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PREPARATION AND INVITRO EVALUATION OF SIMVASTATIN MICROPARTICLES BY IONIC GELATION TECHNIQUE

***[1]B. Raja Sankar, [2]R. Saravanan, [2]Jalaiah M. and [1]Dhachinamoorthi D.,**

[1]Professor and Principal QIS College of Pharmacy- Ongole, Andhra Pradesh.

[2]Associate Professor QIS College of Pharmacy- Ongole, Andhra Pradesh.

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***Corresponding Author**
B. Raja Sankar
Professor and Principal QIS College of Pharmacy-Ongole, Andhra Pradesh.

ABSTARCT

The overall prevalence of dyslipidemia in India in 2013 was 10 % to 73 %. The prevalence of hyperlipidemia is more in females (33.2 %) than in males (32.4). On an average 32.8 % population is suffering from hyperlipidemia. The objective of the present study is to prepare and evaluate the microspheres of simvastatin. Simvastatin microspheres were prepared by ionotropic gelation method using polymers. The simvastatin beads were successfully formulated by ionic gelation technique by using TPP as a curing agent. The formed beads were developed nearly spherical shape with rough surface with slight pores present along the surface which was confirmed by SEM studies. The FTIR, DSC and XRD studies were conducted and given confirmation that there will be chance of getting interaction among used all excipients. The average size of wet uncoated bead was 2.23 ± 0.19 mm. On drying the size reduced drastically to 0.60 ± 0.09 mm.On particle size studies it was clearly indicates that as the amount of chitosan increases particle size also increases simultaneously. i.e. maximium size were found to be 830 µm in batch D. In entrapment efficiency studies, 68 % was observed in batch D. On basis of invitro data it was clearly indicates that as the concentration of chitosan increases, the rate of drug release was delayed and produces zero order pattern release of the drug.

KEYWORDS: Simvastatin, microbead, ionic gelation technique.

INTRODUCTION

In current scenario, broad efforts are being made in pharmaceutical research laboratories for the progress of novel and targeted drug delivery system with the purpose of better therapeutic efficacy, lesser side effects, and dose for the treatment of various diseases[1] Significant

attention is focused on the development of sustained drug delivery systems which have better patient compliance than the conventional regimens that requires frequent dosing[2] Microbeads are small, solid, and free-flowing colloidal carriers containing dispersed active agents either in solution or crystalline form which allows sustained release or multiple release profiles. The benefits of this novel dosage form are improvement in stability, enhancement of solubility, and therapeutic efficacy without major side effects. Simvastatin is an antihyperlipidemic which belongs to the category of statin and inhibits the enzyme HMG-CoA reductase. HMG-CoA reductase catalyzes conversion of HMG-CoA to mevalonate, which is the rate limiting step in de novo cholesterol synthesis. Competitive inhibition of HMG CoA reductase by simvastatin decreases hepatocyte cholesterol synthesis. The associated reduction in intracellular cholesterol concentration induces LDL-receptor expression on hepatocyte cell surface, which results in an increased extraction of LDL-C from the blood and decreased circulating LDL-C concentration. Simvastatin also have beneficial effects on other lipid. parameters such as increase in high-density lipoprotein cholesterol (HDL-C) concentration and decreases in triglyceride concentration. `Simvastatin however is practically insoluble in water and freely soluble in chloroform, methanol and ethanol. It is poorly absorbed from the gastrointestinal (GI) tract. It has a half-life of 3 h, protein binding of 95 % and bioavailability of 5 %. Simvastatin has an absorption window in upper G.I tract and as a result, displays low bioavailability. Simvastatin is difficult to formulate into sustained release dosage forms, because on arrival of colon or even before, its absorption is diminished or non-existent. In the present study, efforts were made to increase the residence time of simvastatin at or above the absorption window through preparation.

MATERIALS AND METHODS

Preparation of Beads

Uncoated Beads

Chitosan solution (2% w/v) containing Simvastatin (1% w/v) was prepared in dilute acetic acid (2% v/v). The bubble free polymeric-drug solution (pH 4–4.5) was added drop wise to a solution of sodium tripolyphosphate using a syringe fitted with a blunt- end needle (23 G, inner diameter, 0.7 mm). After curing to a pre-identified time, the beads were filtered, washed with cold distilled water (thrice, 25 ml), and dried in an oven at 50◦C for 4 hr and then at room temperature (25◦C) for 12 hr.

Evaluation of the Beads Determination of absorption maxima

10 µg/ml solutions were taken to determine absorption maxima. Initially blank buffer solution was kept and scanned in the region of 200-400 nm by using UV-visible spectrophotometer. Then drug sample was kept for analysis and scanned in the above region.

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 (λ max) 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 placed in 100 mL of 6.8 phosphate buffer for 12 h. The filtered solution was measured for estimation of content using a UV spectrophotometer at 238 nm. Drug content was computed using a calibration curve (R2 = 0.9998) prepared using solutions with concentrations of 1-6 µg/mL of drug.

Bead Size and Encapsulation Efficiency

The size of the prepared beads was measured with an optical micrometer fitted with a calibrated eye piece. The mean of 100 beads was noted as particle size. The sizes of both wet and dried beads were measured. All readings are average of three trials ±S.D Fifty mg of beads were crushed in a glass mortar and digested in 0.1N hydrochloric acid (pH 1.2) for 24 hr in a graduated flask. The solution was filtered through a G-2 filter and an aliquot was used to assay for drug content spectrophotometrically (Jasco 7800, Japan) at 276 nm against a suitable blank. The encapsulation efficiency was calculated by expressing the percentage ratio of the actual drug entrapment to drug added. The values are average of three trials± S.D.

$$\text{Drug entrapment (\%)} = \frac{\text{Actual drug concentration} \times 100}{\text{Theoretical drug concentration}}$$

X-ray Powder Diffractometry

X-ray diffraction analysis was performed with an apparatus (Siemens D5000, Munich, Germany), using nickel filtered CuKα radiation (a voltage of 40 KV and a current of 20 mA). The scanning rate was 2˚C/min over a range of 20-70˚C and with an interval of 0.02˚C.

Fourier Transforms Infrared Spectroscopy

A computerized Fourier, which transforms infrared spectroscopy, FT-IR (Bomen, Quebec, Canada) was used to obtain the spectra of various CM samples. The scanning range was 400-4000 cm-1 and the resolution was 1 cm-

SEM Analysis

The surface morphology images were obtained by scanning electron microscope (Philips XL20, Holland) under vacuum. Beads were mounted on brass stubs using silver paste and scanned under vacuum at the required magnification at room temperature.

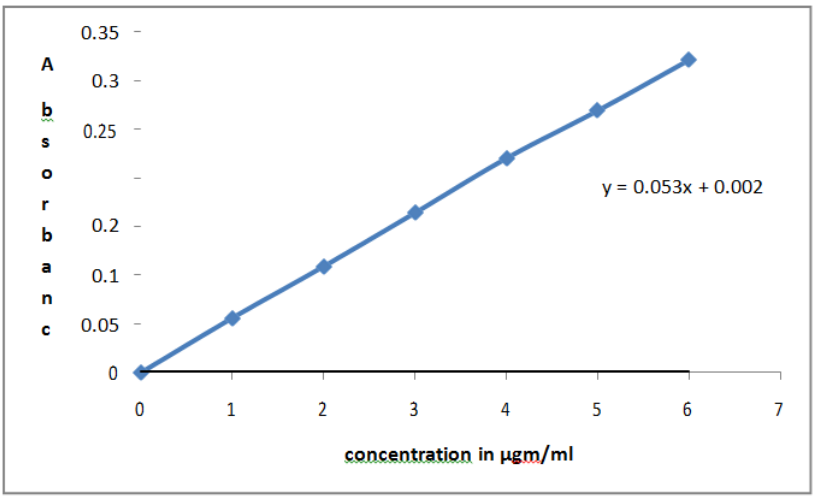
In Vitro Drug Release Studies

In vitro release of Simvastatin from the beads was performed in USP XXIII dissolution apparatus II with a paddle speed of 50 rpm. The dissolution medium was 900 ml of simulated gastric fluid (SGF) without enzyme (0.1N HCl, pH 1.2) for the first 2 hr and subsequently rest of the release study was performed in simulated intestinal fluid (SIF; phosphate buffer, pH 7.4). At predetermined time intervals, 5 ml aliquot was withdrawn and replenished with an equal volume of fresh dissolution medium. The drug content in the aliquot was determined spectrophotometrically at 276 nm (Jasco 7800, Japan). A study was performed concurrently with placebo beads to record for any interference by the bead components.

RESULTS AND DISCUSIONS

Table 1: Standard graph of simvastatin.

Sl.no	Concentration	Absorbance at 238 nm
1	0	0
2	1	0.056
3	2	0.109
4	3	0.164
5	4	0.22
6	5	0.269
7	6	0.321



Slope = 0.053

Linear regression(y) = 0.053x + 0.002

Correlation coeffeceint (R2) =0.999

Ftir Simvastatin

The spectrum of pure simvastatin presented characteristic peaks at various ranges mainly 3392.78 cm-1(alcoholic O-H stretching vibration), 2929.8715 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-1,1159.21 cm-1 and 1029.98 cm-1(lactone C=O and ester C-O-C bending vibration), respectively.

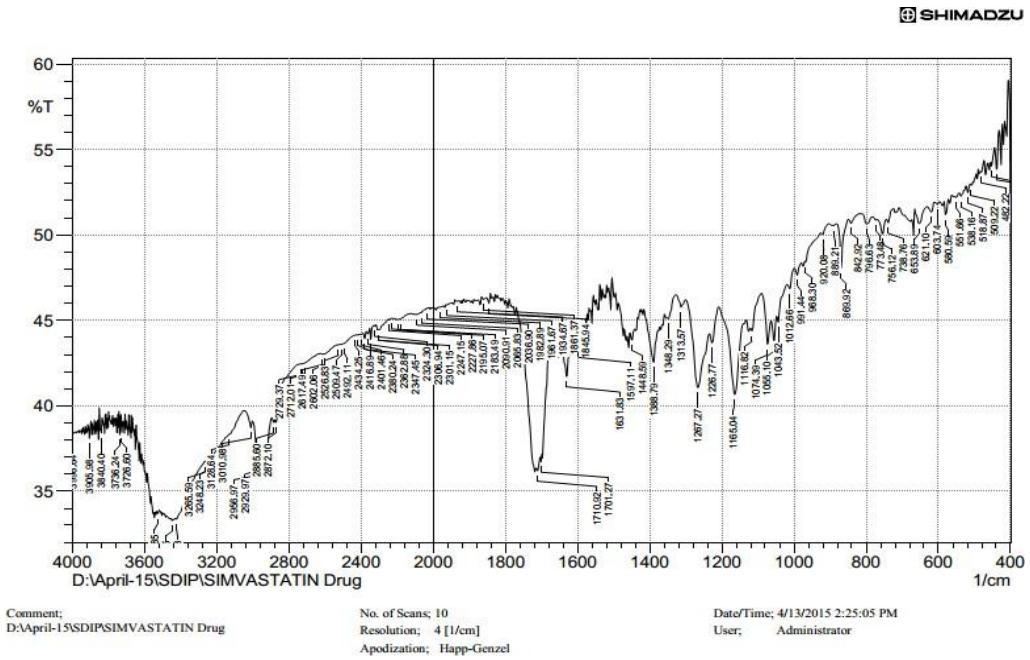


Figure 1: FTIR of simvastatin.

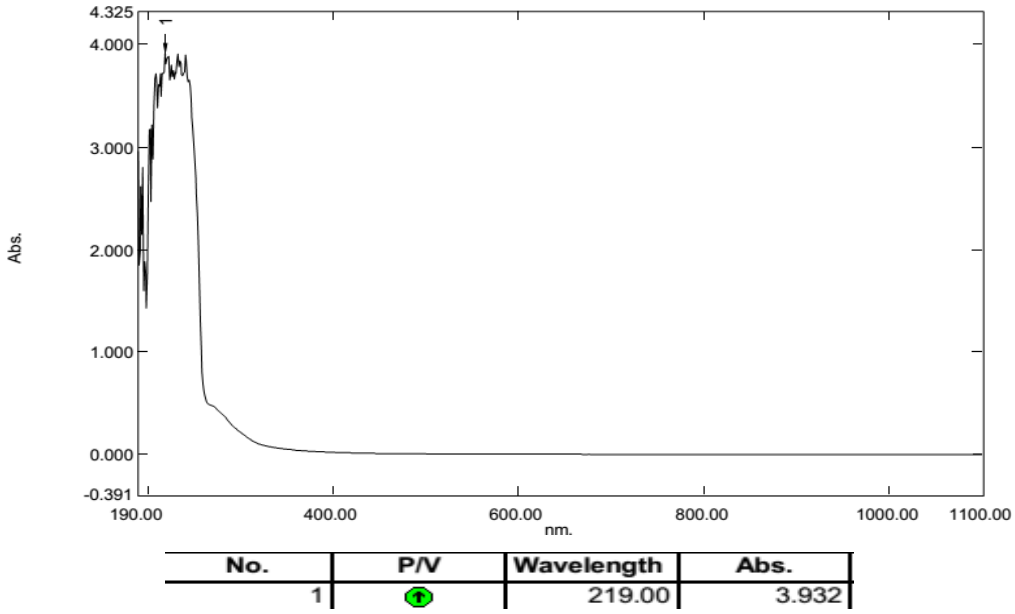


Figure 2: UV spectrum of Simvastatin in phosphate buffer pH 6.8 with 0.03% w/v SLS.

Solubility: Simvastatin showed a solubility of 1.45 µg/mL in distilled water, 14.5 µg/mL in pH1.2buffer, and 24.4 µg/mL in pH 7.0 buffer. SIM exhibits maximum solubility in phosphate buffer pH 7.0 (i.e. SIM solubility increases with an increase in medium pH). In short, SIM exhibits pH-dependent solubility.

Table 2: Formulation of simvastatin microbeads.

CODE	Chitosan	TPP	Particle size(µm)	Entrapment	%CDR
A	1	1.5	650	28	50.12
B	1.5	2	680	47	68.98
C	2	2.5	760	73	84.12
D	2.5	3	830	68	91.01

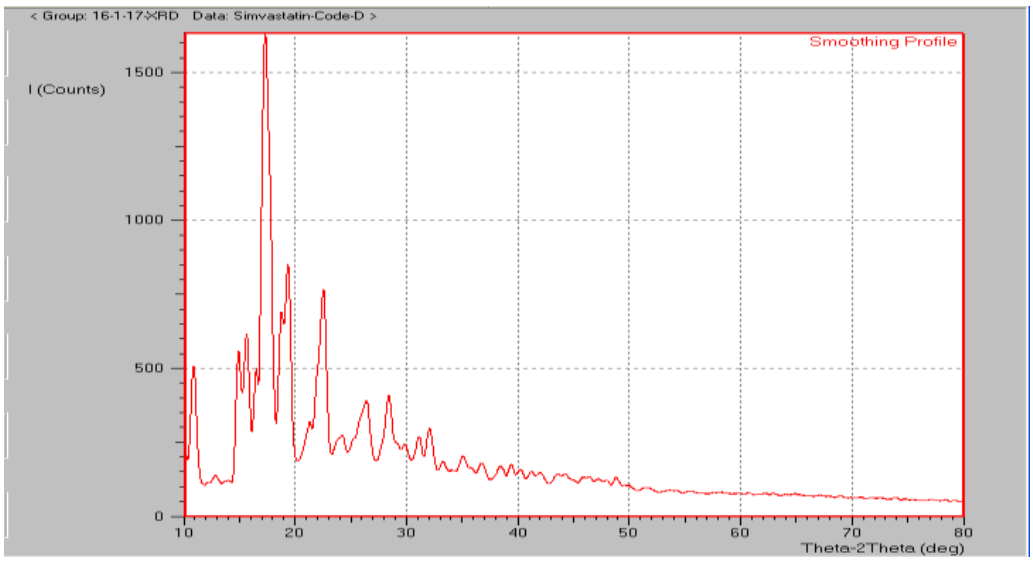


Figure 3: Xrd Of Pure Simvastatin.

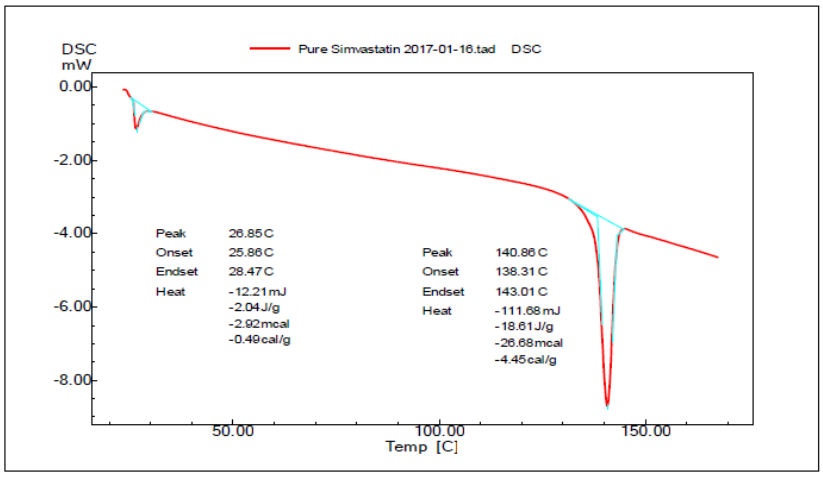


Figure 4: Dsc of Pure Simvastatin.

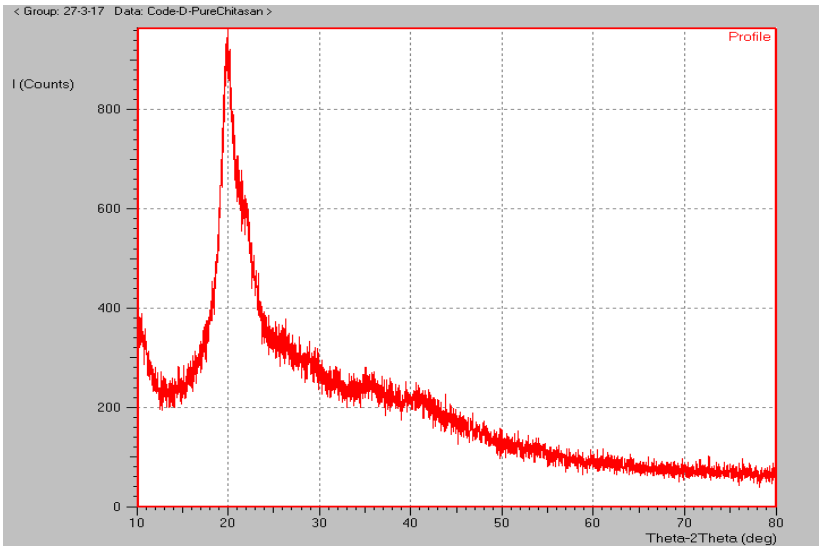


Figure 5: XRD of Pure chitosan.

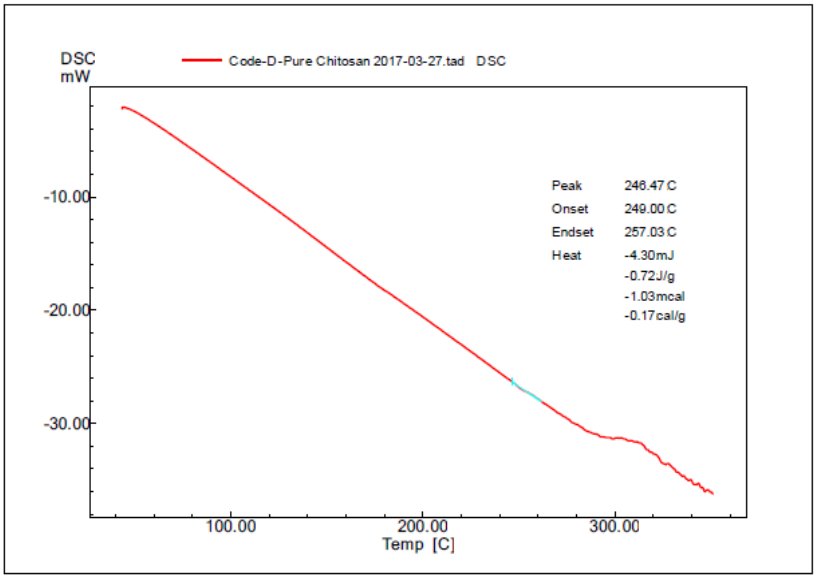


Figure 6: DSC of Pure chitosan.

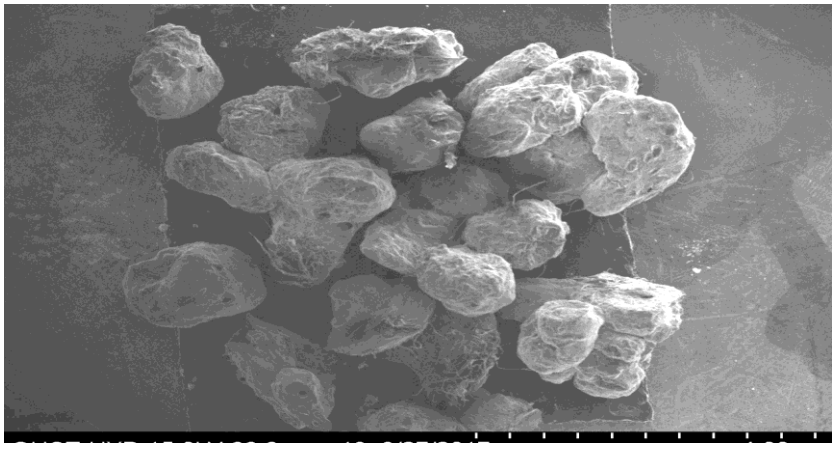
XRD: The diffraction pattern of the pure drug simvastatin shows a highly crystalline nature, indicated by numerous distinctive peaks at a diffraction angle of 2θ (28.4°, 22.6°, 18.8°, 17.2°, 10.9°, and 9.3°) throughout the scanning range. or The diffraction pattern of the pure drug showed a highly crystalline nature, indicated by numerous distinctive peaks at a diffraction angle of 2θ (28.0°, 22.4°, 18.0°, 17.8°, 16.9°,14.8°, 10.8°, and 9.0°) in a good agreement with previously published data (Rao et al., 2010).

DSC: Differential scanning calorimetry (DSC) The DSC thermogram of simvastatin exhibits a sharp melting endotherm at 138 **°C .**Where as the PXRD study demonstrated that there was a significant decrease in crystallinity of pure drug present in surface solid dispersions, which resulted in an increased dissolution rate of simvastatin.

SEM Studies

Morphology of the beads: The selection of drying technique has influence the morphology i.e. size and shape of dry beads. Closed detailed examination by SEM studies, we can observe 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.

On addition of drug containing chitosan solution to sodium TPP solution, ionic cross-linking occurs between the protonated amine group on chitosan and phosphate ions of sodium-TPP(Bodmeier et al. 1989). Takahashi et al. (1990) have previously studied formation of ionic interaction between amino group of chitosan and carboxyl groups of polyacrylate and alginate.



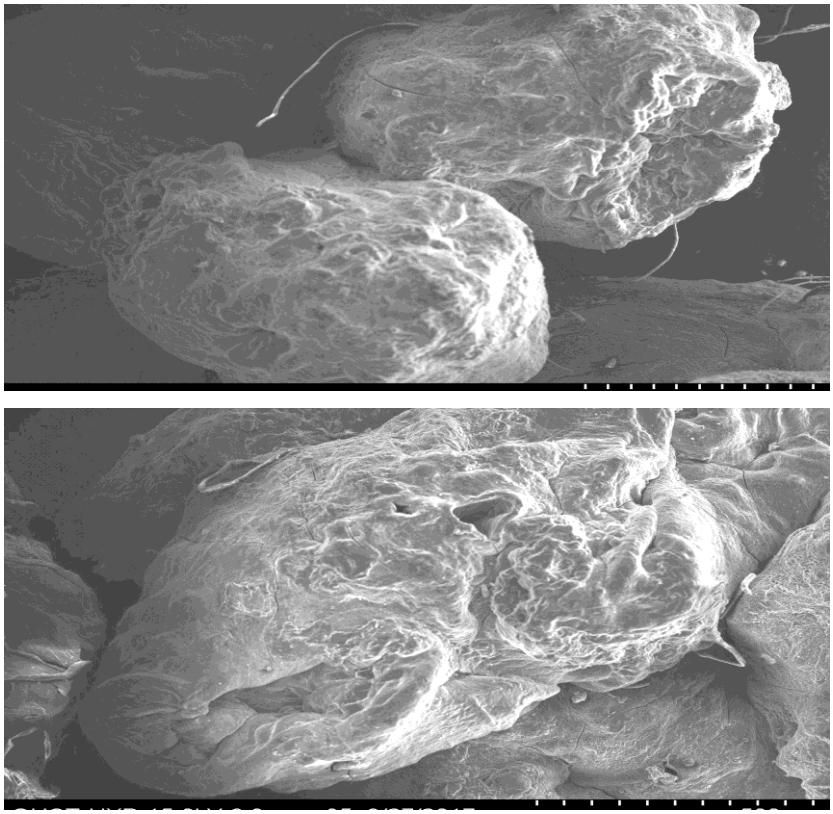


Figure 7: SEM Studies of chitosan beads.

Bead Size and Morphology

The average size of wet uncoated bead was 2.23 ± 0.19 mm. On drying the size reduced drastically to 0.60 ± 0.09 mm

Encapsulation Efficiency

As evident from Table, the encapsulation efficiency of the prepared beads increased with the addition of alginate in the coagulation fluid. The entrapment of drug in uncoated beads was 67.21 ± 1.95 %,

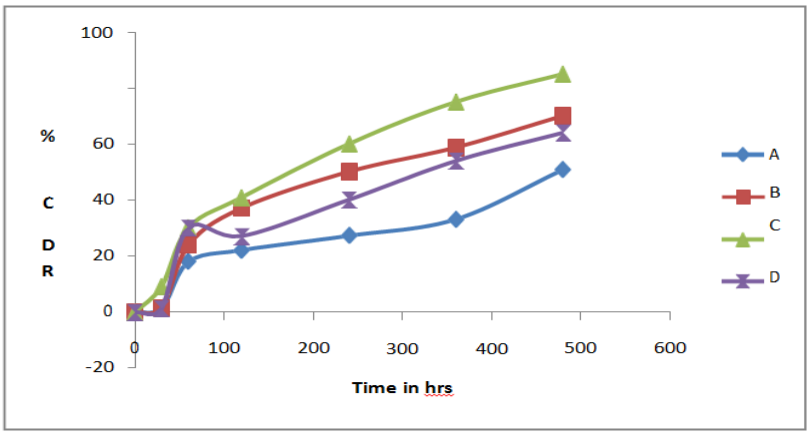


Fig 8: Invitro profile of various batches.

CONCLUSION

The formed beads were developed nearly spherical shape with rough surface with slight pores present along the surface which was confirmed by SEM studies. The FTIR, DSC and XRD studies were conducted and given confirmation that there will be chance of getting interaction among used all excipients. The average size of wet uncoated bead was 2.23 ± 0.19 mm. On drying the size reduced drastically to 0.60 ± 0.09 mm.On particle size studies it was clearly indicates that as the amount of chitosan increases particle size also increases simultaneously. i.e. maximium size were found to be 830 µm in batch D. In entrapment efficiency studies, 68 % was observed in batch D. On basis of invitro data it was clearly indicates that as the concentration of chitosan increases, the rate of drug release was delayed and produces zero order pattern release of the drug. Thus, this study concludes that the performance of the micro beads can be altered by changing the processing variables i.e. chitosan concentration.

REFERENCES

1. Ebtessam Ahmed Essa, Mai Dwaikat Enhancement of Simvastatin dissolution by surface solid dispersion: effect of carriers and wetting agents. Journal of Applied Pharmaceutical Science, May, 2015; 5(1): 046-053.
2. Burra S, Kudikala S, Reddy GJ. Formulation and evaluation of Simvastatin liquisolid tablets. Der Pharmacia Lettre., 2011; 3(2): 419-26.
3. Patil P, Patil V, Paradkar A. Formulation of a self-emulsifying system for oral delivery of simvastatin: In vitro and in vivo evaluation. Acta Pharm., 2007; 57: 111–22.
4. Boppana R, Kulkarni VR, Setty CM, Kalyane NV.Carboxymethylcellulose−aluminum hydrogel microbeads for prolonged release of Simvastatin. Acta Pharmaceutica Sciencia, 2010; 52: 137-43.
5. Singla N, Gupta GD, Kohli K, Jain S. Oral Bioavailability of Simvastatin Novel Formulation in Albino Rats. Journal of Pharmaceutical Science and Technology, 2009; 1(2): 84-87.
6. Gambhire MS, Bhalekar MR, Gambhire VM. Simvastatin loaded Solid lipid nanoparticles: Formulation optimization using Box Behnken design, characterization and in vitro evaluation. Current Pharma Research, 2011; 1(2): 157-164.
7. Pandya1 MV, Patel JK, Patel JD. Formulation and optimization of nanosuspensions for enhancing simvastatin dissolution using central composite: design. Dissolution. Tech., 2011; 3(2): 40-6.

8. tXingna Zhao, Guofei Li, Lili Zhang, Xiaoguang Tao, Tingting Guan, Mo Hong, Xing Tang, Preparation and evaluation of nicotinic acid sustained-release pellets combined with immediate release simvastatin. International Journal of Pharmaceutics, 2010; 400(1–2): 42–48.
9. Hitesh Kulharia, Deep Poojaa, S.K. Prajapatia, Abhay Singh Chauhanb, Performance evaluation of PAMAM dendrimer based simvastatin formulations. International Journal of Pharmaceutics, 2011; 405(1–2): 203–209.
10. Jun Asai, Hideya Takenaka, Satoshi Hirakawa, Jun-ichi Sakabe, Asami Hagura, Saburo Kishimoto, Kazuichi Maruyama, Kentaro Kajiya, Shigeru Kinoshita, Yoshiki Tokura, Norito Katoh, Topical Simvastatin Accelerates Wound Healing in Diabetes by Enhancing Angiogenesis and Lymphangiogenesis. The American Journal of Pathology, 2011; 181(6): 2217–2224.