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Research Article

ORAL NANOSUSPENSION OF SIMVASTATIN BY ANTI-SOLVENT PRECIPITATION ULTRASONICATION METHOD

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ABSTRACT:

The objective of this study is to produce an oral nanosuspension of simvastatin utilising the anti-solvent precipitation-ultrasonication method with different stabilisers and surfactants, including polyvinyl alcohol. Multiple formulation and process factors were optimised to get the desired size and saturation solubility. The characterisation of the produced nanosuspension was conducted concerning particle size, zeta potential, saturation solubility, dissolving rate, morphological analysis (SEM), and in vitro dissolution research. The zeta potential value for the optimised formulation (F12) was determined to be -9.7 mV, which is within the permitted limits. The average particle size of the optimised formulation's nano suspension (F12) was determined to be 66.0 nm. In vitro experiments indicate that formulation F12 exhibits the highest drug release at 99.15% within 45 minutes, while all other formulations failed to release the medication. The drug release from the nanosuspension was elucidated utilising mathematical model equations, including zero-order, first-order, and equation approaches. The regression data indicate that the optimised formulation F12 adheres to first-order kinetics.

Keywords: Simvastatin, Poly vinyl alcohol, SLS, FTIR, SEM.

INTRODUCTION

Simvastatin, a widely used lipid-lowering agent, belongs to the class of statins that function by inhibiting HMG-CoA reductase, a key enzyme in the cholesterol biosynthesis pathway. It is particularly effective in reducing low-density lipoprotein (LDL) cholesterol and is prescribed to manage hypercholesterolemia and prevent cardiovascular diseases. However, like many lipophilic drugs, simvastatin suffers from poor water solubility, which limits its bioavailability and therapeutic efficacy when administered orally.

To overcome these limitations, nanosuspension technology has emerged as a promising approach to enhance the dissolution rate and bioavailability of poorly water-soluble drugs like simvastatin. Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants or polymers. The reduction in particle size to the nanometer range significantly increases the surface area available for dissolution, thus improving drug solubility and absorption.

Simvastatin nanosuspensions have been developed and studied to enhance its pharmacokinetic profile, enabling faster and more complete absorption from the gastrointestinal tract. Various preparation techniques, including high-pressure homogenization, nanoprecipitation, and media milling, have been employed to produce stable nanosuspensions with desired particle size distribution. These nanosystems also offer benefits such as increased stability, controlled release, and the potential for targeted delivery.

Preclinical studies have demonstrated that simvastatin in nanosuspension form significantly improves bioavailability compared to conventional formulations, leading to enhanced therapeutic outcomes. Additionally, nanosuspensions offer flexibility in drug delivery, making it possible to administer simvastatin via different routes, including oral, intravenous, and topical applications, thereby expanding its clinical utility.

Overall, simvastatin nanosuspension represents a significant advancement in the delivery of hydrophobic drugs, providing a platform to maximize therapeutic efficacy while minimizing dosing frequency and side effects.[1-10]

Simvastatin also known as the brand name Zocor, is a lipid lowering drug derived synthetically from a fermentation product of *Aspergillus terreus.* It belongs to the statin class of medication, which used to lower the risk of CVS and manage abnormal lipid levels by inhibiting the endogenous production of Cholesterol in the liver.

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The main objective of the present work is to develop oral Nanosuspension of Simvastatin by Anti-solvent precipitation- ultrasonication Method using various Stabilizers & Surfactants such as Poly vinyl alcohol.

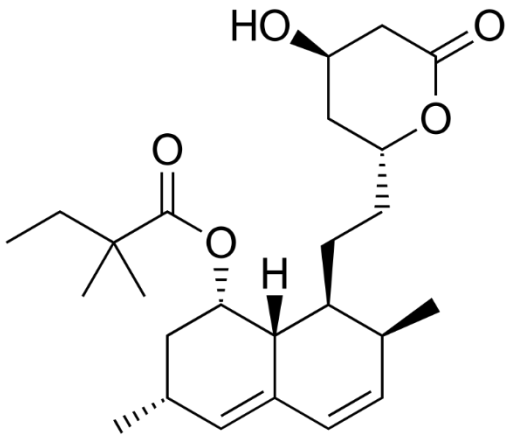

Figure 1. Structure of Simvastatin

MATERIALS AND REAGENTS

Simvastatin gift sample was obtained from Spectrum Pharma Research Solutions. Sodium Lauryl Sulphate, Poloxamer, PVA, Ethanol were supplied by BMR chemicals, Hyderabad.

INSTRUMENTATION

Dissolution test apparatus, UV- Visible spectrophotometer, Particle size analyzer, Hot air oven, Digital balance

Solubility studies:[11-18]

The solubility of Simvastatin was assessed in several solvents, including 0.1N HCl, pH 6.8 buffer, pH 7.4 buffer, ethanol, and methanol. Saturated solutions were prepared by incorporating an excess of the medication into the vehicles and agitating on a shaker for 48 hours at 25°C with continuous vibration. Filtered samples (1 ml) were analysed spectrophotometrically at 238 nm.

Determination of Calibration Curve

To make a 1 mg/ml stock solution of Simvastatin, 100 mg of the medication was dissolved in a tiny amount of methanol and then diluted with 100 ml of phosphate buffer (pH 7.4). In order to get solutions ranging from 2-12 µg/ml, the stock solution was progressively diluted, and the maximum concentration (λmax) of the solution was determined. A UV-Visible spectrophotometer was used to test the absorbances of the various diluted solutions at 238 nm. By plotting solution concentration on the X-axis and absorbance on the Y-axis, and then calculating the correlation coefficient 'r,' a calibration curve was created.

Anti-solvent precipitation- ultrasonication Method.[19-27]

Simvastatin was entirely dissolved in ethanol to create the organic phase, which was subsequently filtered via a 0.45 µm membrane. Filtered to eliminate the precipitated contaminants. The anti-solvent phase was generated independently by dispersing the stabiliser Poly-Vinyl Alcohol (PVA) in distilled water. At a constant temperature, 2 ml of organic solution was administered dropwise via a syringe into 20 ml of anti-solvent using a mechanical stirrer (Remi 125, 51 D Mumbai). At 3600 revolutions per minute for one hour. The generated nanosuspension samples were subjected to ultrasonication using a Probe Sonicator, maintained in a cold bath, and sonicated at 70% amplitude with a 2-second pulse rate for 15 minutes. The operation was done with varying sonication durations to optimise the approach.

Table.1 Formulation of Simvastatin Nanosuspensions

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Simvastatin	10	10	10	10	10	10	10	10	10	10	10	10
Poloxamer 188	10	20	30	--	--	--	10	20	30	--	--	--
PVA	--	--	--	10	20	30	--	--	--	10	20	30
SLS	5	5	5	5	5	5	10	10	10	10	10	10
Methanol (ml)	3	3	3	3	3	3	3	3	3	3	3	3
Water (ml)	40	40	40	40	40	40	40	40	40	40	40	40

Evaluation parameters of Nanosuspension Simvastatin:

The Nanosuspension was evaluated for various parameters: -

1. **Entrapment efficiency**
2. **Particles size analysis**
3. **Zeta potential**
4. **In-vitro drug release studies**
5. **Scanning electron microscopy**

RESULTS AND DISCUSSIONS

Solubility data:

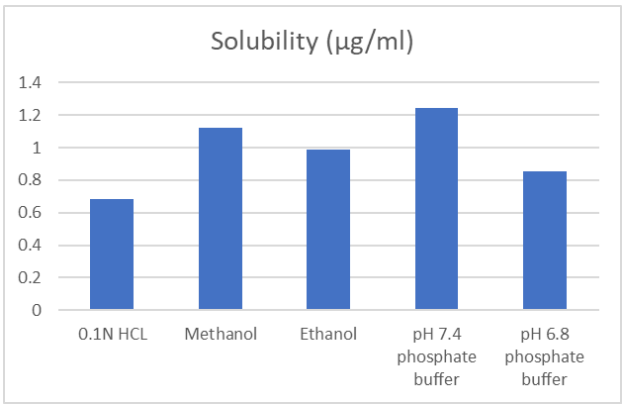

Figure.2 Solubility studies

Discussion: From the above conducted solubility studies in various buffers we can say that pH 7.4 Phosphate Buffer has more solubility when compared to other buffer solutions. So pH 7.4 Phosphate Buffer was used as dissolution medium.

Determination of absorption maximum (λ max):

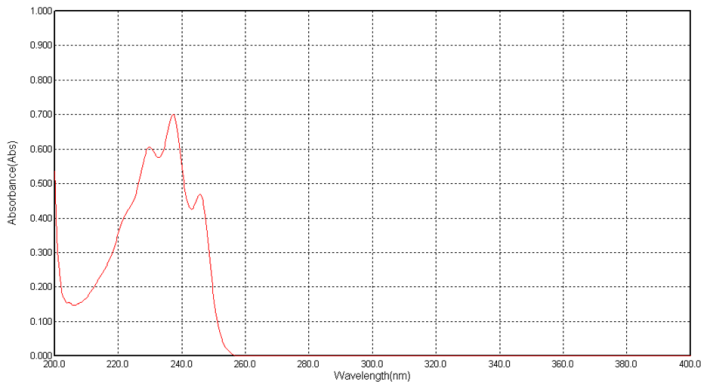

Figure.3 UV Spectrum of Simvastatin

Discussion: The wave length of the simvastatin was found to be 238 nm.

Calibration curve of Simvastatin

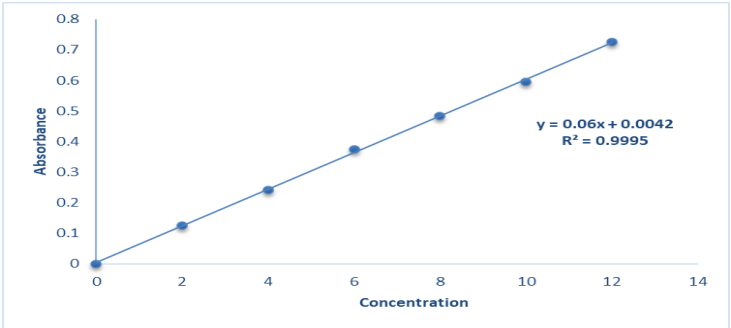

Figure.4 Standard calibration curve of Simvastatin in 7.4 pH Buffer

Discussion: The linearity was found to be in the range of 2-12 µg/ml in acetone, 7.4 pH Buffer. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

Entrapment efficiency of formulated Nanosuspensions

Table.2 %entrapment efficiency

Formulation code	Mean % entrapment efficiency
F1	96.12
F2	95.26
F3	93.65
F4	97.85
F5	95.29
F6	91.89
F7	92.64
F8	90.15
F9	93.69
F10	94.78
F11	96.26
F12	89.84

Discussion: The % entrapment efficacy of formulation F1-F12 was found to be 89.84%- 97.85%.

Zeta Potential: The measurement involves particle electrophoresis, where particle velocity is ascertained by the Doppler shift of laser light dispersed by the moving particles. The applied field strength was 20 V/cm. The electrophoretic mobility was transformed into the zeta potential in millivolts via the Helmholtz-Smoluchowski equation. Under typical measurement circumstances (25 °C, water), this equation may be reduced to the product of the recorded electrophoretic mobility (μm/cm per V/cm) and a factor of 12.8, resulting in the Zeta potential in mV.

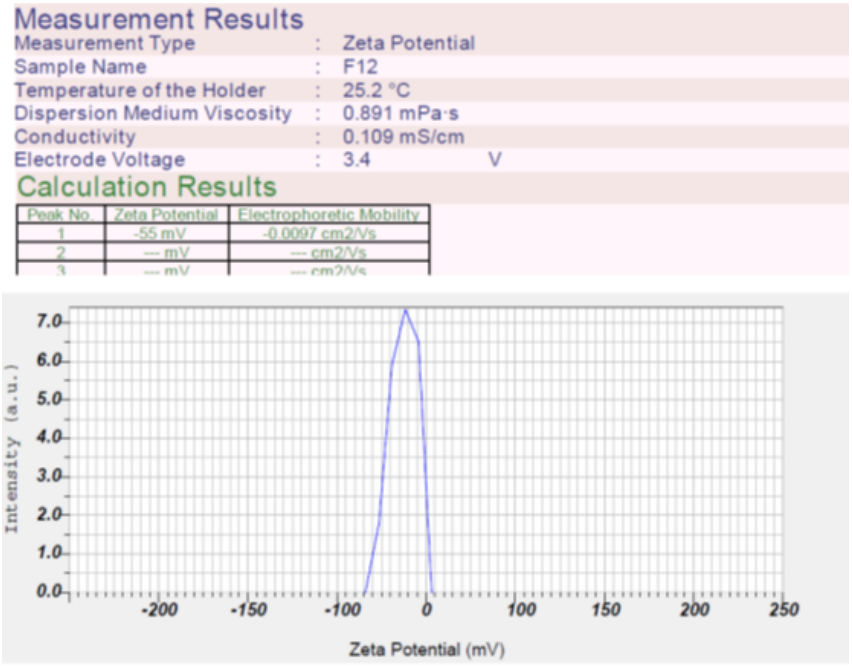

Figure.5 Zeta potential of simvastatin

Discussion: Zeta potential value for the optimized formulation (F12) was found to be within the acceptable limits.

Scanning Electron Microscopy:

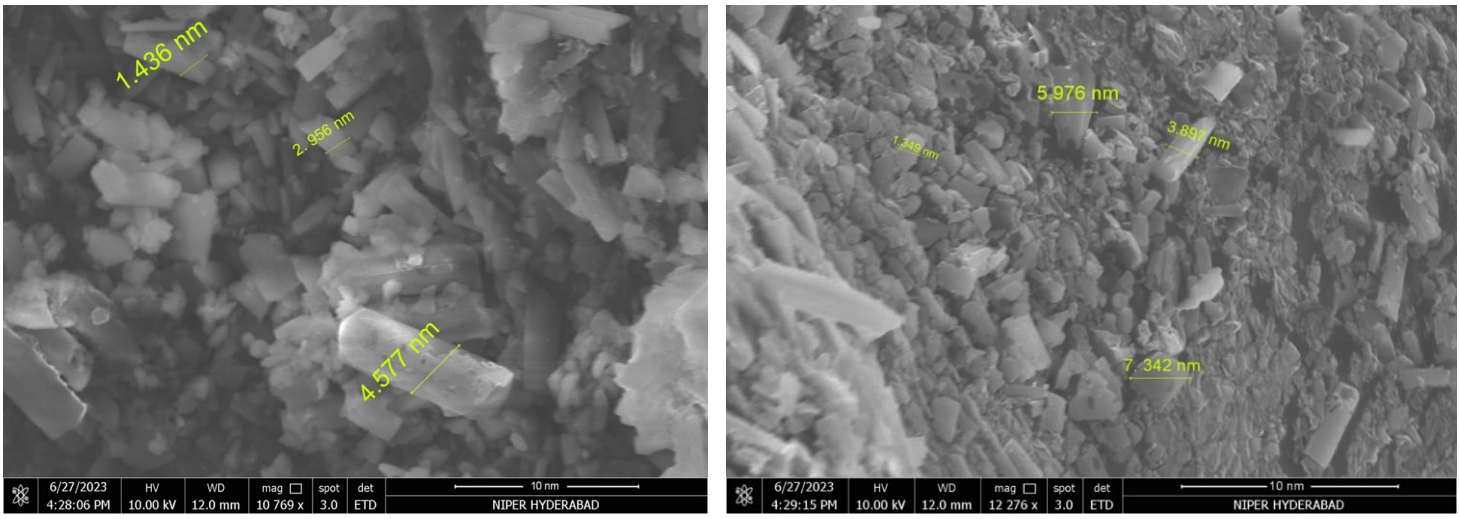

Figure.6 SEM images

Discussions: The size of the particles were reduces upto 10nm.

Dissolution Results:

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	28.74	39.41	46.12	29.47	42.25	54.16	44.18	56.36	63.23	56.16	58.63	**64.34**
10	44.25	52.19	57.45	48.58	56.85	63.24	59.34	68.21	72.23	69.25	73.15	**82.15**
15	59.65	65.16	62.26	56.84	69.85	75.25	72.24	75.53	81.32	81.24	82.36	**89.63**
30	65.89	76.41	76.74	68.57	75.15	83.42	83.28	83.12	88.36	89.29	90.24	**96.24**
45	76.27	85.26	84.28	79.49	85.42	89.36	89.12	92.24	93.21	93.34	95.12	**99.15**
60	89.84	93.94	95.36	91.25	93.48	96.58	94.27	96.98	98.24	98.86	99.48	

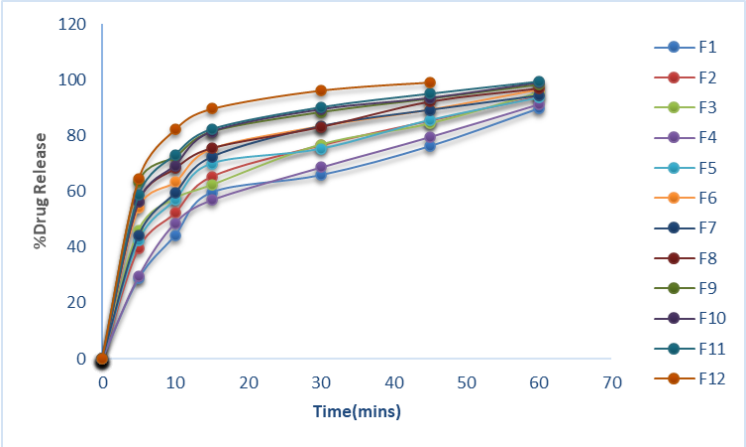

Figure.7 % Drug Release of formulation F1-F12

Discussion: From the above In vitro studies we can say that increase in the surfactant concentration decrease in the dissolution time of all the formulations. So F12 is considered as optimized formulation as it shows drug release with in 45mins.

Dissolution parameters for the formulations F1-F12

Zero order release profile of formulation F12

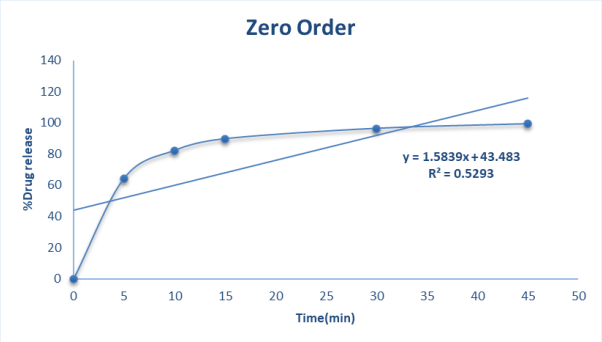

Figure.8 Zero order

First order release profile of formulation F12

Figure.9 First Order

Discussion:

The drug release from the Nanosuspension was explained by using mathematical model equations such as zero order, first order. Based on the regression values it was concluded that the optimized formulation F12 follows First order kinetics.

CONCLUSION

Drug-containing nanosuspension was created via anti-solvent evaporation utilising Soluplus, Poloxamer 188, SLS, PVA, tween 80, and enough water. At 237 nm, Simvastatin was estimated spectrophotometrically. We assessed the Nanosuspension for drug content homogeneity, scanning electron microscopy, particle size measurement, zeta potential, in-vitro release, and drug excipient interactions. Statistics were used to stability data. Capillary technique revealed Simvastatin's melting point at 135-138°C. Solubility was measured at 250C using 0.1N HCL, 6.8 phosphate buffer, 7.4 pH buffer, and tween 80. FT-IR drug excipient compatibility investigations show no interactions between the pure drug (Simvastatin) and optimised Formulation (Simvastatin + excipients), indicating no physical changes. Formulation F12 entrapped 89.84%. Zeta potential for optimised Formulation (F12) was -9.7 mv, which was satisfactory. Optimised Formulations (F12) nanosuspension averaged 179.5 nm. According to invitro investigations, Formulation F12 releases 99.15% of the medication within 45 minutes, while the others do not. Use of zero-order, first-order, and equation approaches described drug release from Nanosuspension. The regression data showed zero-order kinetics for optimised Formulation F12.

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