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DEVELOPMENT AND EVALUATION OF MICROBEADS OF SIMVASTATIN LOADED WITH SODIUM ALGINATE AND ALOE VERA

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Simvastatin, Sodium Alginate, Aloe Vera, Microbeads, Control release

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ABSTRACT: Simvastatin, a lipid-lowering agent, belongs class-II drug of BCS. It has a short biological half-life (3hr), and high first-pass metabolism. The target of the present study was to prepare the microbeads of Simvastatin to provide control release of the drug with enhanced bioavailability through sustained release. The method adopted to prepare Simvastatin loaded microbeads was by the ionic gelation method using a mixture of natural polymers like sodium alginate and aloe vera (1:1). Different crosslinking agents like $BaCl_2$, $FeCl_3$, $ZnCl_2$ and $CaCl_2$ formulated microbeads. The microbeads were spherical, free-flowing with uniformity in drug content and high drug encapsulation efficiency. The swelling and drug release behavior correlate with the crosslinking agent used to prepare microbeads. The FTIR analysis of the drug, polymers, and the optimized formulation confirmed the compatibility of the drug with the polymers. The DSC studies indicated no interaction between the drug and polymer in the microbeads. Formulation FB-1 showed the extended drug release of more than 6 hours. The novelty of a recent study assures that the swelling and In-vitro release behavior of Simvastatin loaded sodium alginate and aloe Vera microbeads crosslinked by FeCl3 can be considered as a promising control release drug delivery system which will be a part of a novel drug delivery system.

INTRODUCTION: The term controlled release is the delivery systems to deliver the drug locally or systemically for a known period [1]. Different techniques are applied to make the formulation so the drug release can be extended. The release of active ingredients from controlled release drug delivery produces the release rate not only in an advanced manner but also repeatedly from one unit to another [2, 3]. Most of the oral control release products enter into the stomach having pH 1.2 and then after about 3 hrs to large intestine pH 7.4.

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To control the release, the drug can be coated to prepare microbeads. Due to their slow solubility and swelling behavior, microbeads control the drug release from the stomach and extend the release for a longer time than the conventional dosage pattern [4, 5]. Simvastatin is an antihyperlipidemic drug. The oral route of administration is the most common and preferred route of choice for the delivery of drugs. It is rapidly absorbed in the stomach and undergoes rapid first-pass metabolism [6].

The primary action of the drug is to increase the excretion of low-density lipoprotein receptors in the liver, which occurs in response to the inhibition of HMG-COA reductase. It leads to increased clearance of low-density of lipoproteins [7]. Simvastatin arrests a key step of cholesterol biosynthesis in the liver and is widely used in treating hypercholesterolesterolemia and

dyslipidemia [8]. After, oral administration, Simvastatin is metabolized to its B-hydroxy acid form (Simvastatin acid) by the cytochrome-3A system. The ionotropic gelation technique was selected to prepare Simvastatin-loaded microbeads using sodium alginate and aloe vera as polymer [9]. Aloe vera acts as a stabilizer making sodium alginate coat more elastic and sustainable [10]. The present study aimed to prepare and evaluate the microbeads containing sodium alginate and aloe vera as polymers.

MATERIAL AND METHODS: Simvastatin was procured as a gift sample from Aurobindo Pharma Hyderabad. Sodium Alginate was obtained from nice chemicals, Kerala, and aloe vera was obtained from Natural Industries, Mumbai. All the chemicals were analytical grade for research.

Preparation of Microbeads: 200 mg each of sodium alginate and aloe vera, 40mg Simvastatin, 1.25gm crosslinking agent & distilled water taken to prepare microbeads. 200mg each of sodium alginate and aloe vera were added to 10 ml of distilled water in a 25ml of the beaker and subjected to heat. To the above slurry, 40mg of Simvastatin was added with constant stirring by a magnetic stirrer until a deflocculated suspension was formed. 1.25gm of $CaCl_2$ was dissolved in 25ml distilled water in a 100ml of beaker to get 5% solution. The bubble-free polymer suspension was taken in a 10ml syringe (20mm size) and added dropwise into $CaCl_2$ solution (crosslinking media) to get spherical beads. The drug-loaded microbeads were allowed to stand for 2hrs curing times [11]. After a specific period, microbeads were collected by filtration and dried for 24 hrs. Similarly, the procedure was adopted using crosslinked agents such as $BaCl_2$, $ZnCl_2$ & $FeCl_3$ and three batches of microbeads using each crosslinked agent. The terminology of different batches of drug-entrapped crosslinked microbeads is given in **Table 1.**

Evaluation of Microbeads: Prepared microbeads were evaluated for parameters such as % yield, average particle size, Drug Loading, Drug Encapsulation, Flow properties of microbeads, invitro dissolution study, and compatibility study.

Determination of % of Yield: The yield of formulated microbeads was evaluated by comparing the practical yield with that of the theoretical yield and recorded in **Table 2.**

Determination of Average Particle Size: The particle size of beads was measured by sieve analysis methods. The average particle sizes of different formulations are shown in **Table 3.**

Drug Loading and Encapsulation Determination: 100mg of prepared microbeads weighed accurately and was taken, crushed, and suspended in 250ml of phosphate buffer of pH 7.4. The resulting solution was transferred into a stopper conical flash, and the flask was shaken occasionally for 24 hrs. It was then stirred for 20min. using magnetic stirrer [12].

The solution was filtered through Whatman filter paper. The filtrate's drug content was analyzed using a UV-Visible spectrophotometer (Shimadzu 1800USA) at 238.6nm against the appropriate blank. The beads' drug loading and encapsulation efficiency were calculated using the following formula, and the values are recorded in **Table 4.**

Drug loading (%) = (Amount of drug in the beads) / (Mass of drug-loaded beads) × 100 …. Eq. 1

Drug encapsulation efficiency (%) = (Actual drug content in beads) / (Theoritical drug content in beads) × 100 ……. Eq. 2

Determination of Flow Properties of Microbeads: Bulk volume was measured by taking a known quantity of beads in bulk density apparatus. Bulk density was calculated. The apparatus was tapped mechanically 200 times, tapped volume was measured, and tapped density was calculated.

Carr's Index and Hausner ratio were estimated by using the following formula. Angle of repose of different formulations was quantified following the constant funnel vertical procedure and using the formula [13]. Flow parameters are recorded in **Table 5.**

Bulk Density (gm/ml) = (Mass of the microbeads) / (Bulk volume) ……. Eq. 3

Tapped density (gm/ml) = (Mass of the microbeads) / (Tapped volume) ……. Eq. 4

Carr's index = (Tapped density-Bulk density) / (Tapped density) × 100……. Eq. 5

Hausner ratio = (Tapped density) / (Bulk density) ……. Eq. 6

$$\theta = \tan^{-1} h / r \text{ ……. Eq. 7}$$

Where the angle of repose is θ, the radius is r, and the height is h

Evaluation of Swelling Behavior of Microbeads: 20mg of beads were placed in several watch glasses containing 5 ml of 0.1N HCl in each. The experiment was scheduled at room temperature. Swelled beads were removed at a definite time interval *i.e.* 30 min, 1hr, 1½ hrs, 2 hrs, 3 hrs and dried at room temperature for 24 hrs.

The change in weight was measured by using an electronic digital balance. The test was continued by putting the recovered beads in phosphate buffer pH 7.4. The fractional change in weight was measured at interval of 30 minutes till the beads disintegrated [14]. All the studies were conducted in triplicate (n=3). The findings are recorded in **Table 6.**

***In-vitro* Dissolution Study:** The drug release study was performed using a dissolution test apparatus, USP type-I (TDT-06L), and Electro lab. Mumbai. *An in-vitro* dissolution study is an important tool in evaluating formulation and drug release profile from microbeads of Simvastatin loaded sodium alginate and aloe vera was examined in the buffer solution to imitate the various physiological region of GI-tract. The composition of the dissolution medium was formulated according to I.P., consisting of 0.238gm of phosphate buffer; 0.019 gm of potassium dihydrogen phosphate, and 0.8 gm of NaCl containing 0.5gm (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 microbeads were placed in the dissolution vessel, and the vessel was covered; the apparatus was operated for 8hrs at 50rpm. At definite time intervals, 5ml of the dissolution fluid was withdrawn and equal volume of fresh dissolution medium was replaced to maintain the volume of the dissolution medium constant [15]. The samples were analyzed spectrophotometrically at 238.6nm using UV-Spectrophotometer (Shimadzu 1800USA). The observations are shown in **Fig. 1**. All the studies were conducted in triplicate where (n=3).

Drug-excipient Compatibility Study:

FTIR Study: The FT-IR of drug-polymer interactions was studied by using FT-IR Spectrophotometer (Bruker FTIR Alpha-T Series). The FT-IR Spectra of the pure drug and blends of polymers with crosslinking agents were compared **Fig. 2** & **3.**

Differential Scanning Calorimetric (DCS) Study: The thermal analysis of the drug and the selected formulation prepared with $FeCl_3$ as cross linking agent 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. The heat flow as a function of temperature was measured for the drug and drug polymer mixture **Fig. 4.**

RESULT AND DISCUSSION: The yield percentage ranged from 28.63 to 59.77. The average particle size of all the microbeads ranged from 389.92 µm to 1044.19 µm with particles of different size ranges. The prepared microbeads were spherical in shape and white in colour. All the prepared microbeads showed uniformity in drug content. The percentage of drug encapsulation efficiency ranged from 29.47 to 60.18. Simvastatin-loaded sodium alginate and aloe vera microbeads with the crosslinking agent as $FeCl_3$ has shown a maximum percentage of drug loading & encapsulation efficiency.

The batches of microbeads prepared were evaluated for micrometric study, such as bulk density, tapped density, Hausners ratio, carr's index & angle of repose. The bulk density of different formulation ranged from 0.252 to 0.536 gm/ml. The tapped density of different formulation ranged from 0.326 to 0.618 gm/ml. The carr's index of the different batches of microbeads ranged from 13.26 to 22.69%. The Hausner ratio varied from 1.14 to 1.19. The angle of repose of all formulations ranged from 12 to 17. Based on the above data, it was confirmed that the prepared microbeads had excellent flow properties and encapsulation efficiency. From the study of swelling behavior, it was observed that the beads fabricated by using $FeCl_3$ as crosslinking agent withstand its coating character in 0.1N HCL and phosphate buffer pH 7.4. This showed better formulation for extended drug release. Drug release from the microbeads was

determined in phosphate buffer (pH7.4) at different times with specific intervals. The results are shown in **Fig. 1(A)** for beads containing $CaCl_2$, in **Fig. 1(A)** for beads containing $BaCl_2$, in **Fig. 1(A)** for beads containing $ZnCl_2$ and in **Fig. 1(A)** for beads containing $FeCl_3$. Initially, the % release of drugs was low at 23% to 51% (15 min. to 30 min.), but gradually, it showed a better extent of drug release *i.e.* from 79.17% to 98.06% (up to 6 hours). The release of the drug was accelerated by the weight loss of the coated polymers and modulated by the diffusion of the drug through the swollen polymeric matrix. The FT-IR spectroscopic study was carried out to confirm the drug-polymer interaction. From the compatibility study, the FT-IR spectrum of the pure drug showed 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-alv bead exhibited peaks at 1072cm^{-1} & 1704cm^{-1}. Similarly, the FT-IR spectrum of drug-loaded Ba-alg-alv bead exhibited peak at 1076.33cm^{-1} & 1689.29cm^{-1}. The FT-IR spectrum of drug-loaded Zn-alg-alv exhibited peak at 1073.84cm^{-1} &1697.77cm^{-1} and Fe-alg-alv exhibited a peak at 1085.88cm^{-1} & 1712.24cm^{-1}. The result confirmed that the drug and polymers showed no sign of interactions and were compatible. From the above studies, it was observed that the batches of microbeads fabricated by using $FeCl_3$ as the crosslinking agent had the maximum percentage of drug loading & drug encapsulation efficiency and also withstand their coating character both in 0.1N HCL and phosphate buffer pH 7.4 as observed in the swelling study. This showed better formulation for extended drug release. Thus the formulation FB-1 was selected as the most efficient one among all formulations subjected to the DSC study. The pure drug showed an endothermic peak (melting point) at 145.50 °C. The endothermic peak of drug-loaded Fe-Alg-Alv (FB-1) appeared at 152.45 °C. This minor deviation in the peak might be due to some physical interference without any such drug-polymer chemical interaction in the microbeads [16].

TABLE 1: NOMENCLATURE OF DIFFERENT BATCHES OF DRUG ENTRAPPED CROSSLINKED MICROBEADS

Crosslinking agent	$CaCl_2$			$BaCl_2$			$ZnCl_2$			$FeCl_2$		
Batches	CB-1	CB-2	CB-3	BB-1	BB-2	BB-3	ZB-1	ZB-2	ZB-3	FB-1	FB-2	FB-3

TABLE 2: YIELD OF MICROBEADS

Batch no.	Theoretical Yield	Practical yield	% of Yield
CB-1	440	166	37.72
CB-2	440	153	34.72
CB-3	440	154	35.00
BB-1	440	233	52.95
BB-2	440	245	55.68
BB-3	440	239	54.31
ZB-1	440	173	39.31
ZB-2	440	126	28.63
ZB-3	440	174	39.54
FB-1	440	242	55.00
FB-2	440	204	46.36
FB-3	440	263	59.77

TABLE 3: SIEVE ANALYSIS & PARTICLE SIZE DETERMINATION

Batch no.	S-12	S-16	S-18	S-20	S-30	S-36	S-44	Total Wt (gm)	Avg particle size (µm)
CB-1	0.010	0.003	0.024	*	0.129	*	*	0.166	932.41
CB-2	0.009	0.003	0.024	0.007	0.106	0.004	*	0.153	846.46
CB-3	0.012	0.006	0.037	0.009	0.090	*	*	0.154	889.54
BB-1	*	0.003	0.032	*	0.198	*	*	0.233	658.28
BB-2	*	0.012	0.043	*	0.190	*	*	0.245	695.22
BB-3	0.010	*	0.070	0.004	0.155	*	*	0.239	763.09
ZB-1	0.010	0.006	0.059	*	0.098	*	*	0.173	816.47
ZB-2	*	0.004	0.036	0.002	0.072	0.003	0.003	0.126	389.92
ZB-3	0.043	0.014	0.058	*	0.056	0.003	*	0.174	1044.19
FB-1	*	0.006	0.066	*	0.141	0.005	0.024	0.242	695.20
FB-2	*	0.003	0.070	0.009	0.117	0.005	*	0.204	747.99
FB-3	0.009	0.018	0.018	*	0.100	0.004	0.007	0.263	857.60

TABLE 4: % DRUG LOADING & % DRUG ENCAPSULATION EFFICIENCY

Batch no.	% Drug Loading	Drug encapsulation Efficiency
CB-1	23.30	53.82
CB-2	24.50	56.48
CB-3	23.90	55.35
BB-1	16.60	35.52
BB-2	15.30	34.61
BB-3	15.40	34.39
ZB-1	17.30	40.12
ZB-2	12.60	29.47
ZB-3	17.40	40.25
FB-1	24.20	56.03
FB-2	20.40	47.32
FB-3	26.30	60.18

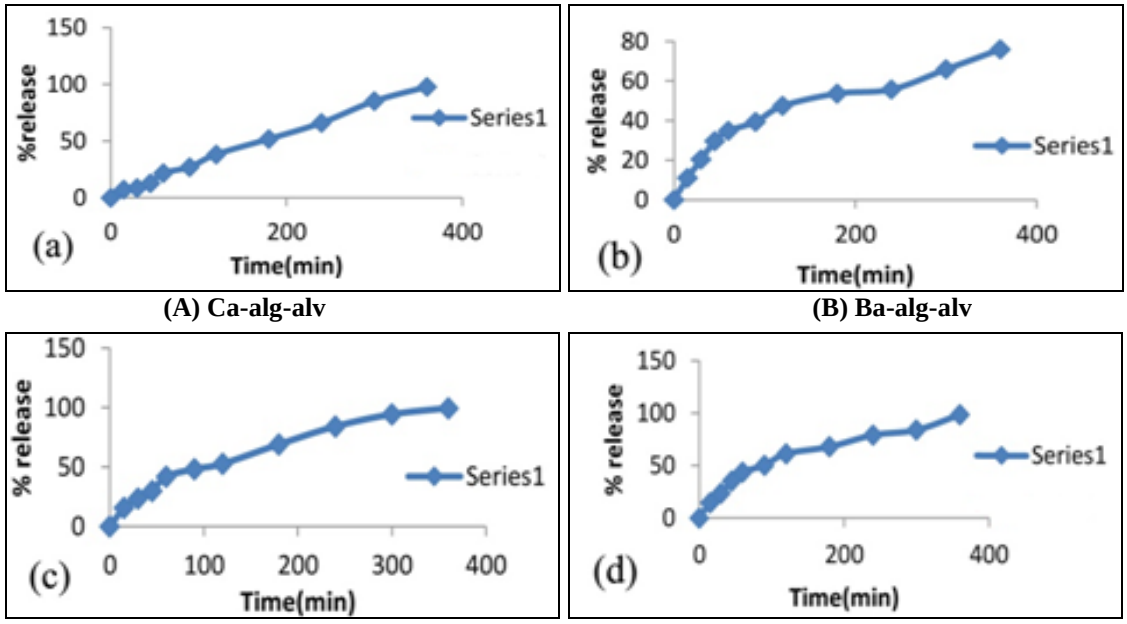
TABLE 5: FLOW PROPERTIES OF DIFFERENT FORMULATIONS

Batch no.	Angle of Repose (Ɵ)	Bulk density (g/ml)	Tapped density(g/ml)	Carr's index %	Hausner ratio
CB-1	15	0.466	0.538	13.38	1.15
CB-2	14	0.490	0.582	15.80	1.18
CB-3	15	0.492	0.578	14.87	1.17
BB-1	16	0.382	0.452	15.48	1.18
BB-2	16	0.295	0.347	14.98	1.17
BB-3	17	0.382	0.342	16.41	1.19
ZB-1	17	0.348	0.412	15.53	1.18
ZB-2	12	0.252	0.326	22.69	1.14
ZB-3	17	0.348	0.417	16.54	1.19
FB-1	13	0.458	0.529	13.42	1.15
FB-2	15	0.463	0.542	14.57	1.17
FB-3	13	0.536	0.618	13.26	1.15

TABLE 6: STUDY OF SWELLING BEHAVIOR

Batch no.	Medium	Int. wt.	30 min	1 hr	1.5 hr	2 hr	3 hr
CB-1	0.1N HCL	0.020	0.021	0.021	0.020	0.018	0.016
	PB-pH7.4*	0.016	0.026	--	--	--	--
CB-2	0.1N HCL	0.020	0.021	0.021	0.021	0.020	0.019
	PB-pH7.4	0.019	0.008	--	--	--	--
CB-3	0.1N HCL	0.020	0.021	0.021	0.021	0.020	0.018
	PB-pH7.4	0.018	--	--	--	--	--
BB-1	0.1N HCL	0.020	0.019	0.019	0.016	0.017	0.016
	PB-pH7.4	0.016	--	--	--	--	--
BB-2	0.1N HCL	0.020	0.021	0.020	0.019	0.019	0.016
	PB-pH7.4	0.016	--	--	--	--	
BB-3	0.1N HCL	0.020	0.021	0.020	0.018	0.018	0.018
	PB-pH7.4	0.018	--	--	--	--	
ZB-1	0.1N HCL	0.020	0.018	0.017	0.010	0.008	0.008
	PB-pH7.4	0.008	0.016	--	--	--	--
ZB-2	0.1N HCL	0.020	0.024	0.021	0.018	0.016	0.014
	PB-pH7.4	0.014	0.025	--	--	--	--
ZB-3	0.1N HCL	0.020	0.020	0.018	0.016	0.011	0.010
	PB-pH7.4	0.010	--	--	--	--	--
FB-1	0.1N HCL	0.020	0.019	0.019	0.018	0.016	0.015
	PB-pH7.4	0.015	0.012	0.010	0.008	0.008	0.008
FB-2	0.1N HCL	0.020	0.020	0.019	0.018	0.018	0.018
	PB-pH7.4	0.018	0.015	0.014	0.014	0.014	0.014
FB-3	0.1N HCL	0.014	0.021	0.020	0.019	0.019	0.019
	PB-pH7.4	0.019	0.014	0.014	0.014	0.014	0.014

*PB-pH 7.4- Phosphate buffer pH 7.4.; -- indicates disappearance of beads.



(A) Ca-alg-alv **(B) Ba-alg-alv**

(C) Zn-alg-alv **(D) Fe-alg-alv**

FIG. 1: DRUG RELEASE PROFILE OF DIFFERENT MICRO BEADS LOADED WITH CROSS LINKING AGENTS

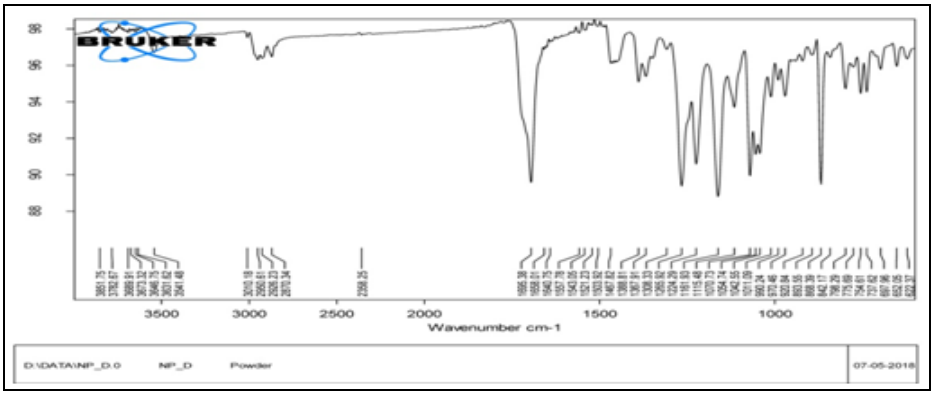
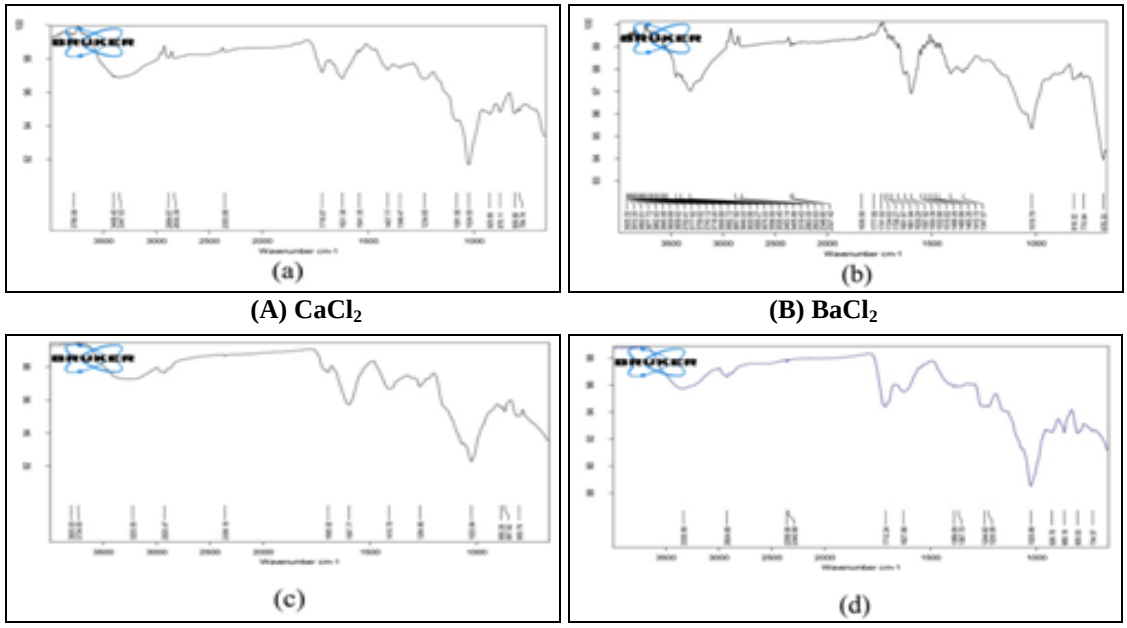


FIG. 2: FTIR SPECTRA OF SIMVASTATIN



(A) $CaCl_2$ **(B) $BaCl_2$**

(C) $ZnCl_2$ **(D) $FeCl_3$**

FIG. 3: DRUG RELEASE PROFILE OF DIFFERENT MICRO BEADS LOADED WITH CROSS LINKING AGENTS

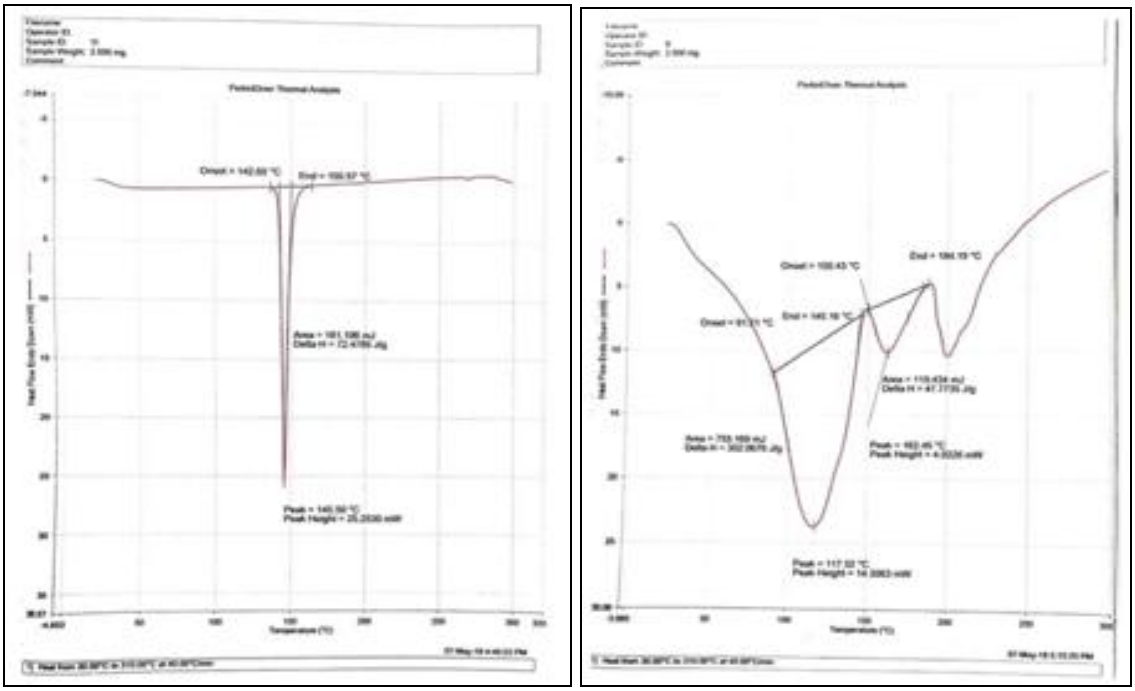


FIG. 4: DSC THERMOGRAM OF (A) SIMVASTATIN (B) FE-ALG-ALV BEADS

CONCLUSION: The microbeads of Simvastatin-loaded sodium alginate and aloe vera demonstrated as a cardinal control release of the drug for 6 hrs. The microbeads formulated with $FeCl_3$ as the crosslinking agent has shown better drug loading & drug encapsulation efficiency in comparison to others. Hence, the batches of microbeads of Simvastatin loaded sodium alginate and aloe vera having $FeCl_3$ as a cross-linking agent was rated the best batch for the preparation of microbeads. The swelling & *in-vitro* release behaviour of Simvastatin-loaded ferric chloride crosslinked sodium alginate with aloe vera microbeads can be considered a promising control drug delivery system and can improve the bioavailability of Simvastatin.

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CONFLICTS OF INTEREST: Nil

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