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Development and effect of drug release from simvastatin loaded sodium alginate micro beads

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Abstract

The objective of the present study was to prepare the microbeads of Simvastatin loaded with sodium alginate to provide control release of drug delivery system. So, the design of drug delivery system was to improve and enhance the bioavailability of drug. The Simvastatin loaded microbeads were prepared by the ionic gelation method using polymer such as sodium alginate as a natural substance. Simvastatin loaded sodium alginate microbeads were formulated by different cross linking agent like $CaCl_2$, $BaCl_2$, $ZnCl_2$ and $FeCl_3$ in different ratio. The microbeads were spherical, free flowing exhibited drug content uniformity and high drug encapsulation efficiency. The swelling and drug release behavior depends upon amount of cross linking agent used in the microbeads. This released the drug up to 24 hours where beads released the drug up to 6 hours. The FTIR analysis of drug, polymers and the optimized formulation indicated the compatibility of the drug with the polymers. The DSC studies confirmed the drug polymer interaction in the microspheres. The SEM studies influence the rate of drug release from the microbeads. The present study concludes that the swelling and *In-vitro* release behavior of Simvastatin loaded sodium alginate microbeads can be considered as a promising control release drug delivery system.

Keywords: Simvastatin; Sodium Alginate; Microbeads; Control release

1. Introduction

The pure forms of drug or therapeutic active substances are not administered as such but they are fabricated as dosage form of specified size, shape and texture. So, all the possible delivery routes like oral, topical and parenteral to maximize therapeutic response must be considered (1). The oral route has been the preferred route of administration for many drugs. The administration of conventional dosage form in a particular dose and time through oral route is possible to control the constant dose concentration in blood plasma (2). This results fluctuation in plasma drug level and leads to several dose related toxic effects and reduces patient compliance (3). After oral ingestion the materials are stored in the stomach and mixed with the GI fluid, converted into liquid mass and then pass gradually into the upper small intestine. Thus, the GIT represents a primary barrier for oral absorption of drugs (4).

The term controlled release is the delivery systems to deliver the drug locally or systemically for a known time period (5). The release of active ingredients from controlled release drug delivery produces the release rate not only in advanced manner but also repeatedly from one unit to another (6). Most of the oral control release products are enter into the GI-tract and the fluid slowly penetrate through the outer layer of polymer matrix which includes the dissolution, swelling and formation of thick hydrodynamic layer (7,8,9).

Simvastatin is an antihyperlipidemic drug. The oral route is the most commonly used and preferred route of choice for the delivery of drugs. It is rapidly absorbed by the liver after oral administration and undergo metabolism(10).

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The primary action is to increase the excretion of low density lipoprotein receptors in the liver which occurs in response to inhibition of HMG-COA reductase. It leads to increased clearance of low density of lipoproteins (11). Cholesterol from the plasma with a subsequent reduction in both low densities. Lipoproteins and cholesterol (12). Thus, Simvastatin arrests a key step of cholesterol biosynthesis in the liver and is widely used in the treatment of hypercholesterolesterolemia and dyslipidemia (13). After, oral administration, Simvastatin is metabolized to its B-hydroxy acid form (Simvastatin acid) by the cytochrome-3A system. So it is used to reduce LDL-cholestrol(14). The ionotropic gelation technique was selected to prepare Simvastatin loaded microbeads such as sodium alginate along with formulated by different cross linking agent due to its simplicity and low cost(15,16). The aim of the present study was to prepare and evaluate the microbeads as a new control release system for Simvastastin.

2. Material and methods

Simvastatin was obtained as gift sample from Aurobindo Pharma Hyderabad. Sodium Alginate was obtained from Nice Chemicals, Kerala and Natural Industries, Mumbai. All the chemicals were analytical grade for the purpose of research.

2.1. Preparation of microbeads

400 mg of sodium alginate, 40mg Simvastatin, 1.25gm cross linking agent &10ml of water taken for preparation of microbeads.4% w/v of sodium alginate was prepared by adding 400mg of sodium alginate to 10 ml of distilled water in a 25ml of beaker and subjected to heat. To the above slurry, 40mg of Simvastatin was added with constant stirring by magnetic stirrer for specific period of time to get deflocculated suspension. Then, 5% $CaCl_2$ was prepared by adding 1.25gm of $CaCl_2$ to 25ml distilled water in a 100ml of beaker. The bubble free polymers was taken in a 10ml syringe (20mm size) and added drop wise into cross-linking media of 25ml cacl2 solution to get spherical capsules. The drug loaded microbeads was allowed to stand for 2hrs curring time(18). After the specific period of time, microbeads were taken out by filtration and allowed to dry for 24 hrs. Similarly, polymers were crosslinked with $BaCl_2$, $ZnCl_2$ and $FeCl_3$. The formulation variables were followed the above procedure and subjected to dry for 24 hrs.

2.2. Evaluation of micro beads

The average particle size of the prepared beads was measured by sieve analysis methods. The average particle sizes of different formulation are shown in the Table 1.The yield of formulated microbeads was evaluated by comparing the practical yield with that of the theoretical yield. Swelling property of microbeads was studied by a measuring the percentage of water uptake as a function of time. Evaluation of swelling behavior of Simvastatin loaded sodium alginate was carried out in phosphate buffer of pH 7.4. 20mg of beads were placed in watch glass containing 5ml of 0.1N HCl in respective media. The schedule experiment was carried out at room temperature. The swelling beads were removed at a definite time interval i.e. 30min, 1hr, 1.30min, 2, 3 and 4hrs. Then dry at room temperature for 24 hrs and then dissolved in phosphate buffer. The fractional change in weight was measured by using digital balance during swelling study. The percentage of water uptake was calculated by using following formula (19). All the studies were conducted in triplicate (n=3)

2.3. Determination of drug loading and drug encapsulation

Accurately weighed 100mg of Simvastatin loaded with sodium alginate was taken, crushed and suspended in 250ml of phosphate buffer of pH 7.4. The resulting solution was transferred into a stoppered conical flash and the flask was shaken occasionally for 24hrs.Next day it was stirred for 20min. using magnetic stirrer(20). The solution was filtered through whattman filter paper. The drug content in the filtrate was analyzed by using UV- Visible spectrophotometer (Shimadzu 1800USA) at 238.6nm against appropriate blank. The obtained absorbance was plotted on the standard curve to get the exact concentration of the entrapped drug. The drug loading and drug encapsulation efficiency of beads were calculated by using following formula. The flow properties of microbeads were evaluated using carr's Index. The results were averaged from three determinations. The angle of repose of the microbeads was determined by the fixed funnel and the free standing cone method. The Hausner ratio was estimated by using following formula.

$$\text{Drug Loading} = \frac{\text{Amount of drug in the beads}}{\text{Mass of drug loaded beads}} \text{ X100}$$

$$\text{Drug Encapsulation Efficiency} = \frac{\text{Actual drug content in beads}}{\text{Theoretical drug content in beads}} \text{ X100}$$

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Bulk volume}}$$

$$\text{Tapped density} = \frac{\text{Mass}}{\text{Tapped volume}}$$

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped volume}} \text{ X100}$$

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.4. *In-vitro* dissolution studies

Drug release study was carried out in dissolution test apparatus, USP type-I(TDT-06L),Electro lab. Mumbai. *In-vitro* dissolution study is an important tool in the evaluation of formulation and drug release profile from microbeads was examined in the buffer solution to mimic the various physiological region of GI-tract. The composition of dissolution medium was consisting of 0.238gm of phosphate buffer; 0.019 gm of potassium dihydrogen phosphate, 0.8gm of NaCl containing 0.5 gm (SLS). The volume of dissolution medium was 500ml of pH 7.4 phosphate buffer using USP type-I dissolution apparatus and the bath temperature was maintained at 37 °C ± 0.5 °C. The micro beads were placed in the dissolution vessel and the vessel was covered, the apparatus was operated for 8hrs at 50rpm. At definite time interval, 5ml of the dissolution fluid was withdraw and equal volume of fresh dissolution medium was replaced to maintain the volume of the dissolution medium constant. The withdrawn samples were analyzed spectrophotometrically at 238.6nm UV-Spectrophotometer (Shimadzu 1800USA). Formulation of Simvastatin loaded sodium alginate Simvastatin loaded sodium alginate was subjected to *In-vitro* dissolution studies. All the studies were conducted in triplicate (n=3)

2.5. FTIR Study

The drug polymer interactions were studied by using FT-IR Spectrophotometer (Bruker FTIR Alpha-T Series). The FT-IR Spectra of the pure drug, Simvastatin loaded sodium alginate polymer beads and its interpretations were observed in the microbeads.

2.6. Differential scanning calorimetric (DCS) study

The thermal analysis of Simvastatin loaded sodium alginate beads was performed by using DSC (DSC-4000 PerkinElmer). The samples were heated from 30°c to 310°c at an increase rate of temperature 40°c/min. so, heat flow as a function of temperature was measured for the drug and drug polymer mixture.

2.7. Scanning electron microscopy (SEM) study

The shape and surface characteristics were determined by SEM method (JSM-IT 700HR) using gold sputter technique. Photographs were scanned with range of 15kv magnification.

3. Results and discussion

3.1. Particle size determination

All the microbeads were prepared by ionic gelation method. The prepared microbeads are dried. The average particle sizes of microbeads of different formulations were measured by sieve analysis method. All the microbeads having its own particle size ranged from 391.36µm to 1063.75µm& represented in table no.1

Table 1 a Sieve analysis & particle size determination With $CaCl_2$

Sl no.	S-12	S-14	S-16	S-18	S-30	Total Wt(gm)	Avg. particle size (µm)
Batch-1	0.031	0.007	0.066	0.085	0.146	0.335	932.41
Batch-ii	0.012	*	0.022	0.092	0.126	0.252	846.46
Batch-iii	0.010	*	0.038	0.111	0.107	0.266	889.54

Table 1 b Sieve analysis & particle size determination With $Bacl_2$

Sl no.	S-12	S-14	S-16	S-18	S-30	Total Wt.(gm)	Avg. particle size (µm)
Batch-1	0.057	*	0.036	0.094	0.172	0.359	932.98
Batch-ii	0.013	*	0.015	0.068	0.256	0.352	738.66
Batch-iii	0.006	*	0.025	0.110	0.162	0.303	812.60

Table 1 c Sieve analysis & particle size determination With $Zncl_2$

Sl no.	S-12	S-14	S-16	S-18	S-30	Total Wt.(gm)	Avg. particle size (µm)
Batch-1	*	*	0.025	0.048	0.210	0.283	716.25
Batch-ii	0.015	*	0.014	0.055	0.128	0.212	816.13
Batch-iii	0.007	*	0.018	0.074	0.160	0.259	781.38

Table 1 d Sieve analysis & particle size determination With $Fecl_3$

Sl no.	S-12	S-14	S-16	S-18	S-30	S-36	S-44	Total Wt.(gm)	Avg. particle size (µm)
Batch-1	0.078	*	0.032	0.160	0.083	0.004	0.001	0.358	1063.75
Batch-ii	0.015	*	0.014	0.055	0.074	*	*	0.360	391.36
Batch-iii	0.007	0.004	0.018	0.074	0.075	*	*	0.315	499.80

3.2. Yield of Microbeads

The yield of microbeads was evaluated by comparing the practical yield with that of the theoretical yield. The percentage of yield was ranged from 48.18 to 81.81. The percentage of yield was calculated & presented in table no.2

Table 2 Yield of Micro beads

SL No.	Batch	Theoritical Yield	Practical yield	% of Yield
1	Calcium Chloride	440	335	76.13
		440	252	57.27
		440	266	60.45
2	Barium Chloride	440	359	81.59
		440	352	80.00
		440	303	68.86
3	Zinc Chloride	440	286	64.31

		440	212	48.18
		440	259	58.86
4	Ferric Chloride	440	358	81.36
		440	360	81.81
		440	315	71.59

3.3. Swelling study

The swelling behaviour of the microbeads were checked in 0.1N HCL & phosphate buffer solution(Ph 7.4) and allow to swell 37°C with a definite time interval. The swelling beads were observed and measured the weight in different interval of time & depicted in table no.3

Table 3 a Swelling Study With $Cacl_2$ (4:0)

Media	Batch	Int.wt.	30min.	1hr	1.5hr	2hr	3hr
HCL	B-I	0.020	0.018	0.013	0.013	0.010	0.009
	B-II	0.020	0.017	0.014	0.015	0.013	0.014
	B-III	0.020	0.017	0.013	0.016	0.014	0.014
PHOSPHATE BUFFER	B-I	0.012	0.023	0.050	*	*	*
	B-II	0.012	0.066	0.069	*	*	*
	B-III	0.012	0.060	0.066	*	*	*

Table 3 b Swelling Study with $Bacl_2$ (4:0)

Media	Batch	Int.wt.	30min.	1hr	1.5hr	2hr	3hr
HCL	B-I	0.020	0.019	0.016	0.016	0.015	0.015
	B-II	0.020	0.020	0.017	0.017	0.017	0.017
	B-III	0.020	0.020	0.020	0.020	0.021	0.015
PHOSPHATE BUFFER	B-I	0.014	0.066	*	*	*	*
	B-II	0.014	0.051	*	*	*	*
	B-III	0.011	0.100	*	*	*	*

Table 3 c Swelling Study With $Zncl_2$(4:0)

Media	Batch	Int.wt.	30min.	1hr	1.5hr	2hr	3hr
HCL	B-I	0.020	0.020	0.014	0.016	0.017	0.016
	B-II	0.020	0.020	0.017	0.018	0.019	0.018
	B-III	0.020	0.020	0.018	0.019	0.020	0.019
PHOSPHATEBUFFER	B-I	0.010	0.016	*	*	*	*
	B-II	0.011	0.025	*	*	*	*
	B-III	0.012	0.029	*	*	*	*

Table 3 d Swelling Study With $Fecl_3$ (4:0)

Media	Batch	Int.wt.	30min	1hr	1.5hr	2hr	3hr
HCL	B-I	0.020	0.021	0.020	0.020	0.020	
	B-II	0.020	0.021	0.021	0.020	0.020	
	B-III	0.020	0.020	0.020	0.020	0.020	
PHOSPHATE BUFFER	B-I	0.019	0.014	0.015	0.013	*	*
	B-II	0.018	0.018	0.017	0.015	*	*
	B-III	0.019	0.018	0.016	0.014	*	*

* Swelling Study for Phosphate Buffer is checked for limited time interval

3.4. Drug Loading and Drug Encapsulation

All the prepared microbeads were found to be spherical with white in colour. The drug loaded microbeads of Simvaststin with sodium alginate are represented in table no.4. All the prepared microbeads formulations show uniformity of drug content. The drug encapsulation efficiency was in range the of 49.26 to 83.58. Simvastatin loaded sodium alginate microbeads with $Bacl_2$ as the cross linking agent has shown maximum percentage of drug loading & drug encapsulation efficiency. Hence the batches of microbeads fabricated by using $Bacl_2$ as cross linking agent was selected as the most efficient one among all the cross linking agent and specifically the DSC & SEM study carried out for this particular cross linking agent. The prepared batches of microbeads were evaluated for micromeritic study such as bulk density, tapped density, carr's index, Hausners ratio & angle of repose i.e. in table no5.The bulk density of different formulation ranged from 0.424 to 0.720 g/ml. The tapped density of different formulation ranged from 0.513 to 0.821 g/ml. The carr's ratio of the different batches of microbeads ranged from 10.20 to 17.78% .The angle of repose of all formulation ranged from 14 to 19.Based on the above micromeritic properties of all the batches, it was concluded that the prepared microbeads had excellent flow properties.

Table 4 a Drug loading & drug encapsulation With $Cacl_2$

Sl no.	% Drug Loading	Drug encapsulation Efficiency
Batch-I	33.50	78.17
Batch-II	25.20	59.27
Batch-III	26.60	64.45

Table 4 b Drug loading & drug encapsulation With $Bacl_2$

Sl no.	% Drug Loading	Drug encapsulation Efficiency
Batch-I	35.90	83.58
Batch-II	35.20	82.89
Batch-III	30.30	71.86

Table 4 c Drug loading & drug encapsulation With $Zncl_2$

Sl no.	% Drug Loading	Drug encapsulation Efficiency
Batch-I	28.60	68.41
Batch-II	21.20	49.26
Batch-III	25.90	59.31

Table 4 d Drug loading & drug encapsulation With $Fecl_3$

Sl no.	% Drug Loading	Drug encapsulation Efficiency
Batch-I	32.02	80.09
Batch-II	33.26	83.31
Batch-III	31.30	69.74

Table 5 Flow properties of different formulations

Cross Linking Agent	Angle of Repose (Θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index %	Hausner ratio
($Cacl_2$)					
Batch-I	18	0.615	0.724	15.05	1.17
Batch-II	15	0.504	0.613	17.78	1.21
Batch-III	16	0.532	0.628	15.28	1.18
($Bacl_2$)					
Batch-I	19	0.718	0.817	12.11	1.13
Batch-II	18	0.704	0.811	13.19	1.15
Batch-III	16	0.532	0.703	13.79	1.16
($Zncl_2$)					
Batch-I	16	0.572	0.637	10.20	1.11
Batch-II	14	0.424	0.513	17.34	1.20
Batch-III	15	0.518	0.619	16.31	1.19
($Fecl_3$)					
Batch-I	19	0.716	0.821	12.78	1.14
Batch-II	19	0.720	0.819	12.08	1.13
Batch-III	18	0.648	0.723	10.37	1.11

3.5. *In-vitro* dissolution study

Drug release from the microbeads was evaluated in phosphate buffer (pH7.4) at different time intervals. The % release of drug has considered from standard curve was plotted in figure1, 2, 3, 4. The order of drug release from the different formulation with interval of time can be arranged in suitable manner that means initially it shows lesser extent of drug release i.e. 21% to 51% (15min. to 30min.) but gradually it shows better extent of drug release i.e. from 70.84% to 98.06% (up to 6hours).The release of drug was accelerated by the weight loss of the mucoadhesive polymers. The release of the drug was modulated by the diffusion of the drug through the swollen polymeric matrix.

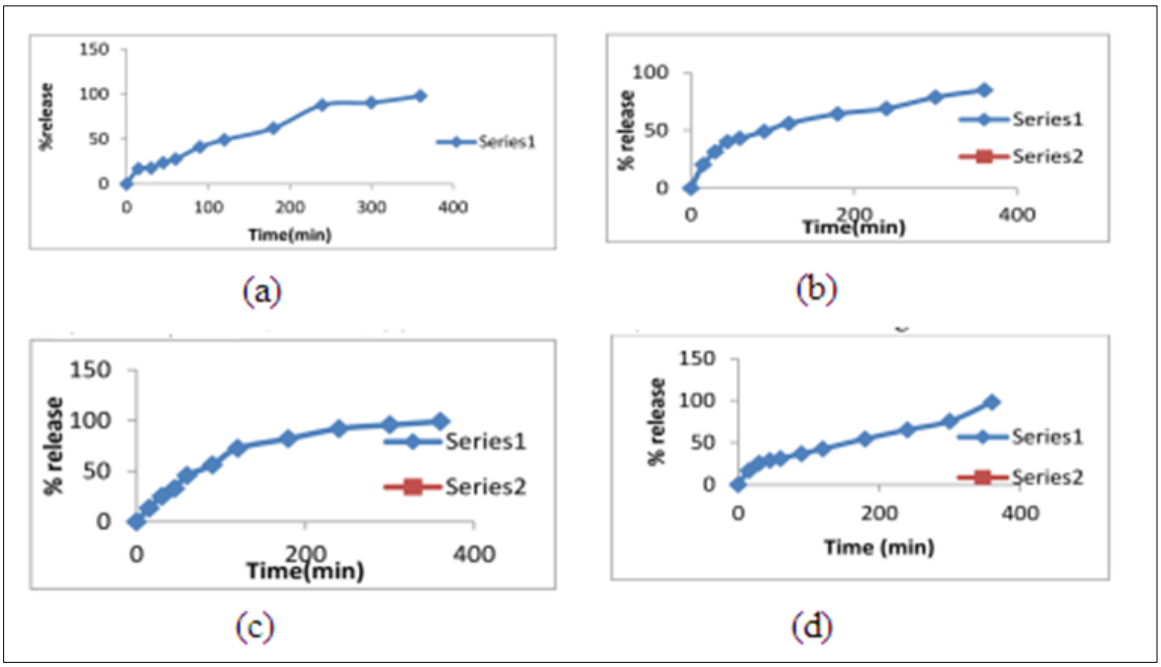

Figure 1 Drug release profile of different micro beads loaded with (a) Ca-alg (b) Ba-alg (c) Zn-alg (d) Fe-alg

3.6. FTIR study

The drug-polymer interaction was carried out by FT-IR spectroscopic study. The FT-IR spectrum of the pure drug shows the characteristic peak at 1070.73cm^{-1}& 1695.35cm^{-1} due to alcoholic and C=O stretching of the ester group. The FT-IR spectrum of drug loaded Ca-alg bead exhibited peak at 1015.14cm^{-1}&1598.97cm^{-1}. Similarly, the FT-IR spectrum of drug loaded Ba-alg bead exhibited peak at 676.50cm^{-1}& 1582.37cm^{-1}. The FT-IR spectrum of drug loaded Zn-alg and Fe-alg exhibited peak at 1022.08cm^{-1} &1590.35cm^{-1} along with 1026.64cm^{-1} &1708.72cm^{-1}. All the peaks are observed by the FT-IR analysis method confirmed that drug polymer interactions was observed in the microbeads &shown in the figure 5,6,7,8,9.

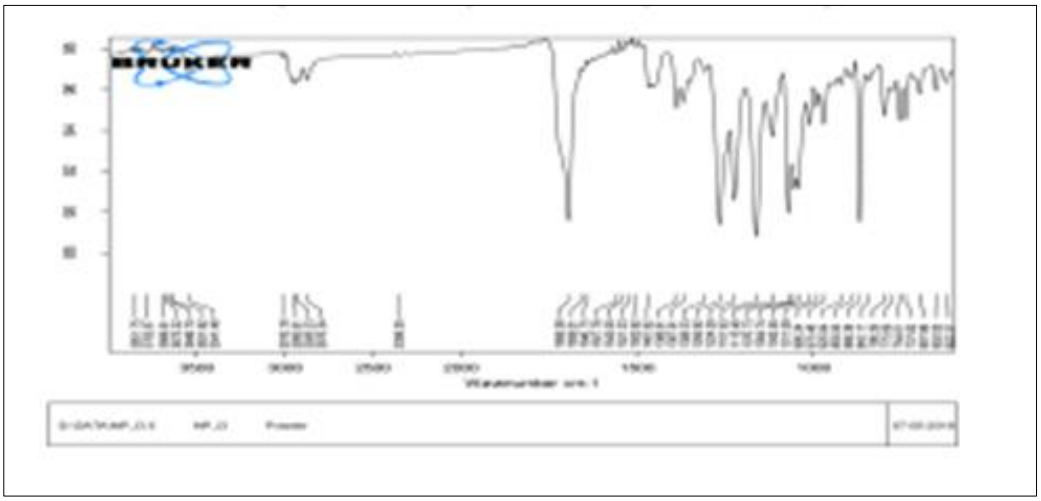

Figure 2 FTIR spectra of Simvastatin

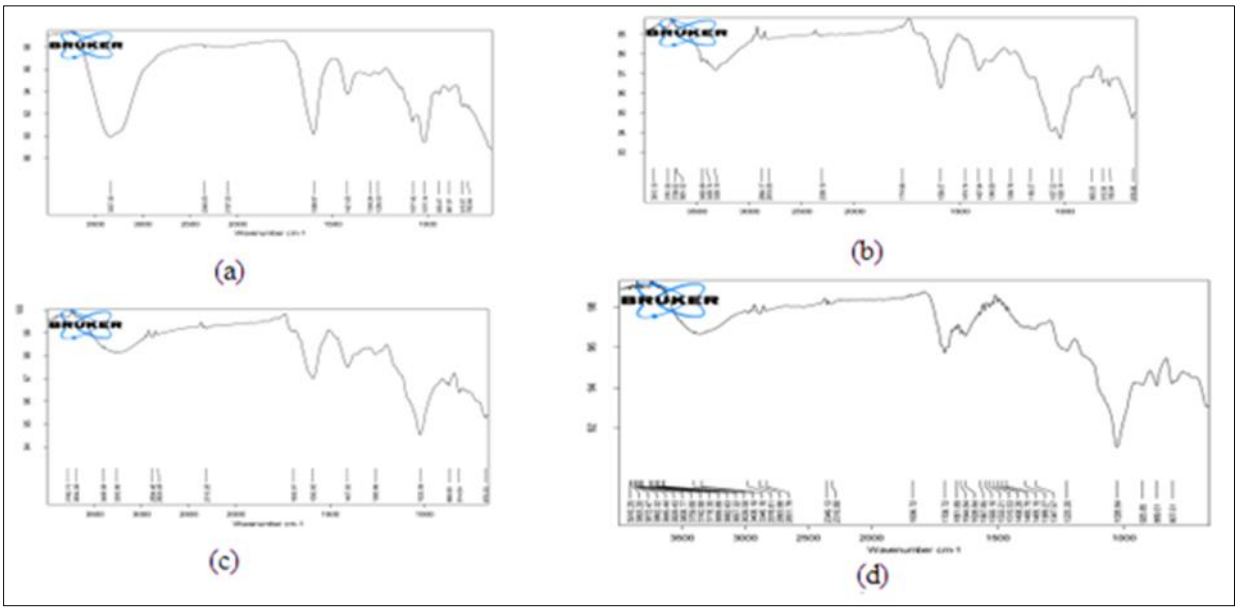

Figure 3 FTIR spectra of microbeads loaded with (a) Ca-alg (b) Ba-alg (c) Zn-alg (d) Fe-alg

3.7. Differential scanning calorimetric study

The pure drug shows endothermic (melting point) at145.50°c.The endothermic peak of drug loaded Ba-Alg. was appeared 147.36°C. The presence of the endotherm clearly indicated the prescence of drug polymer interaction in the microsphere. The endothermic range of the beads may be due to the physical & chemical changes taking place in the microsphere after the entrapment of the drug & shown in the figure 10, 11.

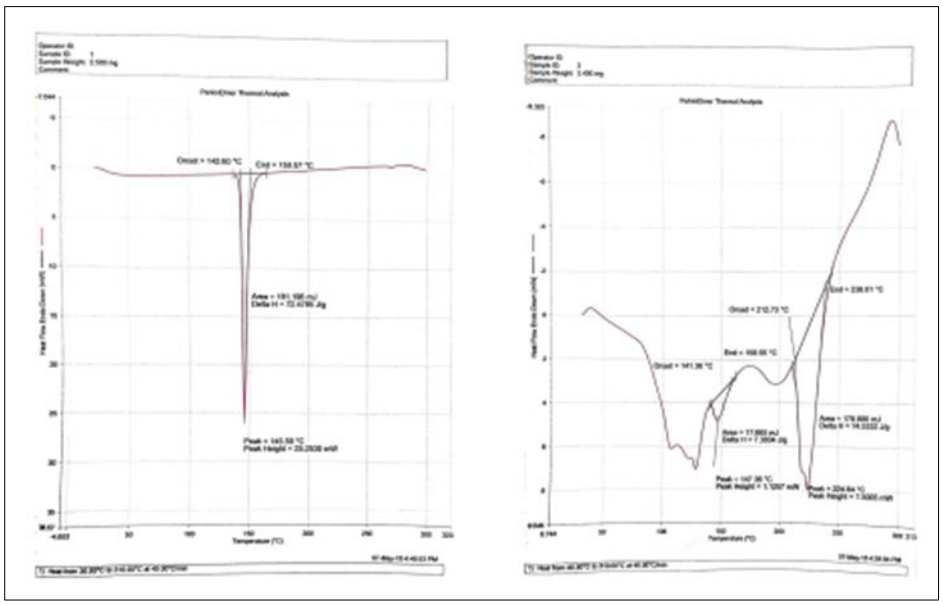

Figure 4 DSC thermogram of (a) Simvastatin (b) Ba-alg beads

3.8. Scanning electron microscopy study

The SEM studies revealed that the simvastatin loaded sodium alginate microbeads was spherical in shape and completely covered with the coat polymer. It can influence the rate of drug release from the microbeads& show in the figure 12,13.

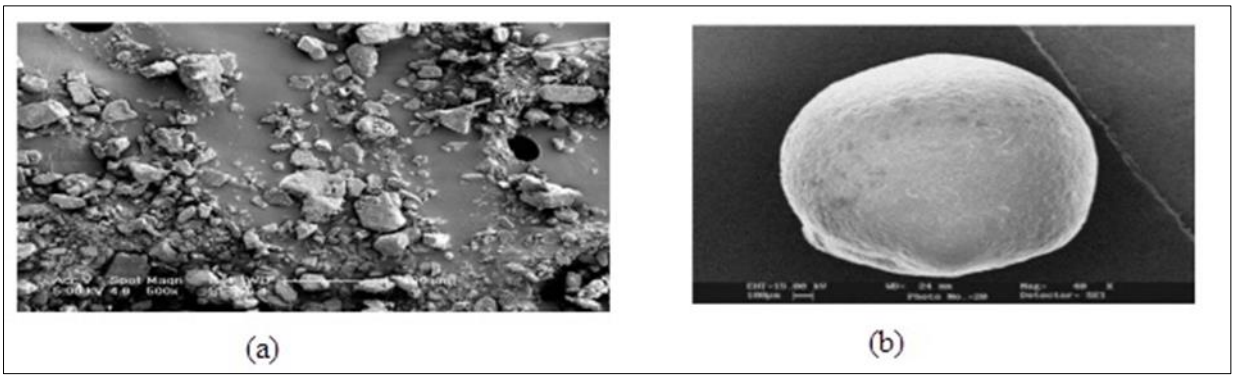

Figure 5 SEM Pattern of (a) Simvastatin (b) Ba-alg beads

4. Conclusion

The microbeads of Simvastatin loaded sodium alginate (4:0 ratio) demonstrated as a cardinal control release of the drug for 6hrs&exhibited good mucoadhesive property. The microbeads of Simvastatin loaded alginate especially with $Bacl_2$ as cross linking agent has shown better drug loading & drug encapsulation efficiency in comparison to others. Hence the batches of microbeads of Simvastatin loaded sodium alginate & with $Bacl_2$ as cross linking agent was rated the best batch for preparation of microbeads. The swelling & *In-vitro* release behaviour of Simvastatin loaded sodium alginate microbeads can be considered as a promising control drug delivery system and can be improve the bioavailability of Simvastatin. The FT-IR & DSC studies revealed the presence of drug polymer interaction. The SEM studied indicated that microbead has spherical in shape.

Compliance with ethical standards

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