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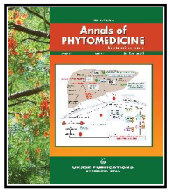

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Design and characterization of simvastatin loaded nanosponges using tamarind seed powder and beta-cyclodextrin

Siddhi J. Rakibe, Ashish Y. Pawar◆, Khanderao R. Jadhav* and Vaishnavi V. Kale

Mahatma Gandhi Vidyamandir's Pharmacy College (Affiliated to Savitribai Phule Pune University, Pune), Panchavati, Nashik- 422003, Maharashtra, India

**R.G. Sapkal College of Pharmacy (Affiliated to Savitribai Phule Pune University, Pune), Sapkal Knowledge Hub, Kalyani Hills, Trimbakeshwar Road, Nashik-42213, Maharashtra, India*

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Abstract

The goal of the current research is to increase the bioavailability of drugs from BGS class II like simvastatin by incorporating them into nanosized drug delivery. Tamarind seed powder and beta-cyclodextrin were used as polymers in this research. A comparative analysis of natural polymer with synthetic polymer was carried out to formulate nanosponges. Nanosponges are mesh-like structures with diameter less than 1µm. Because of their small dimensions and permeable nature, they can easily bind with drug, which improves the solubility and in turn, the bioavailability of the same. Simvastatin, a medication with low solubility, is formulated as nanosponges in this study to improve solubility. Eight different batches were formulated using various amounts of tamarind seed powder and beta-cyclodextrin. The formulated nanosponges were evaluated for entrapment efficiency, drug content, particle size measurement, zeta potential, scanning electron microscopy and drug release. Based on results obtained, F6 batch containing beta-cyclodextrin is found to be optimized batch with particle size 1.62 nm and entrapment efficiency 78.22%. At the same time tamarind seed powder also shows good results which are very nearby to synthetic polymer. This article describes the creation of nanosponges and their appraisal in accordance with the results obtained.

1. Introduction

The term "Nanosponge" refers to nanoparticles with pore-like features. Nanosponges are extremely small sponges, close to size of a virus, having average diameter less than 1µm. They can increase the bioavailability of poorly soluble medications by binding them inside the matrix due to their tiny size and porous nature (Shrishail and Surwase, 2019). This is done by altering the pharmacokinetic characteristics of the actives. Nanosponges are three-dimensional, solid, porous, biocompatible drug delivery system that may entrap both hydrophilic and hydrophobic medications and solve the issues of drug toxicity and low bioavailability (Keerthi *et al.,* 2017). The development of Nanosponges has been a crucial step in conquering the complexity of the newly emerging systems. Nanosponges may adhere to the surface and start releasing the medication in a regulated and predictable way because of their tiny size and porous nature, which enables poorly-soluble medicines bind inside the matrix and increase their bioavailability at particular target sites. Simvastatin is an antihyperlipidemic HMG CoA reductase (3-hydroxy 3-methylglutaryl coenzyme A reductase) inhibitor (Dinesh and Paswan, 2020). This anticholesteremic medication is used to treat dyslipidemia. Due to significant intestinal clearance and first pass metabolism, simvastatin's absolute bioavailability is only approximately 5%. The solubility and rate of dissolution of poorly soluble BCS class II drugs were increased *via* inclusion complex formation, which also improved the drug molecule bioavailability (Shrishail and Surwase, 2019). The present study was undertaken to enhance the bioavailability of the drug using natural and synthetic polymers. Tamarind seed powder and beta-cyclodextrin were used as polymers in this research (Abdulsalam and Ahuja, 2018; Tanikan, 2018). Nanosponges increases the absorption and bioavailability of BCS Class II drugs. Hence, an attempt to formulate novel delivery system of antilipidemic drug was carried out.

2. Materials and Methods

2.1 Materials

Simvastatin was purchased from Swaroop Drugs, Aurangabad, India. Beta-cyclodextrin, ethyl cellulose, dichloromethane and poly vinyl alcohol (PVA) of lab grade. Tamarind seed powder was purchased from the local market. For experimental procedures, distilled water was used.

2.1.1 Organoleptic properties of simvastatin

The colour of a small sample of APIs was taken on butter paper and examined in a well-lit area. The odour of a very small number of APIs was detected (Duraisami *et al.,* 2021; Himangshu *et al.,* 2021). A visual method was used to observe appearance.

Corresponding author: Dr. Ashish Y. Pawar
Associate Professor, Department of Pharmaceutics, Mahatma Gandhi Vidyamandir's Pharmacy College (Affiliated to Savitribai Phule Pune University, Pune), Panchavati, Nashik- 422003, Maharashtra, India.
E-mail: pawarashish23@gmail.com
Tel.: +91-9823481646

2.1.2 Melting point

The sample's purity can first be determined by looking at its melting point. The capillary method was used to determine APIs' melting points. Simvastatin was administered using a glass capillary with a flame-sealed opening (Shrishail and Surwase, 2019). The melting point of the liquid paraffin inside the melting point device was then determined by dipping the capillary into it.

2.1.3 Solubility analysis

Simvastatin solubility in distilled water, 0.1 N sodium hydroxide (NaOH), ethanol and methanol were investigated using the shake flask method. In 1-10 ml of the relevant solvent, the investigated chemical was dissolved in solid excess. The solutions were swirled in a magnetic stirrer for 48 h under thermostatic conditions until they reached solubility equilibrium. The solutions were left to sediment under thermostat conditions to separate the phases. Filtration was performed on the solution. Aliquots of the solution were collected from the clear section (Keerthi *et al.,* 2017). After diluting the aliquots, the absorption was measured using a UV-spectrophotometer (Shimadzu UV-2600). The aliquots' concentrations were calculated.

2.1.4 Determination of λ_{max} by UV spectrophotometric method

The UV spectrum of simvastatin was collected using a Shimadzu 2600 UV. A proper amount of methanol was added to the precisely weighed 10 mg of medication, which was then dissolved, increasing the volume to 10 ml. A 100 ug/ml concentration was achieved by diluting the stock solution. The 1 ml of the aliquot was taken out and the volume was increased to 10 ml using methanol to achieve a concentration of 10 ug/ml. From 200 to 400 nm, the resulting solutions were scanned (Ozoude and Azubuike, 2017; Rathi *et al.,* 2012). To determine the maximum wavelength, the spectrum was recorded.

2.1.5 Simvastatin calibration curve using methanol

A stock solution with a concentration of 100 ug/ml was made in methanol. This stock solution was used to create several dilutions ranging from 5 to 25 ug/ml. A UV visible spectrophotometer was used to measure the absorbance of the resulting solutions at 236 nm.

2.1.6 Drug compatibility study

The Shimadzu 8400 FT-IR spectrometer was used to record the infrared spectra of pure simvastatin. The sample was created using the KBr disc technique, and it was then analyzed in transmission mode. Over the 4000-400 cm^{-1} frequency range, the spectrum was measured (Shrishail and Surwase, 2019). After comparing the typical absorption peaks of the drug and excipients with those of the pure drug, it was found that the drug is compatible with excipients.

2.2 Method of preparation of nanosponges

Tamarind seed powder and β-cyclodextrin were used in varied ratios to develop nanosponges by Emulsion solvent diffusion method as described in Table 1. The dispersed phase, which contained the drug (100 mg) and the necessary amount of ethyl cellulose dissolved in 20 ml of solvent (dichloromethane), was gradually added to the 100 ml of the aqueous continuous phase, which contained a specific amount of polymer. The reaction mixture was stirred at 1000 rpm on a magnetic stirrer for two hours, then homogenized for an additional hour. The created nanosponges were collected *via* Whatman filter paper was placed in an oven set to 50°C for two hours to dry. (Keerthi *et al.,* 2017; Ayesha and Pawar, 2020; Patil and Mohite, 2015). Vacuum desiccators were used to store the dried nanosponges in order to completely remove any remaining solvent.

Table 1: Composition of simvastatin nanosponges

Formulation batch	Drug (mg)	Ethyl cellulose (mg)	Tamarind seed powder (mg)	β- cyclodextrin (mg)	Dichloromethane (ml)	Poly vinyl alcohol (mg)	Distilled water (mg)
F1	100	100	100	-	20	500	100
F2	100	100	200	-	20	500	100
F3	100	100	300	-	20	500	100
F4	100	100	400	-	20	500	100
F5	100	100	-	100	20	500	100
F6	100	100	-	200	20	500	100
F7	100	100	-	300	20	500	100
F8	100	100	-	400	20	500	100

2.3 Evaluation of nanosponges

2.3.1 Visual examination of nanosponges

Visual inspection of the formulated nanosponges was performed. The nanosponges of spherical nature depends upon the viscosity of the polymer solution.

2.3.2 Percentage yield of nanosponges

The percentage yield was calculated using following formula:

$$\text{Percentage yield } \frac{\text{Practical weight of Nanosponges}}{\text{Theoretical weight of Nanosponges (Drug + Polymer)}} = \times 100$$

2.3.3 Drug entrapment efficiency

10 mg of nanosponges were dissolved in 10ml of pH 7.4 phosphate buffer. Following a 24 h incubation period, after filtering the solution, the filtrate was adequately diluted with phosphate buffer and subjected to UV-visible spectrophotometric analysis (Gangad harappa *et al.,* 2017). The formula below was used to get the drug entrapment efficiency.:

$$\text{Drug entrapment efficiency} = \frac{\text{Experimental drug loading}}{\text{Theoretical drug loading}} \times 100$$

2.3.4 Drug content

For an hour, a precisely weighed equivalent quantity of drug-containing nanosponges was maintained with continual stirring in 100 ml of phosphate buffer (pH 7.4). UV-Vis spectroscopy was used to compare the filtered samples to a blank at 236 nm. Results are shown in Table 9.

$$\text{Actual drug content (\%)} = \frac{N_{act}}{N_{ms}} \times 100$$

where,

Nact - Actual drug content in the weighed quantity of nanosponges

Nms - Weight of nanosponges

Nthe - Theoretical drug content in nanosponges

2.3.5 Particle size measurement

The malvern zeta sizer was used to determine size dispersion and average mean diameter of loaded nanosponges (At 25°C). To produce the required light scattering intensity for the optimized batch of simvastatin nanosponges, the dried nanosponges were dispersed in water.

2.3.6 Zeta potential measurement

The zeta potential was measured using the zeta sizer (Malvern instruments). It uses zeta cells and polycarbonate cells with gold-plated electrodes as well as water as the sample preparation medium. The nanosponges surface potential is determined by the zeta potential, which is essential for characterizing the stability of nanosponges.

2.3.7 Scanning electron microscopy (SEM)

The microscopic characteristics (morphology and shape) of the optimized batch of Simvastatin nanosponges were determined by SEM examination. SEM photos were acquired at various magnifications using nanosponges that had been produced and dried thoroughly to reduce moisture content. Samples were placed on glass slides kept under vacuum and then coated with a thin gold coating using a sputter coater device operating at 15kv acceleration voltage (Ayesha and Pawar, 2020).

2.3.8 *In vitro* drug release study

In vitro dissolution analysis of Simvastatin nanosponges were carried out using a USP-type II device (paddle type). The prepared nanosponges powder were placed in size 2. Dissolution investigations were conducted employing a dissolution medium consisting of phosphate buffer with a pH of 7.4, operating at a temperature of 37 ± 2°C and a rotational speed of 100 rpm. From the preparation, 100 mg of nanosponges were added to the dissolution media for each sample. 1ml aliquots of the material were extracted filter *via* a 0.45 membrane filter, and on a regular basis (0, 5 15, 30, 45, 60, 120, 180, 240, 300, 360, 420,480 Min). The removed sample was replaced with the same amount of new dissolving media every time. The filtered solutions were appropriately diluted. Using a UV spectrophotometer with a 236 nm wavelength, the samples were examined for the presence of drugs.

3. Results

3.1 Organoleptic properties

The drug sample's organoleptic properties were investigated and they are shown in Table 2.

Table 2: Organoleptic properties of simvastatin

Properties	Observed results	Reported standards
Appearance	Non-hygroscopic crystalline powder	Non-hygroscopic crystalline powder
Colour	White	White
Odour	Odourless	Odourless

3.2 Melting point

The capillary tube method used to calculate the melting point. The results are shown in Table 3.

Table 3: Melting point of simvastatin

Sample	Observed	Reported
Simvastatin	135° to 138°C	137°C

3.3 Solubility study

Simvastatin's solubility in various solvents, including distilled water, 0.1 NaOH, ethanol and methanol was tested. Results of solubility are mentioned in Table 4.

Table 4: Solubility of simvastatin nanosponges

Solvent	Observed solubility (mg/ml)	Reported solubility (mg/ml)	Inference
Distilled water	0.019	> 10,000	Practically insoluble
0.1 NaOH	68	30 -100	Slightly soluble
Ethanol	157	1-10	Freely soluble
Methanol	196	1-10	Freely soluble

3.4 UV- Visible spectroscopy of simvastatin

Simvastatin's UV spectra when dissolved in methanol showed a maximal absorbance wavelength of 236 nm, suggesting its unique light-absorbing characteristics.

3.5 Construction of beer lamberts plot in methanol

Beer lamberts plot of Simvastatin in methanol shown in Figure 1 and Table 5. Regression analysis showed that the lines produced in methanol had a regression coefficient of 0.9929.

Table 5: Absorbance of simvastatin in methanol

S. No.	Concentration	Absorbance at 236 nm
1.	0	0
2.	5	0.180
3.	10	0.600
4.	15	0.897
5.	20	1.278
6.	25	1.630

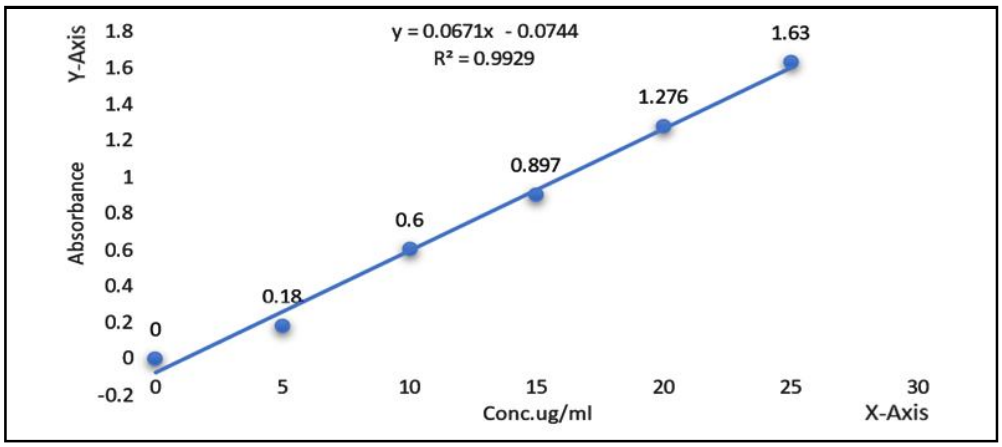

Figure 1: Calibration curve of simvastatin.

3.6 Drug compatibility study

The FT-IR spectra of simvastatin were captured using an FT-IR spectrophotometer. The reported values of simvastatin are consistent with the expected values for its functional groups, showing that the molecular structure is stable (Table 6). Furthermore, the drug-polymer mixture's IR values match those of the drug standard, indicating that the drug and polymer combination is stable. These results support the hypothesis that the polymer demonstrates stability and compatibility with the medication.

Table 6: FT-IR peaks of simvastatin

Functional group	Observed range (cm^{-1})	Standard range (cm^{-1})
O-H stretching	3549.02	3600-3100
C=O stretching	1697.36	1750-1625
-C-O stretching	1165	1000-1300
C-H bending	972.12	650-1000

3.7 Evaluation of nanosponges

3.7.1 Visual examination of nanosponges

The formulated batches of nanosponges were inspected visually for their physical appearance. The nanosponges was observed to be white spongy powder.

3.7.2 Percentage yield of nanosponges

The results of calculating the nanosponges' percentage yield are shown in Table 7.

Table 7: Percentage yield of nanosponges

Formulation code	Percentage yield
F1	27.15%
F2	35.09%
F3	59.23%
F4	65.47%
F5	30.56%
F6	58.09%
F7	67.14%
F8	78.33%

The percentage yield of nanosponges of optimized formulation (F6) and (F3) was found to be 58.09% and 59.23%, respectively.

3.7.3 Drug entrapment efficiency

The simvastatin nanosponges of % entrapment efficiency are shown in Table 8.

Table 8: Drug entrapment efficiency

Formulation batch	Entrapment efficiency
F1	62.31%
F2	69.94%
F3	72.06%
F4	70.40%
F5	73.46%
F6	78.22%
F7	71.43%
F8	65.12%

The entrapment efficiency of all batches was determined. Out of all the formulated batches, formulation batch F1 was found to be lowest entrapment efficiency (62.31%), whereas formulations F3 and F6 was found to be highest entrapment efficiency (72.06%) and (78.22%), respectively.

3.7.4 Drug content

The simvastatin standard calibration curve was used to calculate the drug's concentration. The results are shown in Table 9.

Table 9: Drug content of simvastatin

Formulation code	Actual drug content
F1	52.39%
F2	65.39%
F3	75.09%
F4	72.43%
F5	74.60%
F6	79.20%
F7	69.19%
F8	64.23%

The batch F1 was found to be lowest actual drug content (52.39%) and F3 was found to be (75.09%), whereas formulation F6 had the highest actual drug content (79.20%).

3.7.5 Particle size measurement

One of the most essential parameters is the size of the particles is a characteristic of nanosponges. The malvern zeta sizer was employed to ascertain the average particle size of the produced simvastatin nanosponges.

Table 10: Particle size of optimized batch of nanosponges

Batch No.	Observed particle size
F3	182.5 nm
F6	162.4 nm

According to a particle size investigation, batch F3 and F6 of simvastatin nanosponges had an average particle size of below 1µ and a polydispersity index value of 1.537 and 1.256. The distribution of simvastatin nanoparticle sizes are depicted in Table 10.

3.7.6 Zeta potential measurement

The Malvern zeta-sizer was used to determine the zeta potential. Zeta potential analysis determines the surface charge of particles to evaluate their stability during storage. Formulation batch F3 and F6 were evaluated and the results are shown in Table 11.

Table 11: Zeta potential of optimized batch of nanosponges

Batch No.	Observed zeta potential
F3	-16.5
F6	-21.4

3.7.7 Scanning electron microscopy (SEM)

The SEM images of the optimized F6 batch showed the typical morphological aspects of nanosponges. SEM is used for detailed particle structural characterizations and morphological structures of Nanosponges. The results are shown in Figure 2.

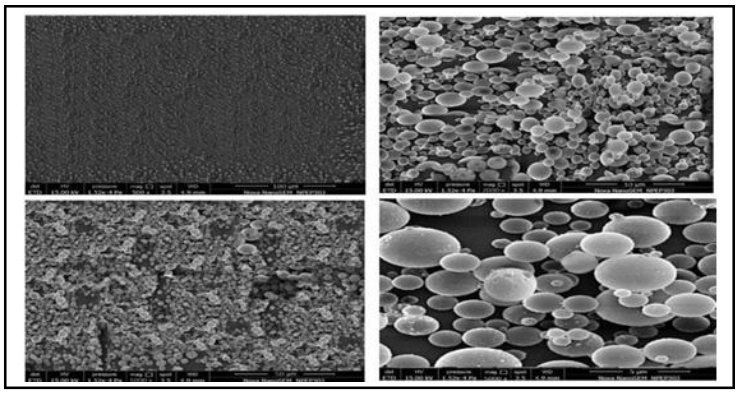

Figure 2: Scanning Electron Microscopy (SEM).

Table 12: *In vitro* drug release study of simvastatin nanosponges

S. No.	Time interval (minute)	%Cumulative drug release							
		F1	F2	F3	F4	F5	F6	F7	F8
1.	0	0	0	0	0	0	0	0	0
2	5	0.59	7.89	11.56	7.71	2.23	9.11	6.9	0.92
4	15	2.36	9.84	16.32	9.05	5.12	15.23	9.12	2.30
5	30	8.96	14.23	21.87	14.63	9.24	22.48	12.49	6.96
6	45	7.02	20.65	25.96	17.84	16.45	27.56	16.59	9.56
7.	60	9.04	24.97	31.7	20.19	22.34	32.16	19.26	11.36
8.	120	11.94	39.62	42.67	33.27	35.62	40.25	23.43	15.60
9.	180	21.93	45.09	50.94	36.88	40.13	46.59	29.09	24.87
10.	240	35.75	51.28	54.13	45.63	49.94	53.56	37.56	31.03
11.	300	45.48	58.53	59.21	50.12	57.23	62.75	42.12	46.78
12.	360	58.4	62.17	65.19	53.19	64.05	76.26	57.89	59.25
13.	420	74.45	69.33	71.45	59.83	75.56	82.17	65.45	67.94
14.	480	79.44	78.75	**82.93**	71.28	81.49	**86.23**	76.95	72.16

3.7.8 *In vitro* drug release study

It was determined the cumulative proportion of drugs released. Results are shown in Table 12 and Figures 3 and 4. The F6 batch shows the highest drug release (86.23 %) amongst all formulations. At the same time F3 formulations containing tamarind seed powder also shows promising results (82.93%) drug release.

3.7.9 Drug release to various kinetics

The kinetic data applied on *in vitro* dissolution studies shows that the Higuchi model and zero order kinetics are used in the optimized batch F6 (Table 13). This demonstrates the diffusion mechanism for drug release. The F6 batch follows supercase II transport drug release mechanism.

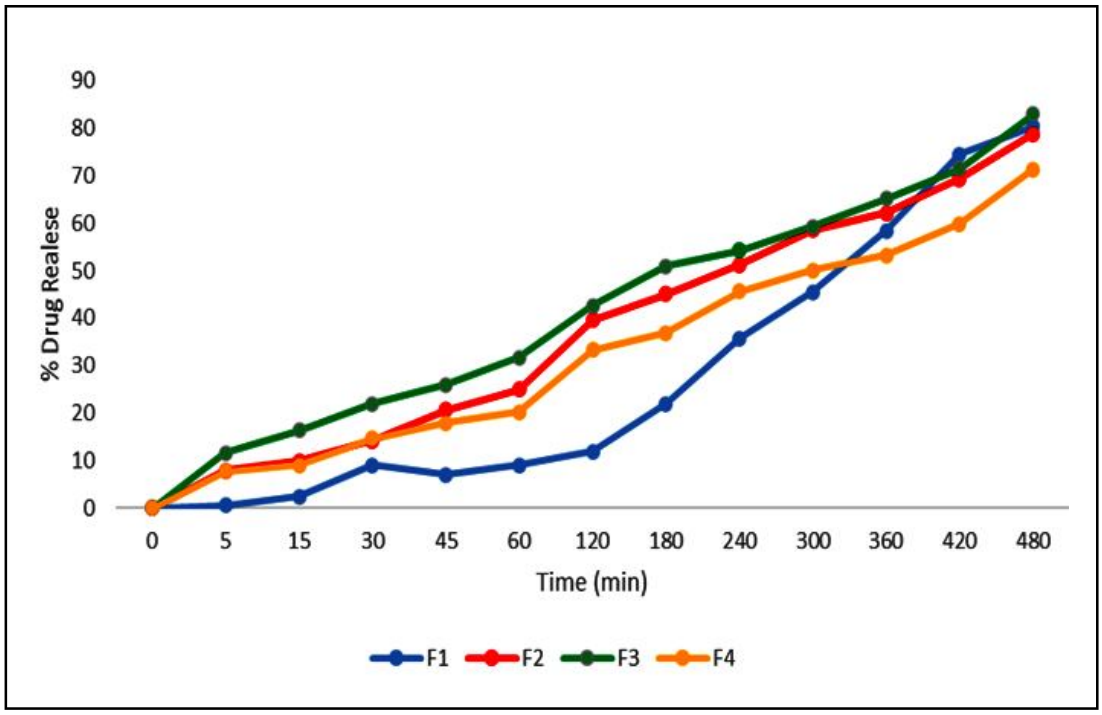

Figure 3: Dissolution study of F1 To F4 batches.

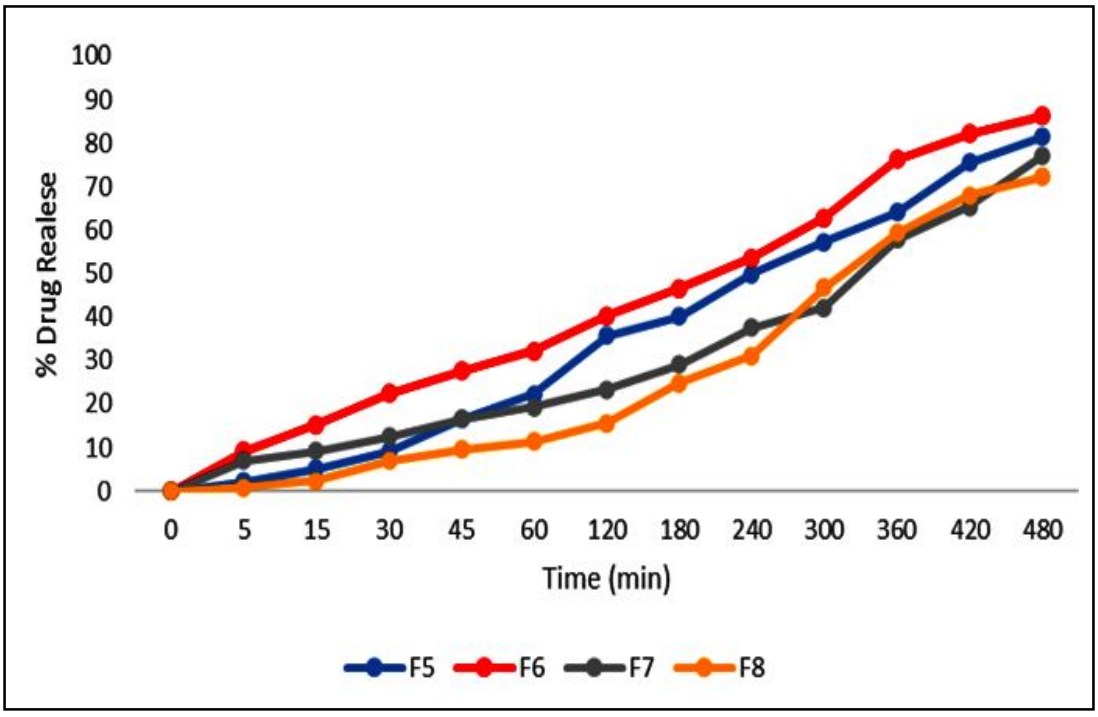

Figure 4: Dissolution study of F5 To F8 batches.

Table 13: Kinetic assessment formulated nanosponges of simvastatin

Release kinetics model	X - axis	Y - axis	Slope	Intercept	R^2	Linear equation
Zero order kinetics model	Time in min	Cumulative % drug release	0.162	14.455	0.9387	y = 0.162x + 14.455 R^2 = 0.9387
First order kinetics model	Time in min	Log % cumulative drug release	0.162	85.545	0.9337	y = -0.162x + 85.545 R^2 = 0.9337
Higuchi model	Sq. root of time	Cumulative % drug release	3.9128	1.5825	0.9825	y = 3.9128x -1.5825 R^2 = 0.9825
Hixon Crowell model	Time in	Cube root of % drug release	0.0044	4.5264	0.9771	Y = -0.0044x + 4.5264 R^2 = 0.9771
Korsmeyer Peppas model	Log time	Log % cum. drug release	29.817	109.06	0.8214	Y = -29.817x + 109.06 R^2 = 0.8214

4. Discussion

The efficacy of simvastatin-loaded nanosponges has been investigated in several studies. These studies have demonstrated enhanced drug delivery and improved therapeutic outcomes compared to conventional simvastatin formulations (Shrishail and Surwase, 2019). The utilization of a natural polymer, specifically tamarind seed powder, in this study yielded comparable outcomes when compared to synthetic polymers.

The solubility assessment of simvastatin revealed a remarkable affinity towards ethanol and methanol, surpassing those observed in alternative solvents or aqueous environments. A Beer-Lambert plot for simvastatin in methanol yielded a regression coefficient of 0.9929 indicating strong linearity. The infrared (FTIR) spectroscopy analysis demonstrated compatibility between simvastatin and the polymer employed in the formulation. The FTIR values of the polymer-drug mixture displayed characteristic peaks at wavelengths corresponding to OH stretching (3549.02 cm^{-1}), C=O stretching (1697.36 cm^{-1}), C-O stretching (1165 cm^{-1}) and C-H bending (972.12 cm^{-1}), falling within the expected range for these functional group. Batch F8 was found to be great percentage yield due to increasing polymer concentration. The % entrapment efficiency of simvastatin nanosponges was found to be F3 batch 72.06% and F6 batch 78.22% containing polymer tamarind seed powder and beta-cyclodextrin, respectively. The drug content analysis of batch F3 yielded a result of 75.09%, while batch F6 showed a drug content of 79.20%. Upon comparison, it can be concluded that the drug content of batch F3 is comparable to that of batch F6, given the numerical values obtained from the analysis.

In this study, we investigated the particle size and zeta potential of batches F3 and F6. Our findings revealed that batch F3 exhibited a particle size of 187.5 units and a zeta potential of -16.4 mV, closely resembling the values of 162.4. units and -21.4 mV obtained for batch F6. The zeta potential, particle size, and SEM analysis indicate the potential of tamarind seed powder and Beta-cyclodextrin to form homogeneous nanosponges. These values were found to fall within the standard range for nanosponges, indicating that the batch exhibited desirable characteristics in terms of its physical properties. SEM analysis demonstrated that the optimized nanosponges batch exhibited segregated, spherical morphology with a smooth surface, porous nature, and particle sizes below 1µ the F6 batch exhibited the highest drug release percentage (86.23%) compared to all other formulation. Additionally, the F3 formulation which include tamarind seed powder also demonstrated promising results with a drug release percentage of 82.93%. The kinetic analysis of *in vitro* dissolution studies revealed that the optimized F6 and F3 batch follows both zero-order kinetics and the Higuchi model.

5. Conclusion

In this study, we designed and characterized simvastatin-loaded nanosponges using beta-cyclodextrin and tamarind seed powder. The nanosponges were successfully synthesized and exhibited uniform particle size distribution as confirmed by SEM analysis. The zeta potential measurements revealed stable colloidal dispersion. Encapsulation efficiency and drug release studies indicated effective loading and controlled release of simvastatin. Furthermore, the nanosponges demonstrated enhanced stability and protection of simvastatin against degradation. Overall, the results suggest that beta-cyclodextrin and tamarind seed powder can be utilized as promising carriers for the development of nanosponges for efficient drug delivery applications. Further investigations are warranted to explore their therapeutic potential and *in vivo* performance. The ability of both tamarind seed powder and beta cyclodextrin-based nanosponges to encapsulate various kinds of therapeutic molecules is one of its most important characteristics. Due to straightforward synthesis, straightforward purification processes, and the use of few chemicals, production costs are lower. Tamarind seed powder shows comparable results which are very close to synthetic polymer. The research being done now demonstrates that the nanosponges being created using natural as well as synthetic polymers are effective and serve their intended purpose.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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