Development and Invitro Characterization of Nanosponge Formulation of Lovastatin for Oral Delivery Using a Central Composite Design

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Abstract:

Nanosponges are new colloidal drug carriers with nanosized cavities to encapsulate both lipophilic and hydrophilic drug moieties. They can circumvent the various formulation challenges associated with poor water solubility, low bioavailability, targeting, and controlled release of actives. Lovastatin, a hypolipidemic drug encounters the major problems of poor water solubility and oral bioavailability. Hence the attempt was made to formulate and characterize lovastatin-loaded nanosponges. In this study, Eudragit L-100 was used as a polymer, Dichloromethane as a solvent, and PVA as a stabilizing agent to formulate lovastatin-loaded nanosponges. Different formulations with varying proportions of Eudragit L-100 and PVA were designed by using Design of experiments studies and nanosponges were prepared by the Emulsion solvent evaporation method. The FTIR spectra showed a stable character of lovastatin in a mixture of polymers and revealed the absence of drug-polymer interactions. The optimized formulation shows the average particle size of 251.6 nm, PDI was 0.428, the zeta potential was -22.7mv, percent entrapment efficiency was 95.18±0.15 and CDR was 97.35± 0.19. Conclusions: The release kinetics of the improved formulation demonstrated zero-order drug release and were best suited to the Higuchi model, indicating that drug release occurs via diffusion.

Keywords: Nanosponges, Hypolipidemic agent, Eudragit-L100, zero-order release.

1. Introduction:

H. Roy et al. (eds.), *Proceedings of the International Symposium on Sustainable Drug Design and Nanoparticle Development: Quantum and Computational Perspectives (SDDNDQCP 2025)*, Advances in Health Sciences Research 89,
https://doi.org/10.2991/978-94-6463-813-4_12

Figure 1 shows chemical structure of Lovastatin is a lipid-lowering statin used for managing hypercholesterolemia and preventing cardiovascular diseases [1,2]. As a prodrug, it is hydrolyzed to its active β-hydroxy acid form, inhibiting HMG-CoA reductase, the key enzyme in cholesterol synthesis. Due to its poor aqueous solubility and extensive CYP3A4 metabolism, advanced formulation strategies are needed to enhance its bioavailability and therapeutic efficacy [3,4].

Nanosponges are innovative nanoparticle-based drug delivery systems designed to enhance drug solubility, stability, and controlled release. Their porous structure enables them to encapsulate drugs efficiently, protecting them from degradation while ensuring targeted delivery. This technology has significant applications in pharmaceuticals, particularly in improving bioavailability and minimizing side effects [5,6].

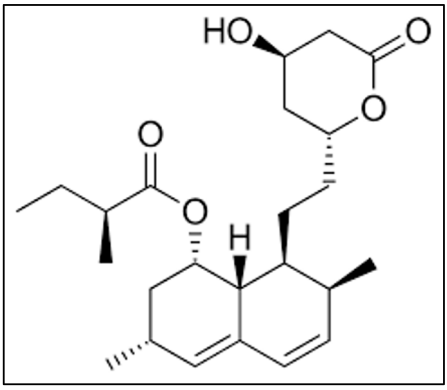

Figure 1: Chemical Structure of Lovastatin

Previous studies have explored nanosponges for various drug delivery applications, demonstrating their potential in enhancing solubility, stability, and controlled release. Pavan and Rama (2018) formulated and characterized Flurbiprofen nanosponges [7], while Penjuri et al., (2016) developed Lansoprazole-loaded nanosponges for improved gastric stability [8], Cavalli et al., (2010) investigated nanosponges as oxygen delivery systems, highlighting their versatility [9]. Other studies focused on targeted drug delivery (Ahmedkhan et al., 2016; Mathew et al., 2014), [9,10] topical applications (Priyanka et al., 2018; Aggarwal & Nagpal, 2016), [11,12] and various formulations including Glipizide (Arvapally et al., 2017) and Ibuprofen (Kumar et al., 2012) [13,14].

2. Material and Method:

2.1. Materials: Hyderabad-based Hetero Drugs gave me Lovastatin as a sample. A gift sample of Eudragit L-100 (EL-100) was obtained from Lee

Pharma Limited, Visakhapatnam, India. SDFCL, Mumbai supplied solvents, Poly Vinyl Alcohol, and other AR-grade chemicals.

2.2. Methods:

2.2.1. Identification and Confirmation of Drug: Melting point determination is a primary confirmation test for Lovastatin, where the drug is filled into a capillary tube, tied to a thermometer, and dipped in a liquid paraffin bath to observe its melting range. FTIR Spectroscopy was conducted by mixing ground Lovastatin with KBr (1:100 ratio) to form pellets under 10-12 metric tons of pressure, which were scanned over 4000–400 cm^{-1} using an FTIR spectrometer. A Mettler DSC 1-star system was used to encapsulate the medication in a perforated aluminum pan and heat at 10°C/min from 30–350°C under nitrogen purging (20 ml/min) to get the thermogram.

2.2.1. Standard Calibration Curve in Methanol: A standard calibration curve for Lovastatin was prepared by dissolving 100 mg of the drug in methanol, making up the volume to 100 ml, and preparing dilutions (1-10 µg/ml). The solutions were scanned using a UV spectrophotometer, with the maximum absorption (λ max) observed at 240 nm. The absorbance values were plotted against concentration, forming a straight line as per Beer's law. This standard curve was used to determine drug release during in vitro dissolution studies.

2.2.2. Optimization by Factorial Design: Lovastatin nanosponges were optimized using RSM-CCD to systematically evaluate the effects of formulation variables. Eudragit L-100 (X_1) and PVA (X_2) were selected as independent variables, varied between 50 mg and 100 mg, to assess their impact on nanoparticle characteristics. The responses analyzed included particle size (Y_1) and entrapment efficiency (Y_2) across 13 formulations (F1–F13). The experimental design was executed using Design Expert 10 (Stat-Ease 10.0.3.1), which facilitated statistical analysis and model fitting. A polynomial equation was generated to predict the optimal formulation parameters with minimal experimental trials. The optimization process helped identify the ideal concentrations of polymer and surfactant for improved nanosponge characteristics.

2.2.3. Preparation of LOS nanosponges: Using Eudragit-L100 polymer and PVA surfactant, emulsion solvent evaporation produced lovastatin nanosponges (F1–F13). The formulation parameters were adjusted using RSM-CCD to regulate particle production. The prepared batches' composition and process factors are in Table 1.

Table 1: Formulations Batches as per RSM-CCD design

Formulation Code	Eudragit L-100 (mg)	PVA (mg)
F1	170.711	100
F2	50	150
F3	100	100

F4	100	29.2893
F5	29.2893	100
F6	100	100
F7	100	170.711
F8	50	50
F9	150	150
F10	100	100
F11	100	100
F12	100	100
F13	150	50

2.2.4. Particle Size, Zeta Potential, and Drug Loading: The particle size, PDI, and zeta potential of Lovastatin nanosponges were analyzed using a Zetasizer (Malvern Nano ZS) at 25°C. Encapsulation efficiency and drug loading were determined via UV-visible spectrophotometric analysis after dissolving the nanosponges in phosphate buffer (pH 6.8).

2.2.5. In-Vitro Drug Release Study: The USP-II dissolving equipment was used to measure in-vitro drug release at 37±0.2°C with 900 mL phosphate buffer (pH 6.8) at 100 rpm. Nanosponges (equivalent to 40 mg drug) were placed in a diffusion sachet, and drug release was measured at 240 nm using UV-VIS spectroscopy over 1 to 12 hours. The release data were analyzed using kinetic models to determine the drug release pattern**.**

2.2.6. Release Rate Kinetics: Zero-order kinetics indicates a constant release over time, while first-order kinetics shows release proportional to the remaining drug concentration. Higuchi's model explains diffusion-based drug release, and Korsmeyer-Peppas characterizes the mechanism based on the release exponent.

3. Result and Discussion:

3.1. Melting Point Determination: The mean melting point was recorded as 175.0°C, confirming the drug's purity and identity.

3.1.1. FTIR Spectroscopy: The FTIR spectrum of Lovastatin confirmed its characteristic functional groups, with C–O stretching at 1066.67 cm^{-1}, C–O–C stretching between 1220.98–1261.49 cm^{-1}, and C–H bending at 1381.08–1458.23 cm^{-1}. Additionally, C–H stretching was observed at 2872.10–2928.04 cm^{-1}, while O–H stretching appeared at 3539.49 cm^{-1}, verifying the structural integrity of the drug in Figure 2 and Figure 3.

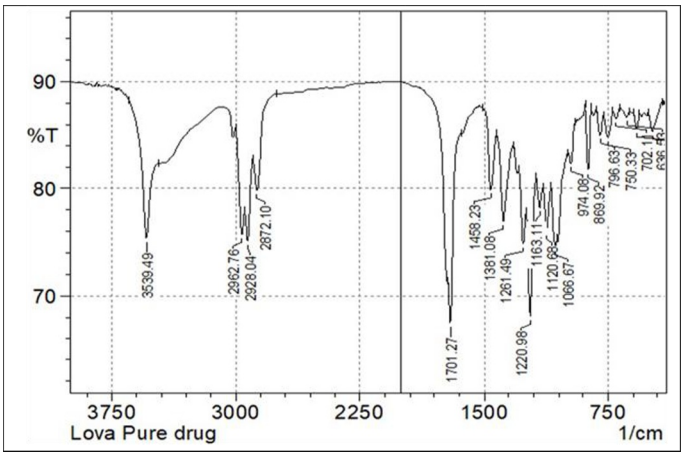

Figure 2: FTIR Spectra of Lovastatin

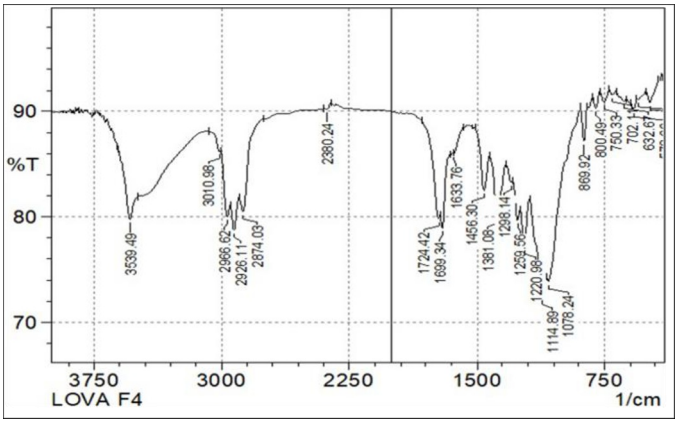

Figure 3: FTIR Spectra of Optimized formulation

3.1.2. Differential Scanning Calorimetry: The Differential Scanning Calorimetry analysis was performed to assess the thermal behavior of the excipients used in the Lovastatin nanosponge formulation. Eudragit L-100 exhibited a sharp endothermic peak at 207.17ºC, which aligns well with its reported melting point range of 150-210ºC, confirming its thermal stability and purity. This peak represents the polymer's phase transition, indicating no significant impurities or structural modifications.

Similarly, Polyvinyl Alcohol showed a distinct endothermic peak at 224.89ºC, consistent with its specified melting point range of 200-250ºC. The well-defined peak suggests the presence of a crystalline region within the polymer, ensuring its integrity during formulation processing. The absence of additional peaks or shifts in the thermogram indicates that both Eudragit L-100 and PVA retained their thermal properties without significant degradation under experimental conditions.

Figure 4 and 5 present the corresponding DSC thermograms, further validating the excipients' thermal stability. These results confirm that Eudragit L-100 and PVA are suitable for the formulation process, as they can withstand the temperatures involved in nanosponge preparation without undergoing undesirable thermal degradation or phase transitions.

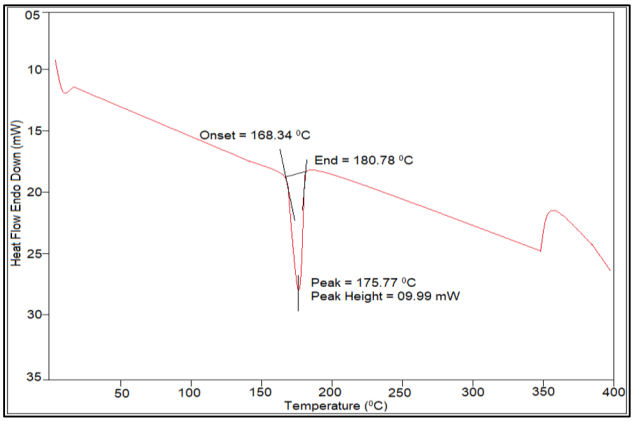

Figure 4: DSC of Lovastatin

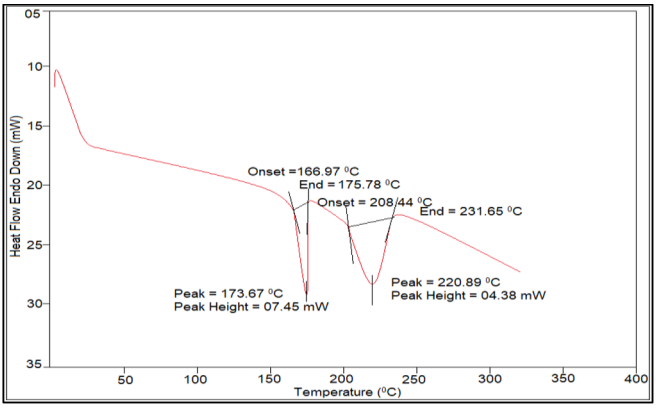

Figure 5: DSC graph of optimized formulation

3.1.3. Curve of Lovastatin in Methanol: In the linear equation, y=0.0619x−0.0037 y represents the absorbance calculated for a given concentration (x) based on the slope (0.0619) and intercept (-0.0037). The outcomes, presented in Table 2 and Figure 6, illustrate the correlation between the compound's concentration and the corresponding absorbance values from Figure 6.

Table 2: Standard calibration curve of Lovastatin in Methanol

Concentration (µg/ml)	Mean Absorbance (n=3; ± SD)
0	0
2	0.121±0.01
4	0.235±0.04
6	0.366±0.06
8	0.489±0.03
10	0.633±0.07
12	0.729±0.02

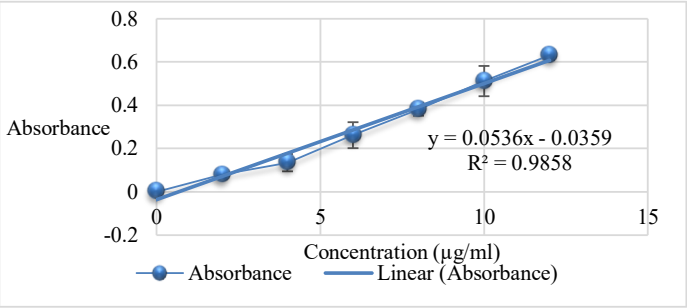

Figure 6: Standard calibration curve of Lovastatin in Methanol

3.2. Formulation Design: Various Formulation batches of nanosponges were prepared by based on RSM factorial designs (Table 3).

Table 3: Design Batches

Code	X1 (mg)	X2 (mg)	Y1 (nm)	Y2 (%)
F1	170.711	100	330	82.21
F2	50	150	350	82.12
F3	100	100	329	82.27
F4	100	29.2893	377	82.11
F5	29.2893	100	343	82.23
F6	100	100	251	84.17
F7	100	170.711	390	82.24
F8	50	50	356	82.14
F9	150	150	325	82.19
F10	100	100	290	83.86
F11	100	100	265	83.84
F12	100	100	270	83.90
F13	150	50	312	82.17

3.3. Response Surface Plot Analysis: The optimized batch, F6, exhibited the smallest particle size (251 nm), indicating that a balanced concentration of X1 and X2 (100 mg each) promotes stable nanoparticle formation. The highest %EE (84.17%) was also observed in F6, followed by F10, F11, and F12, suggesting a correlation between smaller particle size and higher encapsulation efficiency. The results emphasize that an optimal ratio of X1 and X2 is crucial for achieving stable nanosponges with enhanced drug entrapment (Figure 7 and 8).

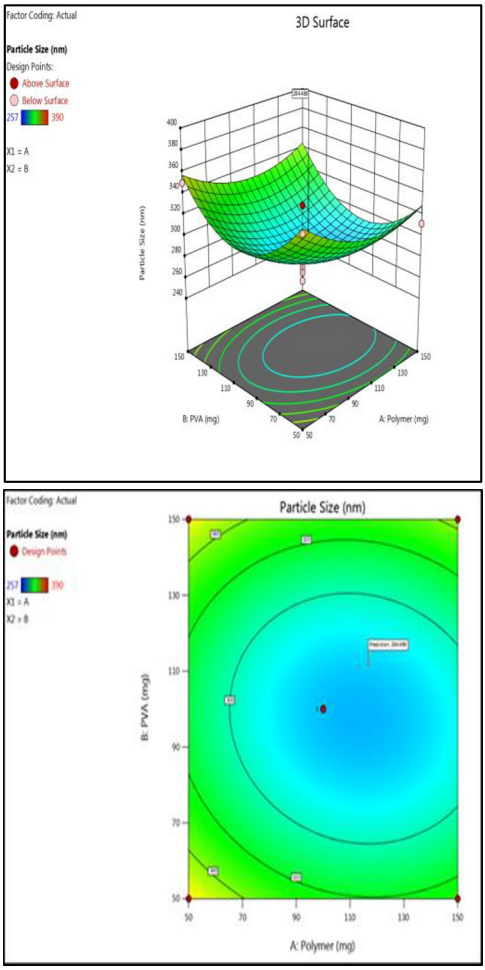

Figure 7: 3D surface plot and Contour Plot of Particle size

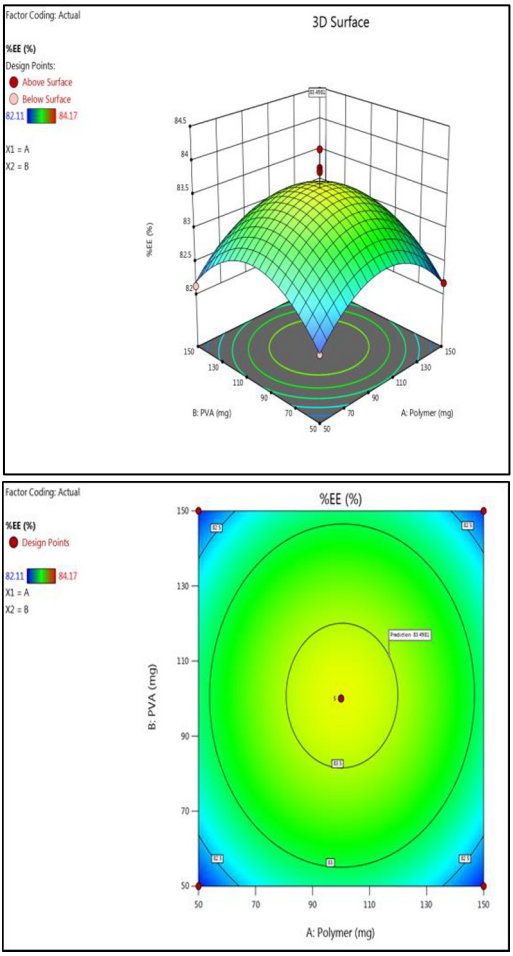

Figure 8: 3D surface plot and Contour Plot of Entrapment efficiency

3.4. Nanosponges Characterization: Size, Surface Charge, and Distribution: The Lovastatin nanosponges demonstrated an average particle diameter of 251.6 nm, confirming their nanoscale formulation. The surface charge potential was recorded at -22.7 mV, indicating good colloidal stability and reduced chances of aggregation. Furthermore, the size distribution index (PDI) was measured at 0.428, suggesting a moderately uniform particle dispersion within the formulation.

3.5. % EE and drug loading capacity: The encapsulation efficiency and drug loading of the Lovastatin nanosponges (F1–F13) ranged from 82.11±0.12% to 84.17±0.15% and 70.93±0.19% to 80.32±0.20%, respectively. These results indicate a high drug entrapment within the nanosponges, ensuring effective drug incorporation. The variations in %EE and %DL suggest formulation-dependent efficiency in encapsulating and loading Lovastatin.

3.6. In-vitro drug release study: The in-vitro drug release study for different batches of Lovastatin nanosponges showed cumulative drug release (CDR) ranging from 82.45% to 97.35%, with batch F6 exhibiting the highest release (97.35%), making it the optimized formulation. A comparative study between F6 and pure drug demonstrated a sustained release pattern for nanosponges, where F6 released 26.24% at 2 hours, 56.26% at 6 hours, and 97.35% at 12 hours, while the pure drug showed faster release, reaching 97.42% at 8 hours. The controlled release behavior of nanosponges highlights their potential for prolonged drug delivery (Figure 9).

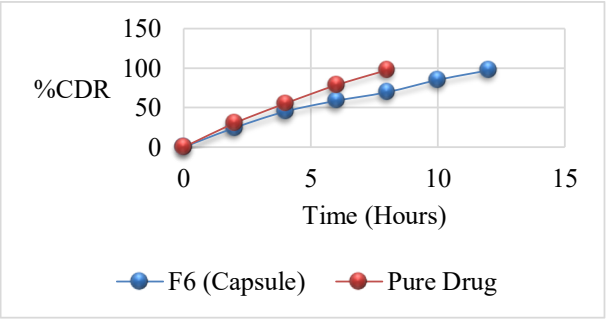

Figure 9: In-vitro drug release of nanosponges

3.7. Formulation of Capsule using optimized nanosponges: Of all the formulations, selected nanosponges (Nanosponges: F6) is added in hard gelatin capsules. These capsules had a theoretical lovastatin content of 40mg. As a reference, capsules from a plain drug (i.e. without any polymer) are made to compare the dissolution behavior of both the formulations. The capsule formulation (F6 Cap) of Lovastatin nanosponges was evaluated for uniformity of content and drug content. The uniformity of content was recorded as 0.1849±0.04, while the drug content was 97.89±0.022%, ensuring consistent dosing and effective drug loading within the capsule.

3.8. In-vitro dissolution: The in-vitro dissolution study of the capsules was conducted in a pH 6.8 buffer, revealing that formulation F6 exhibited an optimal drug release over a 12-hour period. The dissolution profile, presented in Table 4 and Figure 10, confirms the formulation's ability to achieve sustained drug release, making it suitable for extended therapeutic action.

Table 4: In-vitro release profile of F6 Capsule

Time (Hours)	F6 Cap
0	0
2	24.42±0.05

4	45.04±0.09
6	58.62±0.03
8	69.52±0.04
10	85.02±0.06
12	97.24±0.01

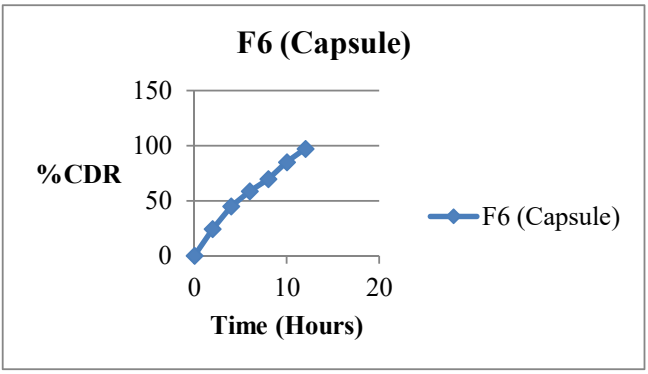

Figure 10: In-vitro drug release study F6 Capsule

3.9. Kinetics of drug release: The constant rate release model (R^2 = 0.9810) exhibited the best fit, indicating a time-independent drug release. The diffusion-controlled release model (R^2 = 0.9698) also showed a strong correlation, suggesting a porous matrix-based diffusion mechanism. In contrast, the concentration-dependent release model (R^2 = 0.8503) and the polymer matrix diffusion model (R^2 = 0.8184) demonstrated lower correlation, confirming that the F6 capsule follows a controlled and sustained drug release profile suitable for long-term therapeutic efficacy.

4. Conclusion:

The present study successfully developed and characterized Lovastatin-loaded nanosponges using Eudragit L-100 and PVA via the emulsion solvent evaporation method, optimizing the formulation through RSM-CCD. The optimized formulation (F6) exhibited small particle size (251.6 nm), high entrapment efficiency (84.17%), and sustained drug release (97.35% over 12 hours), following zero-order and Higuchi diffusion-controlled kinetics.

The capsule formulation of optimized nanosponges ensured uniform drug content (97.89%) and prolonged release, demonstrating its potential for enhanced oral bioavailability and controlled drug delivery. These findings highlight nanosponges as a promising strategy for improving Lovastatin's solubility, stability, and therapeutic efficacy.

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