Section A-Research paper

FORMULATION AND EVALUATION OF SIMVASTATIN DRUG BY VIRTUE OF PULSATILE DRUG DELIVERY SYSTEM

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Abstract:

The aim of this study was to create a tablet for reducing lipid levels in the blood, which would contain nanosponges and be designed to release the drug in a pulsatile manner. The emulsion solvent evaporation was used to develop SIM loaded nanosponges with the use of analytical

grade of chemical and reagents and direct compression method was used to formulate tablet. The findings indicate that the concentration of polymers has increased. increased the effectiveness of drug entrapment, but after a certain concentration, as polymer concentration rose, entrapment effectiveness fell. In comparison to other formulations, F5 (90.048%) and F6 (86.52%) were found to have superior entrapment efficiency. The formulations F5 and F6 were selected as the most favorable options because of their higher entrapment efficiency and prolonged drug release duration in the in vitro experiments. The objective of this research was to develop nanosponges of Simvastatin, a drug with low solubility and short half-life, to achieve controlled release, improve solubility, reduce adverse effects that depend on dosage, and increase patient adherence.

Keywords: Nanosponges, Characterization, Bioavailability,

1. Introduction:

Simvastatin is a cholesterol-lowering drug derived synthetically from fermentation products of *Aspergillus terreus* [1]. Simvastatin is administered orally as an inactive lactone which gets hydrolyzed to corresponding β hydroxy leading to the competitively inhibition of cholesterol biosynthesis by HMG-CoA reductase. Inhibiting the catalytic enzyme that controls the conversion of HMG CoA to mevalonate, the rate-limiting step in cholesterol production that results in a decrease in intracellular cholesterol level in hepatocytes, HMG CoA reductase inhibitors bind reversibly to HMG CoA reductase. [2].

Simvastatin is chemically modified 2,2-dimethyll butyrate analogue of lovastatin. SIM is used in conjunction with a healthy diet rich in nutritious meals in order to reduce the level of bad cholesterol and fats (such as LDL and triglycerides) and boost levels of good cholesterol (HDL) in the blood.
SIM is white in color crystalline and non-hygroscopic powder having log and glass transition temperature of 25℃, It is nearly insoluble in water (30 g/mL) [3]. Compounds with extremely low water solubility are thought to display dissolution-controlled absorption, resulting in limited absorption, distribution, and target organ delivery [4].

Nanosponges are tiny wipes, generally the size of an infection, with a typical width of under 1000 nm. These minuscule wipes can move around the body until they get to the ideal area, where they grip and start to deliver the drug in an anticipated and controlled way [5] Because of their incorporation and exclusion conduct, NS have a round colloidal shape and have been shown to have a very high solubilization limit with regards to low solvent prescriptions [6]. Nanosponges can be utilized to work on the bioavailability of prescriptions that are not great solvents in water [7].

A pulsatile drug delivery system, also known as a sigmoidal release system, is created to release a specific amount of medication quickly and briefly during a specific time period

following a predetermined lag time or off-release interval. The goal of this drug delivery method is to ensure that the medication is released at the correct time and place according to a predetermined schedule. In order to synchronize drug release with the body's natural circadian rhythms, the pulsing pattern must be designed to allow for a complete and rapid release of the medication following the lag phase [8]. Due to the drug's entire release occurring after a predetermined lag time, pulsatile devices are attracting a lot of attention. Pulsatile medication delivery systems are site- and time-specific, allowing for personalized and timely delivery while also boosting patient compliance [9]. Circadian rhythms are natural, self-sustaining timekeepers that allow living organisms to adapt their behaviour to a 24-hour cycle based on the Earth's rotation and changes in the environment. These rhythms are not influenced by external time cues, and their duration may be longer or shorter than precisely 24 hours under constant conditions. Therefore, the term "circadian" is used to indicate that it is an internal process that roughly corresponds to a one-day cycle [10]

Circadian clocks and metabolism are linked to physiology through molecular mechanisms: The primary proof that 24-hour occasional events are produced by natural oscillators that inside screen the World's pivot was tracked down in research on plants in the eighteenth hundred years. The "circadian clocks" respond to light and regulate the energy intake and expenditure of living organisms based on the natural cycle of sunrise and sunset [11]

2. EXPERIMENTAL

2.1 Chemical and reagents

Simvastatin (98%) was purchased from GLR Innovation Ltd. Polyvinyl alcohol Ethyl Cellulose, Pluronic F-68, Dimethyl sulfoxide, DMSO, Microcrystalline Cellulose, Magnesium Stearate was kindly provided by Noida Institute of Engineering and Technology. Every other chemical and solvent used were of analytical grade.

2.2 Instrumentation

Digital Balance CY204, Citizen, Magnetic Stirrer with Hot plate - Remi Motors Mumbai, Ph meter Analyzer LI 614 New Rea Scientific Corp. UV Visible spectrophotometer UV-1700, Shimazdu. Sonicators Bransonic Ultrasonic Corporation, Homogeniser IKA@RT25 Digital TURRAX@R, Hot Air Oven – NSW-143, Narang Scientific works Pvt. Ltd, India. FTIR spectrum 65, perkin Eimer, Particle Size Analysir Anton Paar.

3. Methods

3.1 Preparation of Simvastatin loaded Nanosponges.

Emulsion Solvent evaporation method was used to develop simvastatin loaded nanosponges. Different percentage of ethyl cellulose, polyvinyl alcohol and Pluronic F68 was used while the quantity of drug simvastatin was kept constant, disperse phase was prepare by adding 100 mg of simvastatin and a measured amount of ethyl cellulose (as mentioned in Table 3) was dissolve in

30 ml of dimethylsulfoide. This mixture was then slowly mixed with a precise amount of PVA in 100ml of aqueous continuous phase drop wise under constant stirring of 1000rpm for 2hr. the dispersion was then filtered and dried in oven for 24 hours at 40℃.

3.2 Characterization of Nanosponges

Simvastatin loaded nanosponges were assessed for various parameters such as the amount of drug present, drug entrapment efficiency, the size distribution of the particles and the level of variation in particle size (polydispersity index.

3.2.1 Determination of PDI and particle size: The technique of dynamic light scattering (Anton Paar) was used to measure the particle size and PDI. The detection angle was 90°, and the cell temperature was 25°C. After dilution with deionized (DI) water, all measurements were taken in triplicate. The experiments were repeated three times, and the results are presented as the average value along with the standard deviation (SD)

3.2.2 Determination of drug entrapment efficiency

10mg of nanosponges containing simvastatin were dissolved in a conical flask containing 50ml of DMSO and subjected to an Orbital shaker cum bod incubator for 6 hours. The concentration of the resulting solution was measured using a UV spectrophotometer (UV-1700 Pharma Spec, Shimandzu), with DMSO as the blank.

The proportion of the drug that was successfully trapped within the nanosponge formulation was determined using, Entrapment Efficiency (EE) % = Actual amount of drug encapsulated / Theoretical amount of drug X 100

3.2.3 Morphology of Nanosponge by scanning electron microscopy (SEM) technique:
The surface of the nanosponges and the complex were observed under a scanning electron microscope.

4. FORMULATION OF SIMVASTATIN NANOSPONGE LOADED TABLETS

The direct compression approach was used to formulate simvastatin tablets. The specified amount of simvastatin nanosponges, polymers, and excipients (Table 2) were blended homogeneously before being compressed into tablets (100 mg) using a tablet compression machine (16 station) utilizing an 8 mm, biconcave punch.

4.1 Characterization of Nanosponges Loaded Tablets

4.1.1 Thickness: The thickness of the tablets was measured using Vernier calipers. The measurement was conducted on five tablets, and the average value was computed.

4.1.2 Determination of Weight variation: The average weight of 20 tablets was measured and recorded. Then, the weight of each individual tablet was measured to determine if there was any significant variation. Weight variation was calculated by comparing the weight of each tablet with the average weight.

Table1 : Specification for Weight Variation of Tablets as per USP Average Weight of Tablet

Average Weight of Tablets (mg)	% Weight Variation
≤130	10
130-324	7.5
≥324	5

4.1.3 Hardness

The hardness of the tablet was evaluated using a Monsanto hardness tester. The tablet was placed lengthwise between the plunger and force was applied until it crushed. The pressure required to crush the tablet was recorded and measured in kg/cm2.

4.1.4 Friability

The Roche friabilator was used to determine the friability of tablets, which is expressed as a percentage (%). Six tablets were weighed and placed in the friabilator, which was then operated at 25 rpm for 4 minutes. After that, the tablets were weighed again, and the % friability was calculated using the following formula:

$$\% \text{ Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} \times 100$$

4.1.5 In-Vitro release determination:

The dissolution characteristics of the tablet were examined in an in-vitro release study, which was performed using a dissolution apparatus (DISSO). The conditions for the study were specified in Table 2.

Table 2 Dissolution Parameters Specification

Apparatus	USP Apparatus Type 2 (paddle)
Volume of Medium	900ml
Sampling interval (hrs.)	1,2,3,4,5,6,7,8,9
RPM	50
Temperature	37℃±0.5℃

Table 3: Composition of Nanosponges

F No.	Simvastatin (mg)	Polyvinyl Alcohol (mg)	Ethyl Cellulose (mg)	Pluronic F68 (mg)	DMSO (ml)	Distilled Water (ml)
F1	100	1200	1000	200	30	100
F2	100	1200	400	100	30	100
F3	100	1200	1000	100	30	100
F4	100	600	400	200	30	100
F5	100	600	1000	100	30	100
F6	100	600	1000	200	30	100
F7	100	1200	400	200	30	100
F8	100	600	400	100	30	100

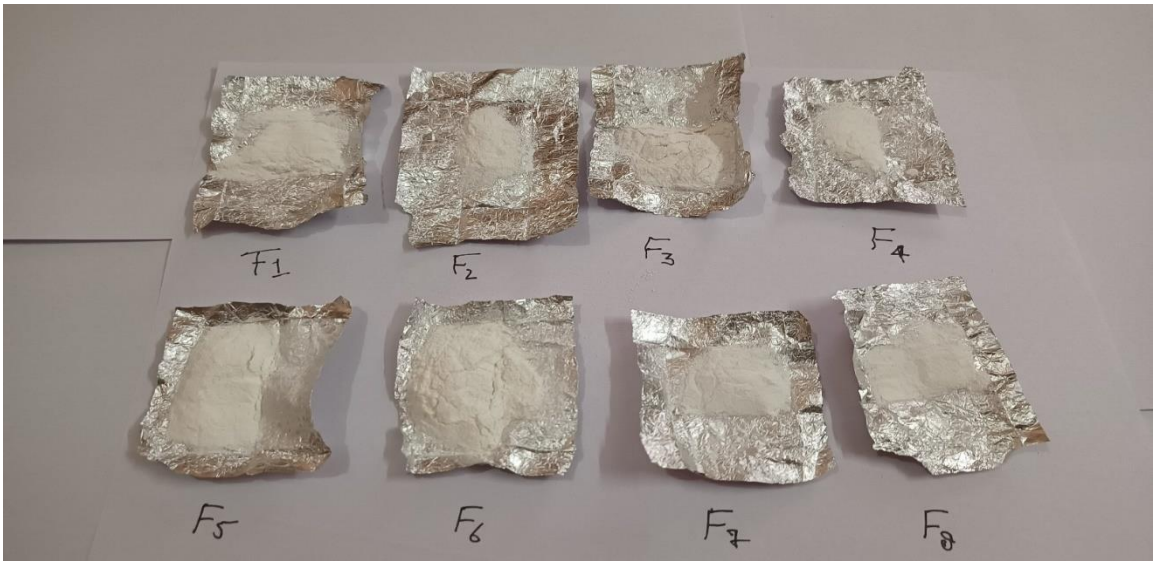


Fig.2 : Schematic Representation of Preparation of Nanosponge

5. Discussion And Result

5.1 Physical Characterization of Model Drug

Description	Crystalline white odorless powder with bitter taste
Bulk Density	0.56 gm / ml
Tapped Density	0.63 gm/ml
Carr's Index	11.11 % (good)
Hausner Ratio	1.12 (good)

Simvastatin drug also known as HMG Co-reductase inhibitor was odorless and are class of lipid lowering medications. A good flow property is indicated by a Hausner Ratio and Carr's index value.

5.2 Compatibility studies of drug with excipients

Visual inspection was used to assess the compatibility between the drug and excipients, and this was later verified using FT-IR. The study was processed according to the procedure given in **4.1.2.** The design like compatibility station and ratio of the study was done as per table. The peak position in the FT-IR spectra of the pure substance was determined.

5.3 Study of λ max and calibration curve of simvastatin

5.3.1 Preparation of the Standard Stock Solution:

A Simvastatin standard stock solution was prepared by dissolving 10mg of Simvastatin in 10ml of 0.1N NaOH, producing a solution with a concentration of 1000µg/ml. To make a solution with a concentration of 100µg/ml, 1ml of the stock solution was taken and mixed with 9ml of 0.1N NaOH (solvent), and thoroughly mixed.

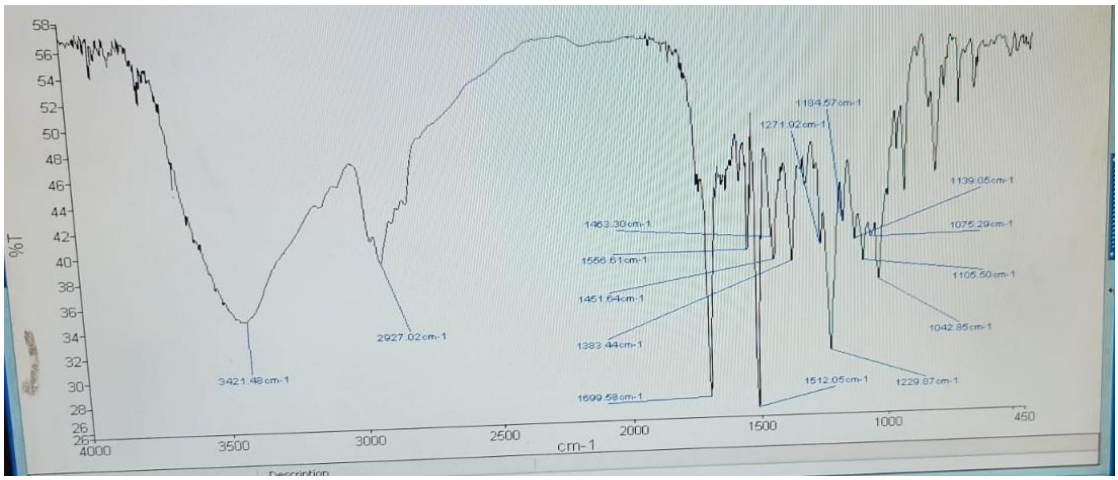


Fig 3: FTIR graph of Simvastin

Fig4 : Simvastatin Peak Detection at 239 nm

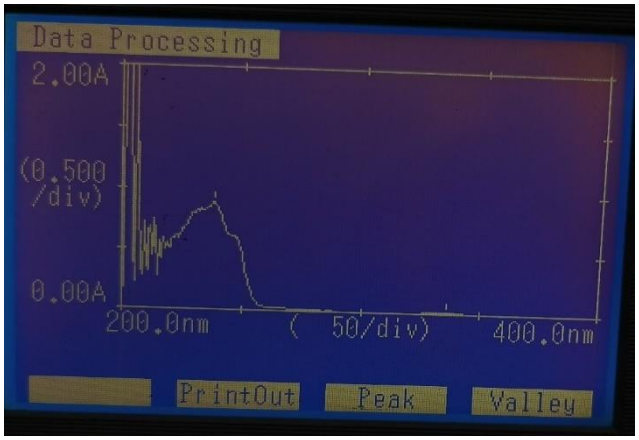
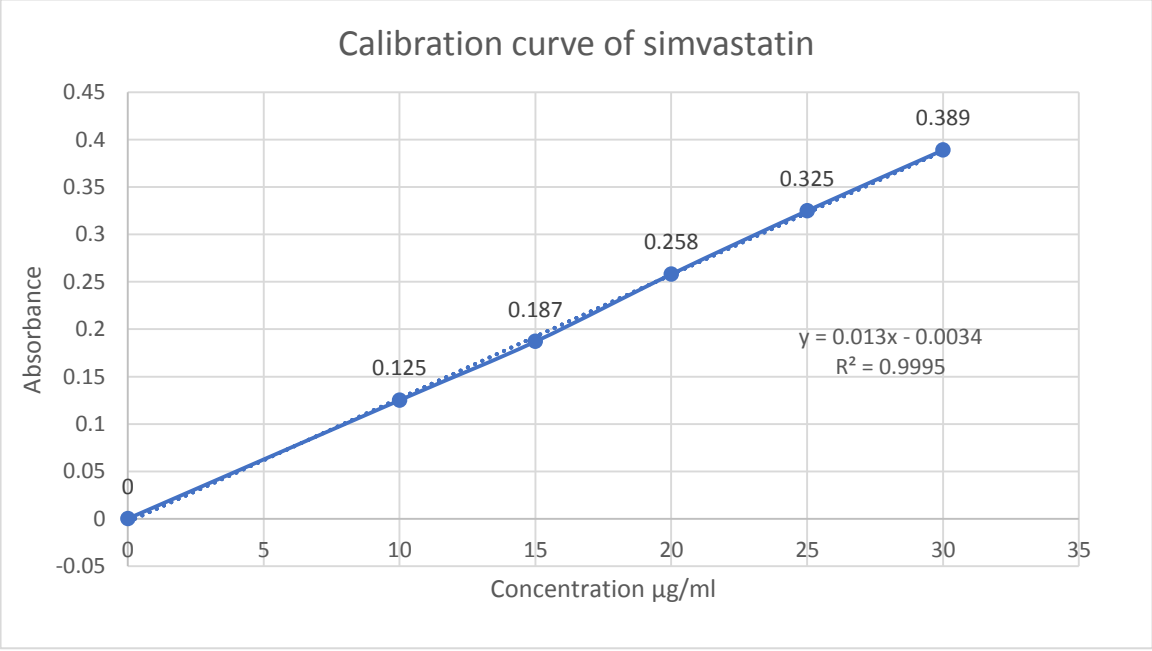


Fig 5: UV Spectrum of Simvastatin at 239 nm

5.3.2 Preparation of Calibration Curve: 1.0 mL, 1.5 mL, 2.0 mL, 2.5 mL, and 3.0 mL of the Simvastatin stock solution were separately transferred into a series of 10 mL volumetric flasks. Each flask was then filled up to the mark with 0.1 N NaOH, resulting in 10 g/mL, 15 g/mL, 20 g/mL, 25 g/mL, and 30 g/mL solutions, respectively. The absorbance of these solutions was measured at 239 nm. After that, a calibration curve was created and confirmed to be linear in the concentration range of 10-30 g/mL.



5.4 Characterization of Nanosponges

Table 3: Characterization of Simvastatin Loaded Nanosponges

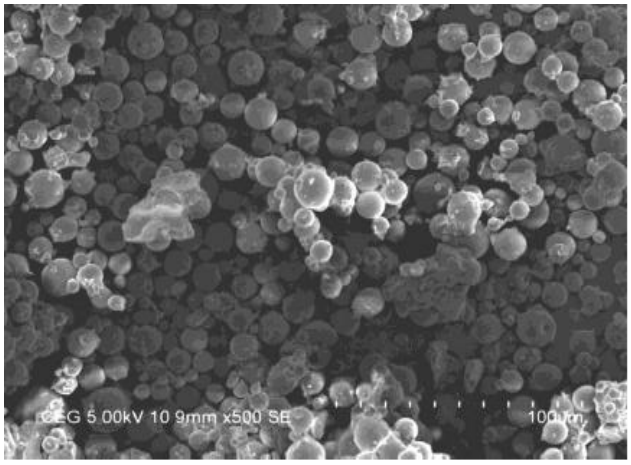
Formulation	Particle Size (nm)	Polydispersity index	Entrapment Effeciency
f1	414.9	0.22	73.69%
f2	476	6.592	72.03%
f3	496	0.275	64.51%
f4	795.6	7.473	42.51%
f5	234	0.14	90.08%
f6	273	0.353	86.52%
f7	622.8	0.275	45.76%
f8	572.6	0.326	44.64%

5.4.1 Drug Content: The drug content of the simvastatin loaded nanosponges ranged from 42.51 to 90.08.

The Highest Drug Content was observed 90.08 & 86.52 for the formulation F5 &F6 respectively.

5.4.2 Entrapment Efficiency: The Simvastatin Loaded Nanosponges showed an entrapment efficiency ranging from 42.51% to 90.08%. The Highest Entrapment Efficiency was observed 90.08 & 86.52% for the formulation F5 & F6respectively.

5.4.3 Surface Morphology: The surface characteristics of the Nanosponges were examined through the use of Scanning Electron Microscopy (SEM).



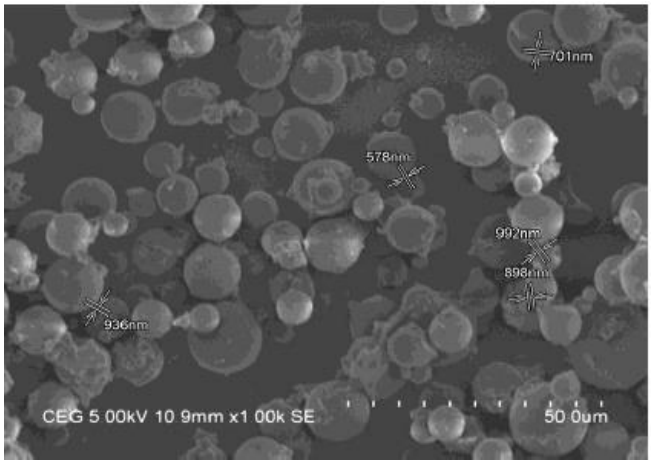


Fig. 6 and 7: SEM image of Optimized Formulation (F5) and (F6) Particle Size

Distribution:

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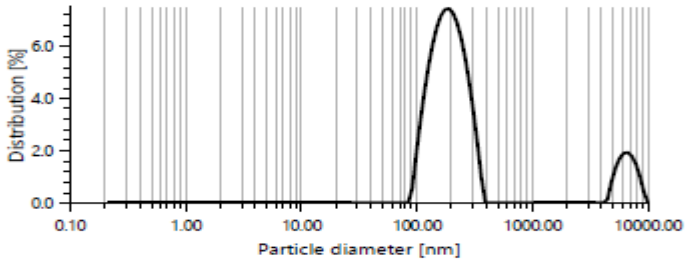
Measurement information

Measurement name	Shubham Pal	User	admin
Method	-	Time	4/26/2022 4:23:24 PM
Status	Succeeded	Instrument type	Litesizer 100
Measurement mode	Particle size	Filter opical density	2.029 (Automatic)
Measurement cell	Disposable	Focus position	0.0 mm (Automatic)
Measurement angle	Back scatter (Manual)	Material	Unknown material
Target temperature	77.00 °F	Material refractive index	-
Equilibration time	0h 01m 00s	Material absorbance coefficient	-
Analysis model	General	Solvent	Water
Cumulant model	Advanced	Solvent refractive index	1.3303
Processed runs	6 (Automatic)	Solvent viscosity	0.0008903 Pa.s
Time for each run	0h 00m 10s (Automatic)		

Particle size distribution (intensity)



Results

Hydrodynamic diameter	234.0 nm	Mean intensity	309.5 kcounts/s
Polydispersity index	14.0 %	Absolute intensity	33059.0 kcounts/s
Diffusion coefficient	2.1 $\mu m^2/s$	Intercept $g1^2$	0.7067
Transmittance	83.3 %	Baseline	1.045

Particle size distribution peaks (intensity)

Peak name	Size [nm]	Area [%]	Standard deviation [nm]
Peak 1	193.41	87.53	61.99
Peak 2	6612	12.47	1176.5
Peak 3	-	-	-

Fig. 7: Size Distribution of optimized formulation F5

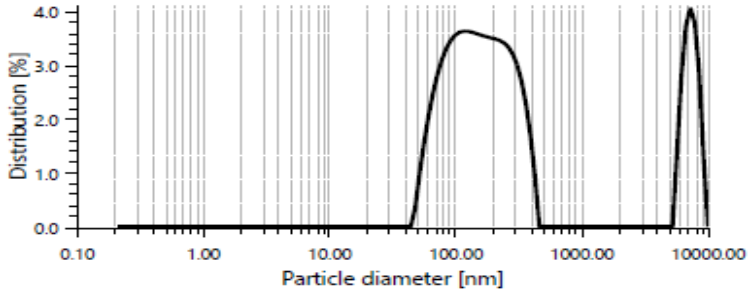
The mean particle size of simvastatin loaded Nanosponges formulation 5 is 234nm and the polydispersity index was observed 14%.

Noida Institute of Engineering & Technology

Measurement information

Measurement name	Shubham Pal	**User**	admin
Method	-	**Time**	4/26/2022 3:23:03 PM
Status	Succeeded	**Instrument type**	Litesizer 100
Measurement mode	Particle size		
		Filter opical density	2.188 (Automatic)
Measurement cell	Disposable	**Focus position**	0.0 mm (Automatic)
Measurement angle	Back scatter (Manual)	**Material**	Unknown material
Target temperature	77.00 °F	**Material refractive index**	-
Equilibration time	0h 01m 00s	**Material absorbance coefficient**	-
Analysis model	General	**Solvent**	Water
Cumulant model	Advanced	**Solvent refractive index**	1.3303
Processed runs	6 (Automatic)	**Solvent viscosity**	0.0008903 Pa.s
Time for each run	0h 00m 10s (Automatic)		

Particle size distribution (intensity)



Results

Hydrodynamic diameter	273.8 nm	**Mean intensity**	261.5 kcounts/s
Polydispersity index	35.3 %	**Absolute intensity**	40342.5 kcounts/s
Diffusion coefficient	1.8 µm²/s	**Intercept g1²**	0.2641
Transmittance	79.7 %	**Baseline**	1.097

Particle size distribution peaks (intensity)

Peak name	Size [nm]	Area [%]	Standard deviation [nm]
Peak 1	7286	19.97	968.1
Peak 2	172.21	80.03	67.68
Peak 3	-	-	-

Fig8: Size Distribution of optimized formulation F6

The mean size of the simvastatin loaded Nanosponges Formulation 6 is 273.8nm and the polydispersity index was observed 35.3%

6. EVALUATION OF POST COMPRESSION PARAMETERS OF TABLETS (F5): -

This comprised an evaluation of the tablet's weight variation, thickness, friability, and hardness parameters, which are collectively known as IPQC (In Process Quality Control) parameters.

6.1 Description of tablets:

Tablets were7.00mm, round, biconvex, plain on both sides and white in Colour.

Tablets were evaluated for their weight variation, thickness, friability, and hardness as per procedure. And were tabulated below in table.

Table 5: Weight Variation of Tablet

Tablet	Weight of tablet(mg)	Deviation %
1	213.3	1.2
2	220.1	2.03
3	209.7	2.8
4	217.5	0.83
5	210.98	2.2
6	220	2.8
7	218.7	1.3
8	210.5	2.4
9	205.4	4.7
10	217	0.6
11	219.4	1.7
12	218	1.06
13	217	0.6
14	214.9	0.37
15	217.4	0.78
16	219.4	1.71
17	210.4	2.4
18	220	1.9
19	218.9	1.4
20	217.4	1.2

Average weight of 20 tablet: total weight of 20 tablet / 20

= 4315.98 / 20

= 215.799 mg

Table 6: Physical characterization of simvastatin loaded nanosponges Tablets

Tablet	Thickness(mm)	Hardness(N)	Diameter(mm)
1	3.01	205	7.9
2	3.09	217.1	6.7
3	3.56	201	8.14
4	3.92	216.4	7.19
5	3.65	214.8	6.9
6	3.9	220	5.98

7	3.45	215.7	7.47
8	3.78	214	8.45
9	3.2	218.9	7.9
10	3.29	217.5	7.25
total	34.85	2140.4	73.88

6.2 Thickness: Average thickness of the 10 tablets was found to be 3.485mm.

6.3 Hardness: Average thickness of the 10 tablets was found to be 214.04N.

6.4 Friability: The percentage loss of tablet weigh calculated by following formula:

Friability (%) = $Friability\ (\%) = \frac{(W1-W2)}{W1} \times 100$

Initial weight = 4.675g

Final Weight = 4.634g

Weight difference = 4.675 g–4.634 g= 0.041 g

Percentage loss of weight = $\frac{0.041\ g}{4.675\ g} \times 100\ \%\ = 0.88\ \%$

6.5 In Vitro Release Study: Simvastatin Nanosponges loaded tablet was analyzed for drug release in dissolution apparatus in dissolution media mentioned in 4.4. Dissolution parameter was kept as given in **Table in 4.3**

Table 7: In-vitro analysis table of F5.

Time	Absorbance	Concentration	Dilution factor	mg	5ml	900ml	Cumulative drug release	Cumulative drug release%
0.5	0.145	2.051643192	20.51643	0.002052	0.010258	1.846479	1.846479	6.15493
1	0.158	2.661971831	26.61972	0.002662	0.01331	2.395775	2.406033	8.02011
2	0.195	4.399061033	43.99061	0.004399	0.021995	3.959155	3.972465	13.24155
3	0.278	8.295774648	82.95775	0.008296	0.041479	7.466197	7.488192	24.96064
4	0.193	4.305164319	43.05164	0.004305	0.021526	3.874648	11.36284	37.87613
5	0.415	14.72769953	147.277	0.014728	0.073638	13.25493	13.27646	44.25485
6	0.479	17.73239437	177.3239	0.017732	0.088662	15.95915	16.03279	53.44264
7	0.588	22.84976526	228.4977	0.02285	0.114249	20.56479	20.65345	68.84484
8	0.645	25.5258216	255.2582	0.025526	0.127629	22.97324	23.08749	76.95829
9	0.714	28.76525822	287.6526	0.028765	0.143826	25.88873	26.01636	86.72121

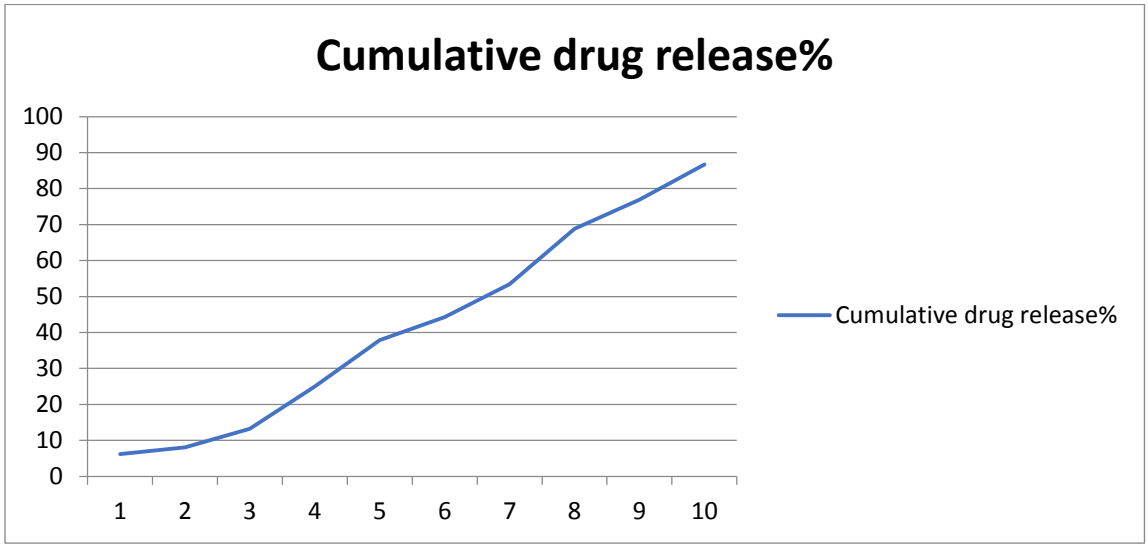


Figure: In-vitro analysis graph of F5

7. CONCLUSION

The objective of this research was to develop nanosponges of Simvastatin, a drug with low solubility and short half-life, to achieve controlled release, improve solubility, reduce adverse effects that depend on dosage, and increase patient adherence. Simvastatin was selected as a model drug for the nanosponge delivery system due to its ability to release the drug over an extended period while being regulated. The invention of hypolipidemic medication tablets including nanosponges, as well as their optimization using 23 factorial designs and coating, are the subjects of the current work.

The study evaluated the physical compatibility of Simvastatin with various excipients, and the results indicated that there was no physical incompatibility between the drug and the excipients. Chemical compatibility tests were also performed using an FTIR Spectrometer, which confirmed that there was no chemical interaction between the excipients and Simvastatin.

When a calibration curve for lovastatin was plotted, it was discovered that the solutions adhered to Beer's and Lambert's laws and were linear (0.999). The researchers utilized the emulsion solvent evaporation technique to synthesize the Simvastatin nanosponges. In varying quantities, ethanol, polyvinyl alcohol, and pluronic F68 were used. All of the formulations' entrapment efficiencies were found to range from 42.51 to 90.08%. The findings indicate that the concentration of polymers has increased. increased the effectiveness of drug entrapment, but after a certain concentration, as polymer concentration rose, entrapment effectiveness fell. In comparison to other formulations, F5 (90.048%) and F6 (86.52%) were found to have superior entrapment efficiency. The formulations F5 and F6 were selected as the most favorable options because of their higher entrapment efficiency and prolonged drug release duration in the in vitro experiments.

Surface morphology and particle size studies of the improved formulations F3 and F8 were performed. SEM images of improved formulations showed their shape and surface morphology. The study indicated that the Nanosponges possessed a uniform, sponge-like, and round shape, with numerous pores on their surface. The solvent's diffusion may be the cause of the pores.

The Mal. particle size analyzer was used to evaluate the polydispersity and particle size distribution of the nanosponge formulations. The results showed that the average particle size of F5 and F6 was in the nanometer range, measuring 234.0 nm and 273.8 nm, respectively. It was discovered that the polydispersity of formulations F5 and F6 was 14% and 35.3%, respectively. This indicates that the formulations' particle sizes are uniform.

The optimized formulation F5's invitro release graph explains how the produced Nanosponges released in a regulated manner over the course of nine hours. The aforementioned findings aim to imply that the Nanosponge method could be a potential replacement for the usual oral formulation for highly lipophilic medications like Lovastatin in order to increase their bioavailability.

8. Acknowledgement

The authors would like to thank the Noida Institute of Engineering and Technology (Pharmacy Institute) in Greater Noida, Uttar Pradesh, India, for their excellent assistance and providing of the required facilities to conduct the survey for this study.

9. FUNDING

None

10. AUTHORS CONTRIBUTIONS

All authors have made equal contributions to this work.

11. CONFLICTS OF INTERESTS

The authors have disclosed no conflicts of interest in relation to this work.

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