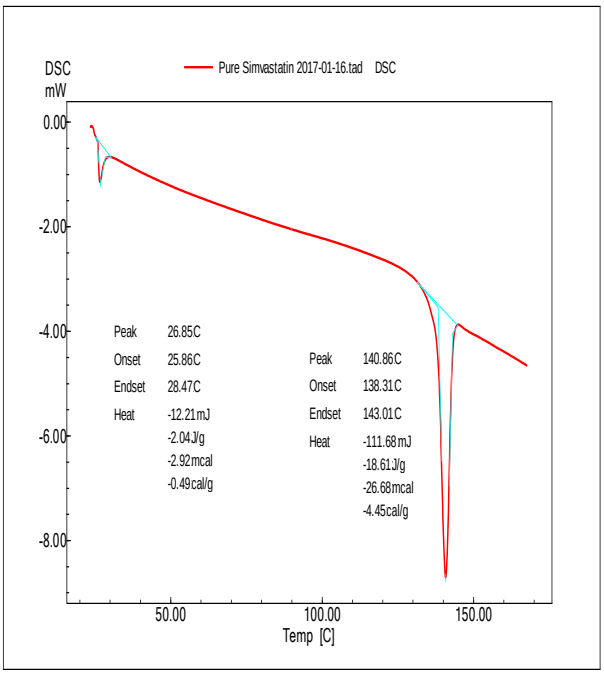

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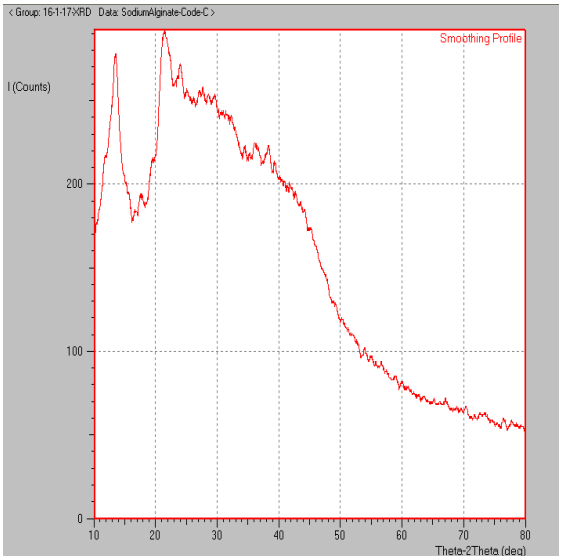

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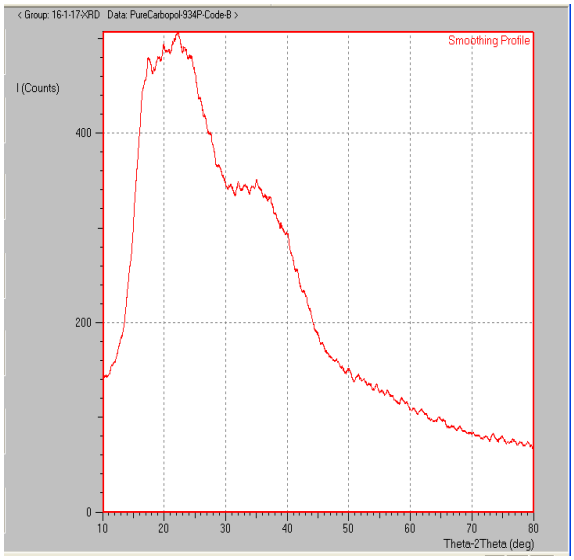

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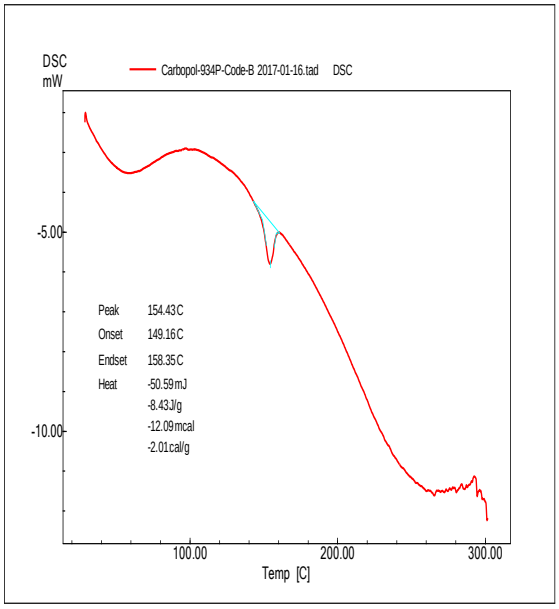

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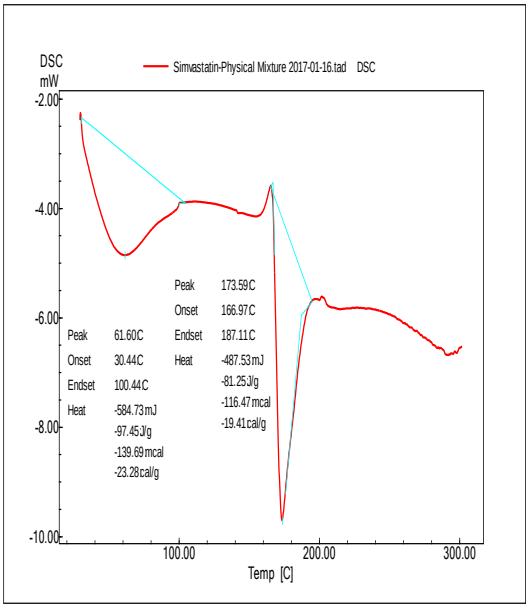

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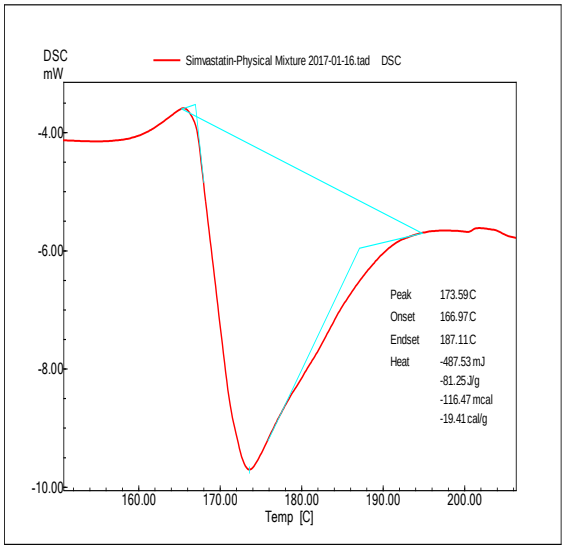

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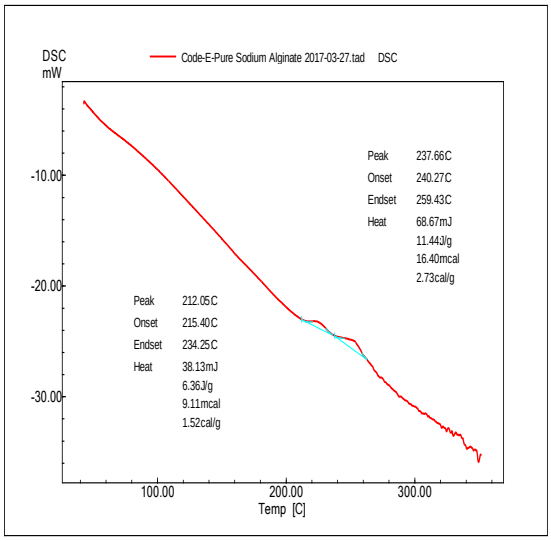

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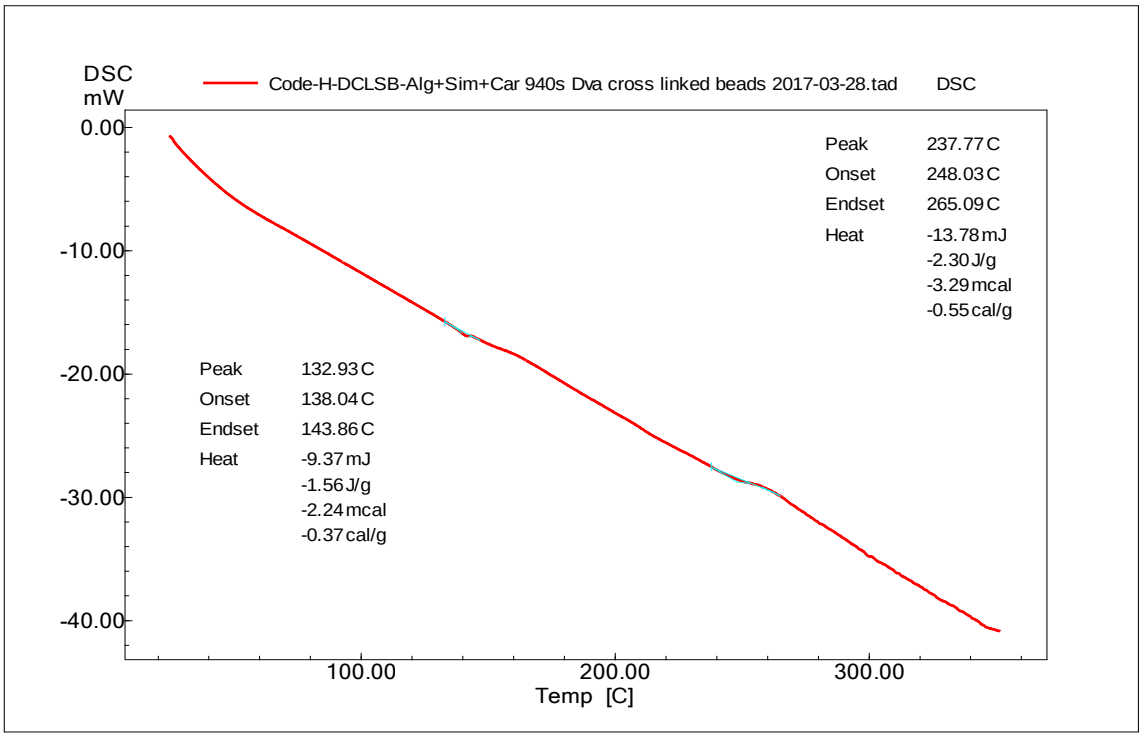

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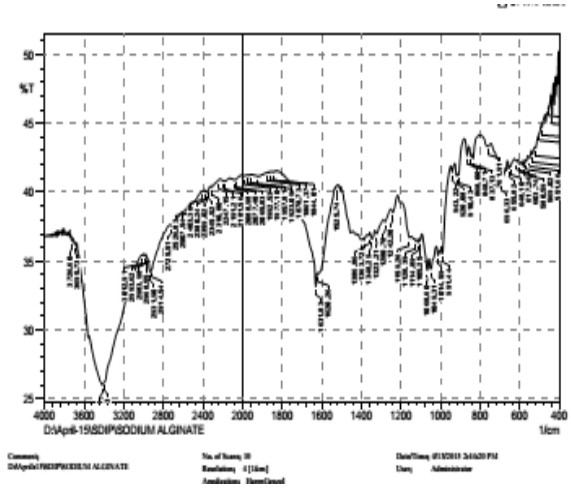

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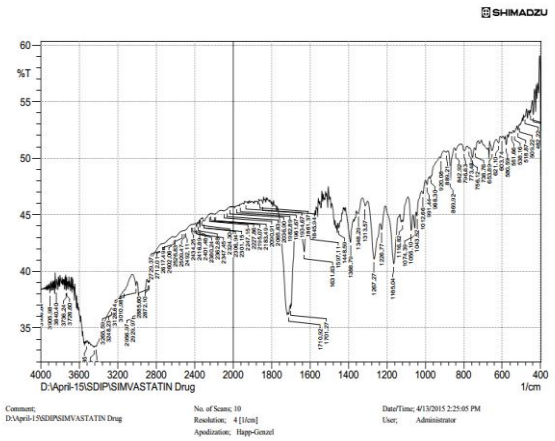

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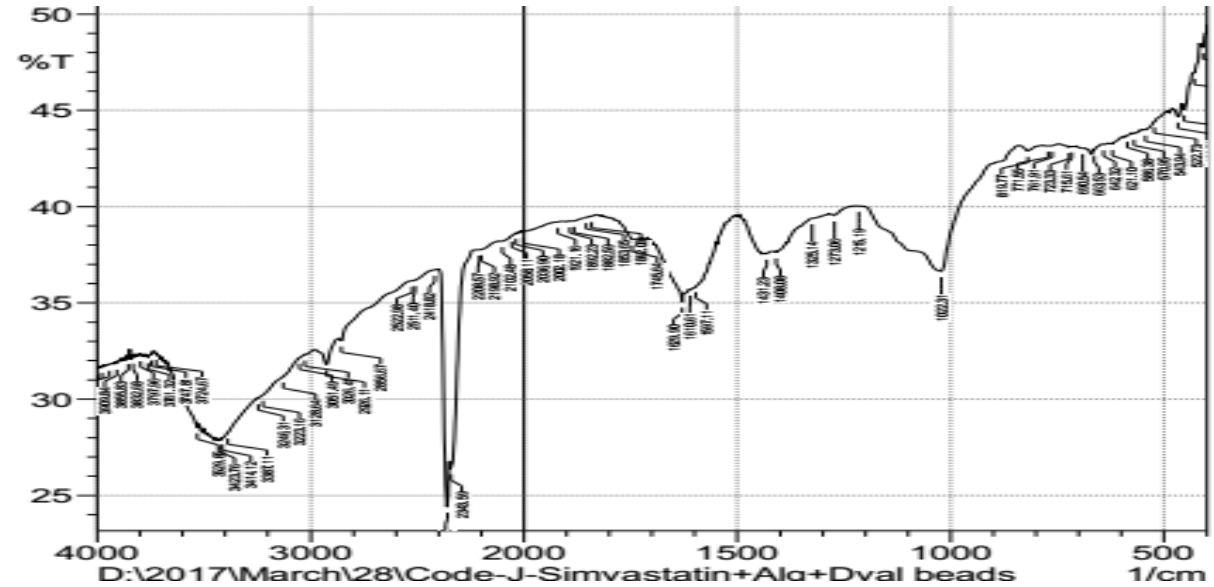

(L)

Figure 4: A) XRD spectra of pure simvastatin B) DSC spectra of pure simvastatin C) XRD spectra of pure sodium alginate D) XRD spectra of pure carbopol 934 P E) DSC spectra of pure carbopol 934 P, F & G) DSC spectra of physical mixture, H) DSC spectra of pure sodium alginate, I) DSC spectra of physical mixture, J) FTIR spectra of pure sodium alginate, K) FTIR spectra of pure simvastatin and L) FTIR spectra of physical mixture.

XRD studies:

The diffraction pattern of the pure drug showed a highly crystalline nature, indicated by numerous distinctive peaks at a diffraction angle of 2θ (28.10°, 21.4°, 18.20°, 15.8°, 16.4°,14.2°, 11.8°, and 10.0°) in a good agreement with previously published data. Whereas the XRD study demonstrated that there was a significant decrease in crystallinity of pure drug present in surface of alginate beads which resulted in an increased dissolution rate of simvastatin

Differential scanning calorimetry

The DSC thermogram of simvastatin exhibits a sharp melting endotherm at 138 .01°C.

Dissolution study of controlled release formulation of simvastatin

The *in-vitro* dissolution profile of the designed formulations of controlled release was carried out using USP type II apparatus under conditions specified (temp 37± 0.5° C, 60 rpm) [27]. The higher amount of drug was released in 6.8 phosphate buffer than acidic buffer, this may be due to the higher swelling rate of the alginates in 6.8 phosphate buffer medium than acidic medium .In 6.8 phosphate buffer, cross linked beads undergoes relaxation of polymers due to the difference or increase in osmotic pressure of beads and this renders the increase in surface area of wet beads, thereby it forms micron size pores and release the drug by diffusion mechanism.

In the case of dry alginate gel beads, the release profiles might be characterized by a biphasic behavior. For example, in the first stage, from zero to about 120 min, two apparent mechanisms, swelling and diffusion occur to govern the overall drug release from the beads. During the second phase, from 120 min. onwards the swelling of the beads is increased. Therefore, only diffusion will affect the release of drug molecules. In both systems, the initial release rate and the total amount of drugs at a given time were in the following order: PBS > pH 3 buffer solution. This indicates that the drug release of the beads is governed particularly by the swelling of the polymer network.

It is observed from the data of cumulative drug release profle (Figure 5) that the more sustained effect occurs with the combination of sodium alginate and carbopol 934 P which may attribute to the formation of larger microspheres due to high viscosity of carbopol 934 P.Hydroxy propyl methyl cellulose was undergoing high swelling than other used polymers.

Pure simvastatinshowed a poor dissolution only 27 % of drugwas released at the end of 120 min.under standard conditions.The drug release of optimized formulation was in controlled manner when compared with pure simvastatin. Results of *in-vitro* dissolution studies obtained were tabulated and shown graphically according to following modes of data treatment.

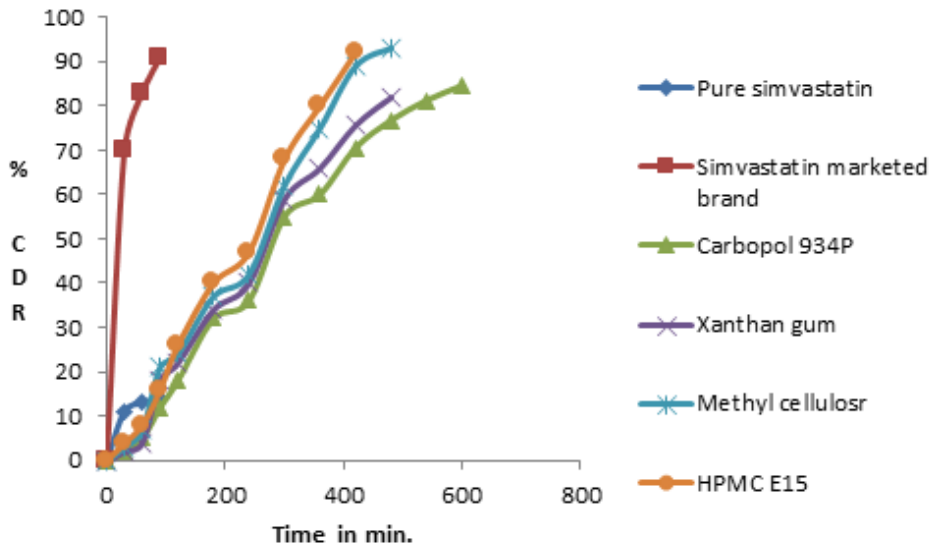

Figure 5: *in-vitro* profile of cross linked hydrogel beads.

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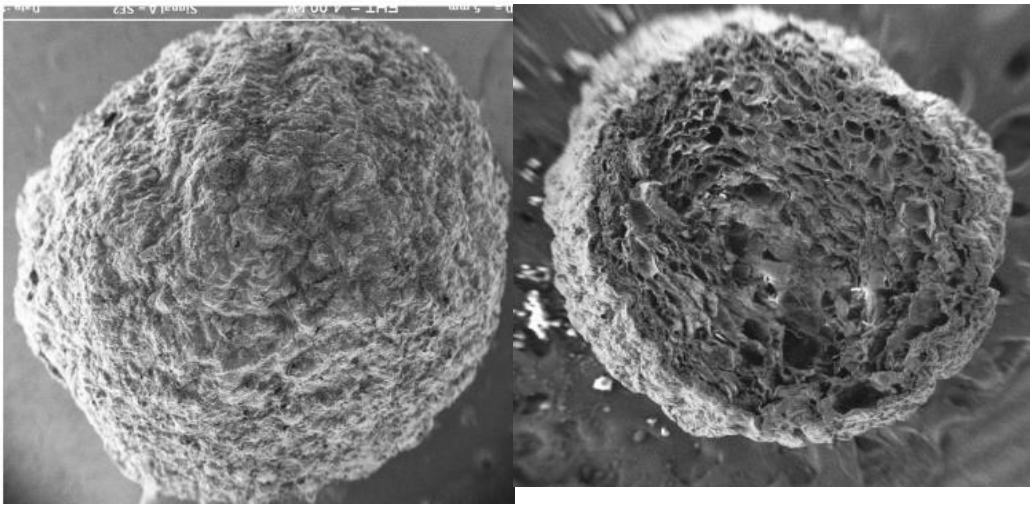
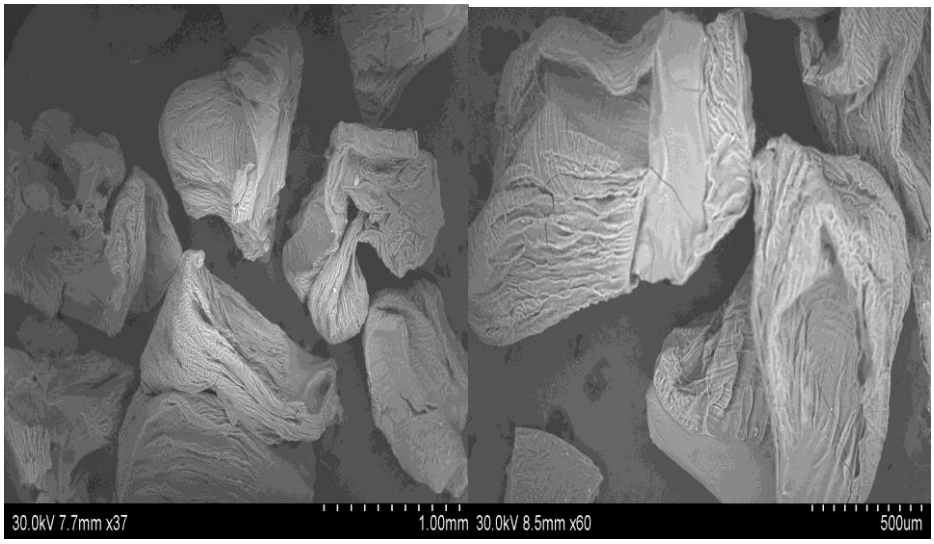
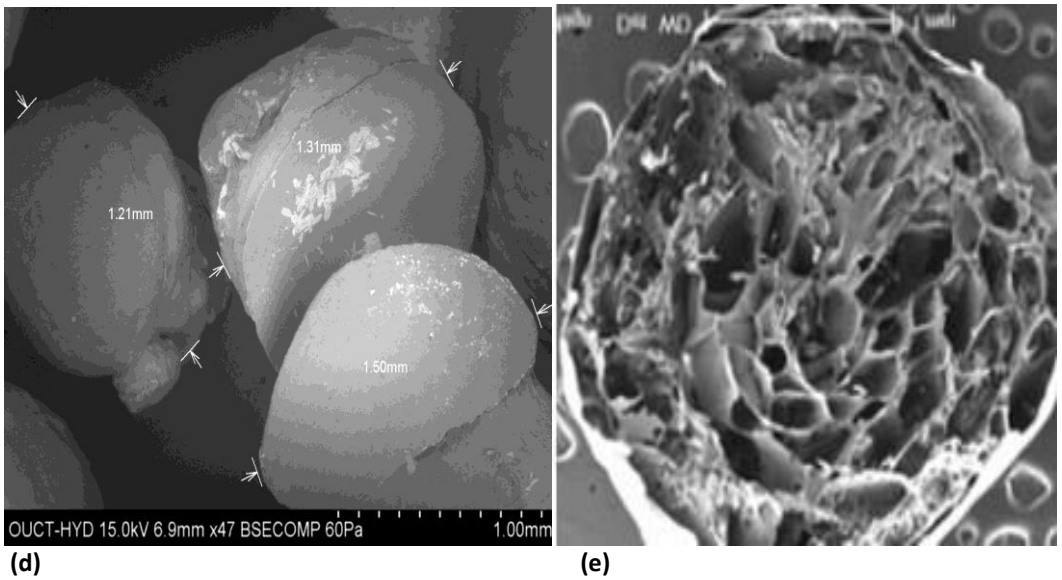


(a) (b)



(c)



(d) (e)

Figure 6: SEM images of the composite sodium alginate hydrogels beads. (a) Freeze dried bead, (b) Fluidized bed dried beads, (c)ethanol dried beads, (d) room temperature dried beads and (e) oven dried beads.

Table 3: Release kinetics data of optimized batch.

Batch code	Zero order	First order	Higuchi	Korsemeyerpeppas
Sodium alginate+Carbopol 934	R^2 =0.979 Y=0.155x0.155	R^2 =0.76 Y=0.002x+0.615	R^2 =0.939 Y=4.125X-18.99	R^2 =0.878 Y=0.802X-0.369

***Results are given in mean of triplicate.**

Table 4: Results of stability study

Parameters*	Before stability testing	After stability testing*
Encapsulation Efficiency	60.90±0.53	59.01±0.21
% CDR	84.5±1.23	83.23±1.63

*** n = 3 (average±SD).**

CONCLUSION

Our study has reported and suggestion microencapsulation done by choosing ionic gelation techniques is inexpensive,producing high yield and easiest over other techniques and maintain sustained release for a period of long time. Formulated beads exhibited nearly zero order kinetics and the release profile was of matrix diffusion type. The *in-vitro* kinetic release obeyed zero order kinetics with mechanism of release was followed by non-fickian diffusion due to more hydrophilic nature of polymer and drug. The increase in concentration of polymer, decreases the release of drug. The drug release mechanism of the dry beads is mainly controlled by the swelling of the polymer network at the early stage. It was found to be a promising formula in the development of a novel sustained drug delivery that helps to reduce the dose of the drug and improve its bioavailability. These results may be due to the prolongation of the contact time of the microbeads to the mucin because of swelling mechanism and which increases the duration of the action of the drug, retention time and its bioavailability. The optimized batch was subjected to one month stability study and did not show any significant physico chemical changes so considered to be stable.

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