



# Preparation and Optimization of Atorvastatin-Loaded Eudragit L100 Polymeric Microbeads by Ionotropic Gelation Method

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## ABSTRACT

Atorvastatin is used with a proper diet to lower cholesterol and triglyceride (fats) levels in the blood. It may be given orally. It is given as tablets of doses like 10-80 mg once daily for oral administration. It falls under the Class II category of Biopharmaceutical Classification System (BCS) i.e., having low solubility and high permeability. Problems regarding atorvastatin are that after administering in tablet formulation, high first-pass metabolism as well as the bioavailability of this drug varies due to instability in the acidic environment of stomach. Hence the patient becomes susceptible to a high chance of adverse effects of the drug which are nausea, vomiting and diarrhoea. To resolve such problems the drug should be incorporated in the microspheres for sustained release action using a suitable polymer. In the present research work atorvastatin drug was prepared into microspheres with sodium alginate, Eudragit L100 to be made as a controlled release formulations using calcium chloride and glutaraldehyde as cross-linking agents. Atorvastatin could be incorporated effectively into a combination of Eudragit and Sodium alginate microbeads by ionotropic gelation method. Several formulation variables were studied to establish the optimum condition for preparing almost spherical Eudragit microspheres with high atorvastatin entrapment. The processing variables affected the properties of the microspheres in different ways. In most cases, the drug release from the microspheres was found to be controlled by Non Fickian diffusion mechanism. No incompatibility was found between drug and polymer as reported after evaluation study.

**Key Words:** Atorvastatin calcium, Microspheres, Bioavailability, Polymer, Ionotropic gelation method

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## INTRODUCTION

Small solid particles that are spherical, typically measuring between 1µm and 1000µm in diameter, are referred to as microspheres (1mm). These are the substances or compounds which having free-flowing properties (powder). Microspheres are also referred to as microparticles. One of the cutting-edge drug delivery technologies that offers a potent therapeutic substitute for instant-release single-unit dose forms is microspheres [1]. When compared to conventional dosage forms, the

effectiveness and method of administration of the microspheres generated using different techniques are altered. A variety of techniques will be used to assess microspheres to analyze their quality. Microspheres are prepared from various types of materials such as polymers, glass, and ceramic material. The densities of solid but hollow microspheres and microparticles differ often, and their intended applications vary as well. By solid microspheres numerous applications prepared which is depending on the materials that are used and the size of the

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materials. As an additive, hollow microbeads serve to reduce a material's density [1, 2]. The two most popular varieties of polymer microspheres are made of polyethylene and polystyrene. Microspheres made of polystyrene are employed in biomedical applications because they make processes easier, like immune precipitation and cell sorting. Polyethylene microspheres can be utilized as a permanent or temporary filler; they can form pores in ceramics and other materials because of their lower melting temperature. Microspheres have a significant impact on reducing side effects and increasing the absorption of conventional medications [2]. A variety of processes, including single and double emulsion, polymerization, phase separation and coacervation, spray drying, solvent evaporation, and ionotropic gelation, are used to produce microspheres. Atorvastatin calcium is a pharmaceutical active ingredient that lowers cholesterol levels in the body. Atorvastatin calcium is primarily used to treat conditions such as dyslipidaemia and avoid cardiovascular disease. It is a competitive inhibitor that works by inhibiting the mevalonate pathway and HMG-CoA reductase. The enzyme that controls the rate of cholesterol production through the mevalonate pathway. When HMG-CoA reductase is present, HMG-CoA converts to mevalonate in the mevalonate pathway. The primary target of ATC is liver cells, which may result in a drop in plasma and hepatic cholesterol levels. ATC had poor solubility and low bioavailability. The upper part of the GI tract had the highest percentage of ATC absorption. Therefore, a suitable polymer should be used to incorporate

the medicine into the microspheres for continuous release to address such issues [3]. By choosing polymers with distinct degradation mechanisms, multiple release profiles with targeted rates of release can be obtained. Due to its benefits, polymers such as Eudragit L100 have attracted a lot of interest in the pharmaceutical industry [4].

- It is an anionic white, freely flowing powder that dissolves in intestinal fluid starting at pH 6.
- Use as an enteric coating and release control.
- Keep dry and at a regulated room temperature.

The goal of the current study is to formulate and assess polymeric microspheres containing calcium atorvastatin and examine the drug's release profile using sodium alginate with Eudragit L100.

## MATERIALS AND METHODS

### Materials

Atorvastatin calcium gifted by Sun Pharmaceuticals Industries Ltd., Punjab. Eudragit L100 was supplied by Evonik Health Care Ltd., Calcium chloride & Sodium alginate were supplied by Loba Chemie Pvt Ltd. Acetone, Methanol was supplied by Pure Chems. Glutaraldehyde purchased from Merck lab, Mumbai.

### Methods

#### Preparation of drug loaded microbeads

**Table 1.** Preparation of drug-loaded microbeads using the following composition

Formulation code	Amount of Drug (mg)	Eudragit L100 (mg)	Sodium alginate (gm)	Acetone (ml)	Methanol (ml)	Calcium chloride (%w/v)	Glutaraldehyde (ml)
F1	100	20	2	5	5	5	1
F2	100	30	2	5	5	5	1
F3	100	40	2	5	5	5	1
F4	100	20	2	5	5	5	2
F5	100	30	2	5	5	5	2
F6	100	40	2	5	5	5	2

As per the formula given in **Table 1** initially blank microbeads were prepared to optimize the concentration of polymer and crosslinking agents. Then, 5ml of acetone and 5ml of methanol were mixed with 30ml of water. Then the drug Atorvastatin calcium and Eudragit L100 were added to the previous solution. On the other, side Sodium alginate of different concentrations was mixed with 20ml of water in a homogenizer at about 15 min [5, 6]. Then in this solution the drug and Eudragit L100 solution were added properly. The final dispersion was taken into a glass syringe and added drop by drop to a combination of cross-linking agent solutions containing  $\text{CaCl}_2$  and

glutaraldehyde [7, 8]. The crosslinking agent caused microbeads to develop, which were then separated with muslin cloth and cleaned with water. They were also dried during the night in an oven with hot air at a temperature between  $42^\circ$  and  $45^\circ\text{C}$ . The medication atorvastatin was not added to the blank microbeads, which were made identically [9].

#### Characterization of microbeads

##### Swelling study

For two hours and three hours, respectively, the swelling tendencies of blank microspheres cross-linked using

CaCl<sub>2</sub>-Glutaraldehyde (CCG) complex have been studied independently in solutions of acid buffer and phosphate buffer. Samples weighing 10mg were added to 100 ml of the medium being studied and left to swell. Periodically, the enlarged beads were taken out, dried with the help of tissue paper, and quantified. Every sample had three evaluations. The equation was used to compute the swelling ratios [9, 10].

$$\text{Swelling Ratio} = \frac{W_2 - W_1}{W_1} \times 100 \quad (1)$$

Where W<sub>2</sub> is the weight of swollen particles and W<sub>1</sub> is the Initial weight of particles under study [10, 11].

#### *Gelation study*

Using a 21-gauge flat-tipped hypodermic needle, different concentrations of sodium alginate as well as Eudragit L100 polymer complex (pH 7.0) were produced and extruded dropwise over 100 ml containing 1-5% (w/v) CaCl<sub>2</sub>-Glutaraldehyde (CCG complex) solution. Twenty beads were taken out at a predetermined 10-minute interval, the surface wetness was wiped off with blotting paper, and the beads were weighed. For two hours, the process was continued. The equation was used to compute the percentage of water lost [11, 12].

$$\% \text{ Loss} = [(w_1 - w_2) / w_1] \times 100 \quad (2)$$

Where w<sub>1</sub> is Weight of 20 wet beads of Sodium alginate and Eudragit L100 complex and w<sub>2</sub> is the Weight of 20 beads at gelation time t.

#### *Scanning electron microscopy (SEM)*

The dried microsphere's shape and surface morphologies were examined using the Scanning Electron Microscope (Joel, JSM-IT510, Japan). Before being examined, the samples were vacuum coated with a 2 nm thick layer of gold palladium film using an Edward-S-150 UK sputter coater to make them electrically conductive. The samples were then mounted onto stubs utilising double-sided dry carbon type [11].

#### *Percentage yield value*

The number of microspheres generated as an indicator of loaded medication and polymer is known as the percentage yield value [13].

$$\% \text{Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug with excipients}} \times 100 \quad (3)$$

#### *Determination of drug entrapment efficiency (DEE)*

About 20 mg of precisely weighed Atorvastatin calcium-loaded microbeads were submerged in 100 millilitres of mixed phosphate-buffered solution (pH 6.8) and kept aside

overnight. The solution was then filtered, and each experiment was run in triplicate using spectrophotometric analysis at 252 nm. By doing recovery study with known dosages of Atorvastatin calcium in presence or absence of polymer, the method's reliability was assessed, and the recovery average is 98.37 ± 0.33 [13, 14].

#### *Particle size analysis*

The atorvastatin-loaded microspheres' particle sizes were examined using a sieve technique. To create a nest of sieves, several British standard sieves with mesh sizes ranging from 25 to 150 were arranged neatly and their mesh aperture became progressively smaller. After weighing the samples, a Vibratory Sieve Shaker from Lab India, was used to shake the nest of sieves. Each sieve's retained samples were gathered and weighed. Following the charting of the cumulative percentage through the smaller sieve versus the smaller sieve aperture, the weight-size distribution was depicted and the average arithmetic diameter was determined using the method previously reported (Parrott 1991) [15].

#### *Attenuated total reflection (ATR) Spectroscopy*

ATR FTIR Spectra of finely powdered dried pure atorvastatin, atorvastatin loaded microspheres were recorded using Lab solution software (SHIMADZU ATR-IR). Each sample was gently taken on the ATR plate and the interpretation process was done properly. The disc was placed in the sample holder and scanned from 4000 to 400cm<sup>-1</sup> at a resolution of cm<sup>-1</sup> [16].

#### *Differential scanning calorimetry (DSC)*

DSC thermograms of pure Atorvastatin and Atorvastatin loaded microsphere were recorded using Perkin-Elmer on an apparatus (Pyris-diamond TG/DTA, Singapore). Samples were precisely weighed and placed into a 40µl hermetically sealed aluminium pan. At a heating speed of 100°C/min, the measurements were carried out in a nitrogen atmosphere with temperatures ranging from 30 to 5000°C [16, 17].

#### *"In vitro" release studies*

Enzyme-free, gastric, and intestinal fluids were used to investigate the in vitro release of atorvastatin from a mixture of Eudragit and sodium alginate microsphere using a USP Type II dissolution test device (Lab India). A mixture of 900 ml of pH 6.8 phosphate buffer solution was used to suspend about 20 mg of precisely weighed dry microspheres. The temperature was calibrated to be 37±0.5°C and the paddle was revolved at 100 rpm. Five millilitres of the sample were removed and replaced with new buffer solution at prearranged intervals. The double beam spectrophotometer (Shimadzu UV-Visible

spectrophotometer, UV-1750) operating at 246 nm was used to evaluate the aliquots. Plotting the cumulative proportion of atorvastatin release against time. Triplicate study of each sample was tested [18].

#### Drug release mechanism

By simulating the initial 60% of the drug releasing using Korsmeyer Peppas formula the values of diffusional coefficient (n) were obtained, which allowed for the determination of the biological process of in vitro atorvastatin release from the microsphere:  $M_t / M_\infty = k t^n$ , whereas k is a constant that takes into account the geometric and structural properties of the device and  $M_t / M_\infty$  is the proportionate solute release at moment t. Fickian diffusion when  $n = 0.43$  or less, anomalous movement from  $n = 0.43$  to  $0.85$ , and case II movement when  $n = 0.85$  may be the mechanisms underlying drug release through spherical polymeric devices. According to Ritger and Peppas (1987), a super case II transportation system is indicated by a coefficient value of n above 0.85 [14, 18, 19].

#### Drug release kinetics

Data from in vitro drug release research were plotted in three different kinetic models to study the release kinetics: Higuchi's model (equation 3), which represents the cumulative percentage of drug released vs the square root of time; zero order (equation 1), which represents the

cumulative percentages of drug released vs time; and first order (equation 2), which represents the log cumulative percentage of drug left vs time.

$$C = K_0 t \quad (4)$$

where t is the duration in hours and  $K_0$  is the zero-order constant for rate given in percentage terms / time. A concentration vs. time graph would intersect at the start of the axes and produce a straight line having a slope of  $K_0$ .

$$\log C = \log C_0 - kt / 2.303 \quad (5)$$

Where  $C_0$  is the initial concentration of drug, k is the first order constant, and t is the time.

$$Q = Kt^{1/2} \quad (6)$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time [20].

## RESULTS AND DISCUSSION

#### Swelling study

Swelling study was done in both acidic and Phosphate buffer solution.

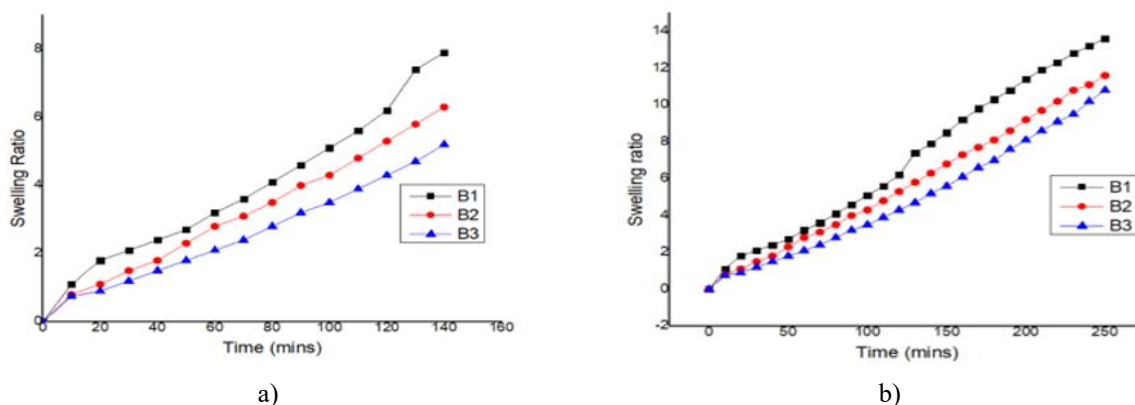


Figure 1. a) Swelling behavior of the beads in acid buffer solution. b) Swelling behavior of the beads in mixed phosphate buffer solution

Percentage particle yield, Average particle size and Entrapment Efficiency

The entrapment efficiency of microbead particles of different formulations was calculated and results given below in Table 2.

Table 2. Effect of different concentrations of Eudragit L100 and  $CaCl_2$  on % yield, particle size & entrapment efficiency

Formulation Code	% Particle Yield	Average Particle size ( $\mu m$ )	Entrapment Efficiency (%)
F1	96.25±0.248	1389 ± 2.78	85.39± 0.35
F2	98.36±0.233	1096±8.45	88.37±0.33

F3	93.45±0.631	1152±5.39	91.72±0.35
F4	92.85±0.789	1100±5.89	98.37±1.21
F5	95.45±0.968	1280±6.25	97.52 ± 1.97
F6	92.75±0.789	1245±3.12	93.93±.65

Microscopic images of microbeads using Scanning Electron Microscope (SEM)

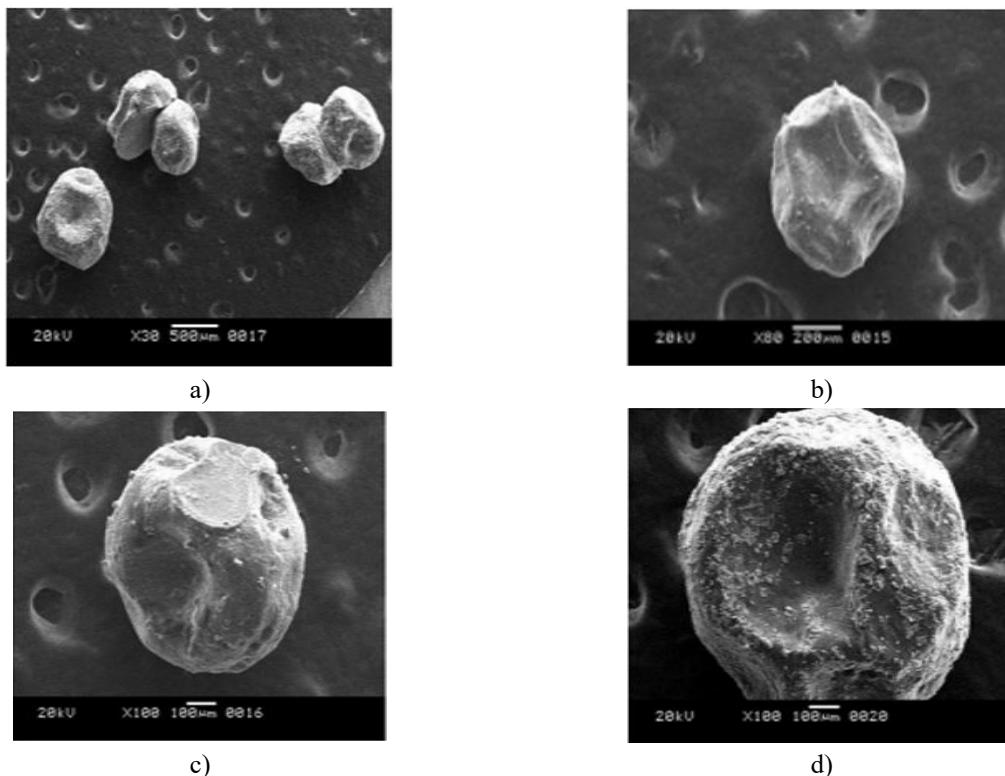


Figure 2. SEM images for the atorvastatin-loaded Eudragit and sodium alginate combination microbeads prepared by varying concentrations of Eudragit L100

ATR IR Spectra

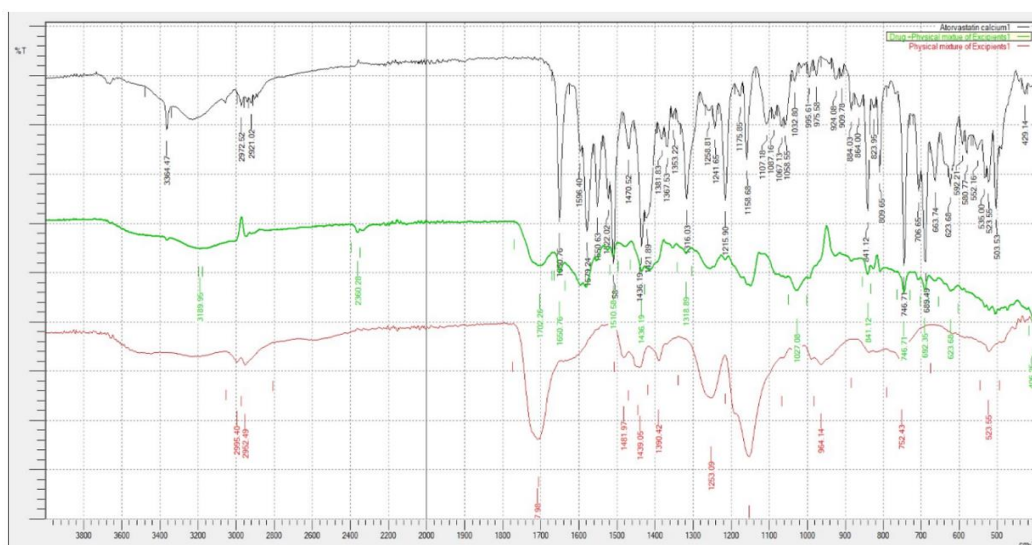


Figure 3. ATR -IR Spectra of Atorvastatin calcium, Physical mixture of excipients and Drug loaded in microbeads

Differential scanning calorimetry (DSC) study

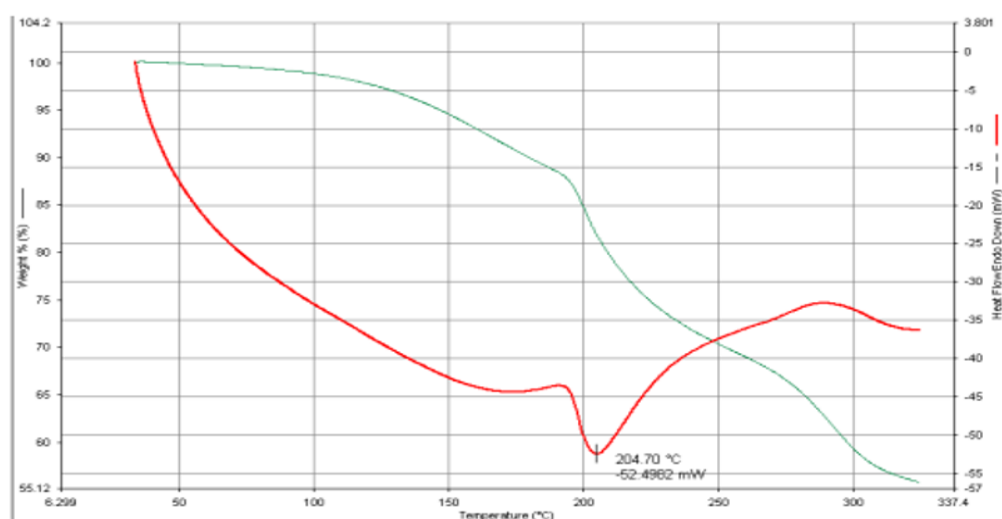


Figure 4. DSC study of Atorvastatin loaded Eudragit -alginate microbeads

“In-vitro” drug release study

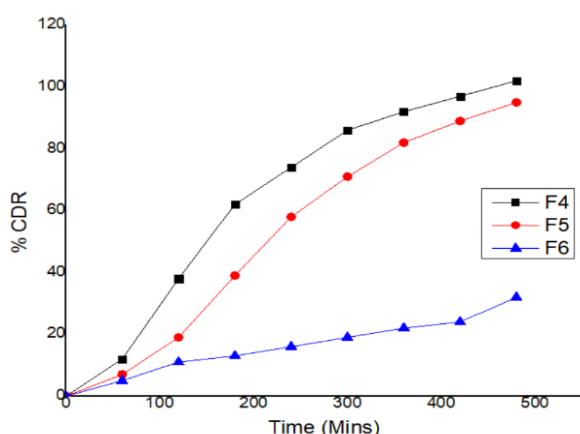


Figure 5. Release Profile of Atorvastatin Loaded Microbeads in Phosphate Buffer pH 6.8 at different concentration of Eudragit L100

Swelling study

When the amount of Eudragit L100 was increased from 10mg to 20mg the swelling ratio fell abruptly from 13 to 2.5 in phosphate buffer pH6.8. Similarly, the swelling ratio was again increased when 30 mg of Eudragit L100 was taken instead of decreasing. The same case also happens in the swelling behavior of the beads in acid solution pH1.2. Since we know that EudragitL100 dissolves in the range 6-7 so, the maximum swelling ratio was found in phosphate buffer compared to that of acid buffer solution as shown in **Figures 1a and 1b**. On the other hand, when the amount of Eudragit L100 was 20 mg it showed a minimum swelling ratio both in the acid & buffer solution. This may be explained by the fact that 20mg of Eudragit L100 gives the most stable polymeric hydrogel network system, where

the water cannot hydrate them easily. But when 30mg of Eudragit L100 was taken instead of decreasing the swelling ratio it increased rapidly providing that no stable hydrogel network system formed along with Eudragit L100 [7, 15].

Percentage particle yield and average particle size

The percentage yield of all the formulations (F1-F6) was found to be within the range of 92.75% to 98.36% as shown in **Table 2**, which denotes the suitability of the method of formulation. The percentage practical yield of all the formulations is shown in the table. Prepared microbeads were evaluated for average particle size. The average particle size was found to be within the range of 1096-1389  $\mu\text{m}$ . So, the average particle size for all the formulations was within the range [15].

Entrapment efficiency

Prepared microbeads were evaluated for entrapment efficiency. The entrapment efficiency was found to be in the range of 85.39% to 98.37% as shown in **Table 2**. Amongst formulations (F1-F6), F4, F5 and F6 showed good entrapment efficiency. Based on good entrapment efficiency F4, F5 and F6 formulations were subjected to in vitro dissolution studies. The entrapment efficiency of all the formulations is shown in the table [20].

Gelation study

Gelation behavior of the blank beads found that with an increase in the concentration of the  $\text{CaCl}_2$  from 1%, 3%, up to 5% (w/v) the percentage water loss was decreased inversely. This may be explained by the fact that with the increase in the concentration of  $\text{CaCl}_2$ , the beads formed a tight network structure formed because of the ionotropic gelation method. So minimum water loss of near about

80% was observed when 5% w/v  $\text{CaCl}_2$  was taken as compared to 1%w/v  $\text{CaCl}_2$  [21].

#### *Microscopic images of microbeads using scanning electron microscope (SEM) study*

The SEM micrographs shown in **Figure 2**, revealed that the resulting microbeads were spherical with rough surfaces containing cracks and holes over their surface. The micrographs showed almost spherical but the morphology appeared to be rough in some cases. The reason behind this morphology change can be attributed to the faster evaporation of water forming a pore-like structure. Irregular surfaces & loss of individuality of particles were observed from SEM photographs when the concentration of  $\text{CaCl}_2$  decreased from 5%, 3%, and 1% w/v [21, 22].

#### *Fourier transform -attenuated total reflectance (FTIR-ATR) study*

Infrared spectroscopy with ATR was utilized in drug-polymer suitability studies to determine whether the model drug and the polymers employed in the formulation could interact in any way. The formulation's FTIR and the pure drug's FTIR spectra were contrasted. The outcomes showed that, following effective encapsulation, the distinctive peak absorption of the raw model drug had emerged in the formed microbeads with no discernible shift in location, suggesting that there had been no chemical reaction between the model drug and the polymers employed. Due to hydroxyl, carboxy, and aromatic amines, pure atorvastatin had distinct peak values at  $3364\text{cm}^{-1}$ ,  $1650\text{cm}^{-1}$ , and  $2921\text{cm}^{-1}$ , respectively shown in **Figure 3**. These peaks persisted in atorvastatin when the microbeads were processed [9, 10, 23].

#### *Differential scanning calorimetry (DSC) study*

The endothermic peak observed in atorvastatin is sharp and correlates to a melting point between 250 and 300°C as shown in **Figure 4**. During the encapsulation process, Atorvastatin inside the Eudragit microbeads exhibited a comparable characteristic peak with decreasing intensity, indicating its stability [24, 25].

#### *"In vitro" release study*

The effect of the concentration of Eudragit L 100 in the in vitro release of Atorvastatin calcium in both acidic and alkaline dissolution mediums was checked as predicted in **Figure 5**. It was found that 7% and 5% of the drug were released within 1 hour, when, 30 mg and 40 mg of Eudragit L100 were taken along with 2% sodium alginate in formulations F5 and F6 respectively. In an alkaline medium (pH6.8 Phosphate buffer), near about 99% of the drug was released for up to 8 hrs, when 20mg Eudragit

L100 was used along with 2% Sodium alginate in formulation F4. But this release rate decreased to 75% in formulation F5 where 30mg EudragitL100 was used along with 2% Sodium alginate. The drug release rate slowed down and only 32% release occurred up to 8 hrs in formulation F6 due to the high content of Eudragit L100 along with 2% sodium alginate in the beads, there may be a chance of rigid matrix beads formation which reduces the release rate of the drugs from the beads matrix [25]. Thus, examining all the release profiles of the microbeads, we can say that the formulation containing EudragitL100 30 mg with 2% Sodium alginate is the best one. The maximum stable hydrogel network was found in this formulation (F5).

#### *"In vitro" drug release kinetics*

To comprehend the drug release mechanism and dosage form release kinetics, the in vitro drug dissolution data was fitted to multiple mathematical models, including the Zero order, First order, Higuchi matrix, and Korsmeyer Peppas Model as shown in. A system in which the release rate varies irrespective of the species concentration is described by the zero-order rate equation [26]. The release from the framework is described by the first-order equation. where the percentage of the dissolved species affects the rate of dissolution Higuchi has examined the rate law anticipated by the various dissolution mechanisms, both in isolation and in combination. When the release of a pharmaceutical polymeric form of dosage is unknown, the Korsmeyer-Peppas formula is employed to assess the release. Most of the formulations were released in both acidic as well as alkaline environments followed a non-Fickian mechanism [24, 26].

## CONCLUSION

By using the ionotropic gelation technique, atorvastatin may be efficiently added to a mixture of EudragitL100 and Sodium alginate microbeads. To determine the ideal conditions to produce nearly spherical Eudragit microparticles with high atorvastatin entrapment, several formulation variables were investigated. The characteristics of the microspheres were impacted by the processing variables in various ways. A non-Fickian diffusion mechanism was discovered to oversee releasing drugs from the microspheres in most of the cases. Fourier Transform Infrared- Attenuated Total Reflectance Infrared Spectroscopy and Differential Scanning Calorimetry analyses show that no incompatibility between the polymer medication was discovered. All the formulations follow non-Fickian diffusion except Formulation F5 which follows Fickian diffusion and all variables of F5 formulation were found to be satisfactory. Thus, the F5

formulation is the optimized one and needs to be evaluated further on a scale up basis.

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**Ethics statement:** None

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