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Development and characterization of simvastatin loaded Chitosan nanoparticles for sustained drug delivery

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A B S T R A C T
The present study focuses on the development, optimization, and in-vitro evaluation of Simvastatin-loaded Chitosan nanoparticles for sustained release. FTIR and DSC studies confirmed the compatibility of Simvastatin and Chitosan. Nanoparticles were formulated using the nanoprecipitation method, with various concentrations of Chitosan, achieving maximum drug loading in formulation F3. Scanning Electron Microscopy (SEM) revealed that the nanoparticles were spherical with smooth surfaces, and their sizes ranged from 360 nm to 480 nm. The optimized formulation exhibited a 95.66% drug release over 12 hours, following zero-order kinetics, with diffusion and non-Fickian mechanisms governing the release. Stability studies, conducted per ICH guidelines, demonstrated the nanoparticles' stability without significant changes in physical characteristics, drug content, or dissolution profiles. Overall, formulation F3, with a 1:3 drug-to-polymer ratio, was identified as optimal for sustained drug release.

Keywords: Simvastatin, Chitosan, Scanning Electron Microscopy, Chitosan nanoparticles

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Simvastatin (SV) is a cholesterol-lowering agent that's derived synthetically from a fermentation product of Aspergillus terreus and widely accustomed treat hypercholesterolemia.[1] When given orally, SV (a lactone) is quickly hydrolyzed in vivo to the corresponding β, δ-dihydroxy acid form, a potent competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step within the biosynthesis of cholesterol.[2] However, it's a short half-life and is practically insoluble in water.

It is also generally considered that compounds with poor water solubility will show dissolution rate-limited absorption in vivo and hence poor absorption, distribution, and site-specific delivery.[3,4] Conventional drug delivery system has been characterized by immediate release and repeated dosing of the drug which could result in the danger of dose fluctuation.[5] the main objectives of designing nanoparticles as a drug delivery system are very important particle size, surface properties and to deliver pharmacologically active agents at right place, at the rational rate and dose.[6,7] Therefore it's important to introduce effective methods to boost the solubility and dissolution rate of drug, substantially resulting in its improved oral bioavailability. Sustained release formulation, nanoparticles, are reported to resolve these problems because of the alteration of its tissue distribution,

improving the drug efficacy, reducing the drug toxicity, and prolonging the half-lives in blood.[8,9] Chitosan (CS) may be a natural cationic polysaccharide obtained by the N-deacetylation of chi-tin, a product found within the shells of crustaceans the first amine groups provide special properties and characteristic that make CS very useful in pharmaceutical applications.[10,11] the formed nanoparticles are biocompatible, biodegradable, non-toxic and capable to sustain the release of encapsulated materials more efficiently than either alginate or chitosan alone.[12] This necessitated the development of novel chitosan nanoparticles as novel drug delivery system for Simvastatin order to provide pH dependent, sustained drug release and increase oral bioavailability.

2. Materials and methods

Materials:

Simvastatin was procured as gift sample from Orchid chemicals, Chennai.. Sodium tripolyphosphate was purchased from sigma-Aldrich, Mumbai; Chitosan (high viscosity) was purchased from Central Institute of Fisheries Cochin. All other reagents used were of analytical grade.

Experimental Methods:

Preparation of Chitosan Nanoparticles:

Nanoparticles are prepared by Nano precipitation -solvent deposition method using chitosan as a coating material and Simvastatin as a core material. Drug and polymer in different ratios were weighed and dissolved in suitable organic solvents, Acetone & 1.5% Acetic acid respectively. Both solutions were mixed and added drop wise into water, mixed at 3000 rpm for 2 hrs forming a milky colloidal suspension and homogenised at 25000 rpm. The resultant nanoparticle suspension was recovered by centrifugation (REMI cooling centrifuge) at 12000 rpm for 30 min and lyophilized.

Characterization:

Percentage yield[13]

The nanoparticle yield was calculated according to the equation given below.

$$\text{Process Yield (\%)} = \frac{\text{Mass of nanoparticles}}{\text{Total mass of drug + polymer}} \text{X } 100$$

In-vitro drug release characteristics[14]

The in-vitro drug diffusion from the formulation was studied using cellophane membrane. Phosphate buffer pH 6.8 was used as a dissolution medium solution. Cellophane membrane was previously soaked in the mixture of glycerol & water (1:4 ratio) for 20minutes and the cellophane membrane was tied to one end of a specially designed glass cylinder (open at both ends). 10 ml of formulation was accurately placed into this assembly. The cylinder was suspended in 200 ml of dissolution medium maintained at 37 ± 5ºC. The dissolution medium was stirred at 100 rpm using magnetic stirrer. 10 ml samples were withdrawn at hourly intervals and replaced by an equal volume of receptor medium. The aliquots were analyzed by UV-Vis Spectrophotometer at 238 nm. The cumulative % release of the formulations was calculated.

Pharmacokinetic Studies:

These pharmacokinetic studies are performed based on the following parameters

- Zero order reaction
- First order reaction
- Higuchi kinetics
- Hixson Crowell erosion equation
- Korsmeyer –Peppas equation

Stability studies

Stability of Simvastatin nanoparticles was carried out at room temperature, refrigeration and accelerated condition at 400C/75% RH for a period of 3 months. Then the samples were analyzed spectrophotometrically.

3. Results and Discussion

Pre-formulation Studies:

The optimization of a formulation can be done only after a thorough investigation of its physicochemical properties of the drug and excipient. The drug and the polymer must be compatible for a successful formulation. UV-visible spectroscopy and FTIR spectroscopy gives the possible information about the interaction between the drug and polymer.

Table. 1: Formulation Table

S.No	Formulation	Amount of drug (mg)	Concentration of Chitosan (%)	Acetone (ml)	Acetic acid (ml)	Dis. water (ml)
1.	F1	50	0.1	5	50	60
2.	F2	50	0.2	5	50	60
3.	F3	50	0.3	5	50	60
4.	F4	50	0.4	5	50	60

Table 2: Absorbance of Simvastatin

S.No	Concentration µg/ml	Absorbance
1.	2	0.131
2.	4	0.264
3.	6	0.393
4.	8	0.524
5.	10	0.645

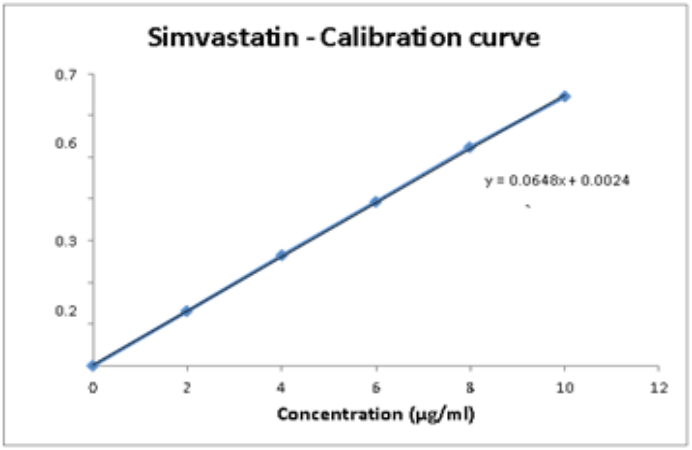
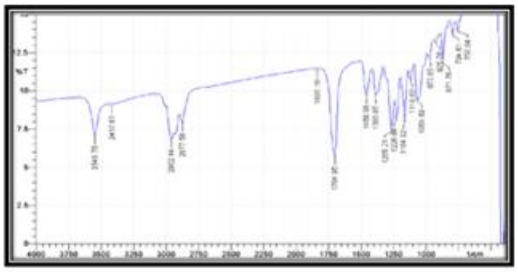


Fig.1: Simvastatin Calibration curve Drug – polymer compatibility studies

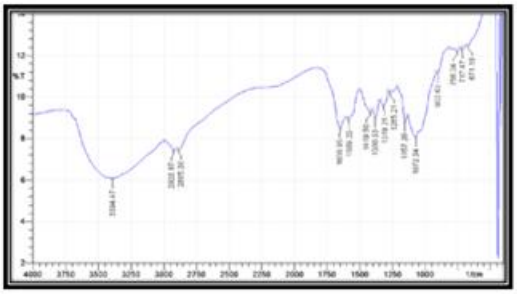
FTIR peaks

S.No	Samples	Wave number(cm⁻¹)
1.	Chitosan	3394, 2923, 2885, 1650, 1589, 1419, 1380, 1319, 1072.
2.	Simvastatin	3548, 3417,2962,2877,1836, 1704, 1458, 1388, 1265, 1064.
3.	Chitosan & Simvastatin	3749, 3548, 3417, 2954,2877,1828,1704, 1458,1388,1265,1064.

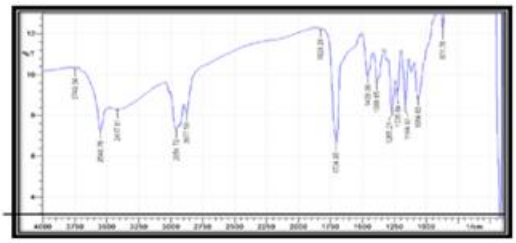
FTIR of Simvastatin



FTIR of Chitosan

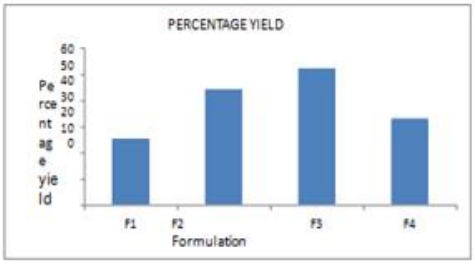


FTIR data of Simvastatin and Chitosan



SIMVASTATIN LOADED CHITOSAN NANOPARTICLES

PERCENTAGE YIELD



CHARACTERISATION

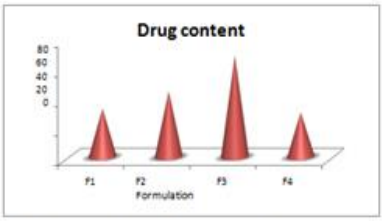
S. No	Formulation	Entrapment efficiency(%)	Percentageyield (%)	Loading efficiency	Drug content
1.	F1	89.15	25.16	16.3	32.68
2.	F2	95.56	44	14.8	44.40
3.	F3	97.43	52	17.07	68.32
4.	F4	93.85	32.9	6.02	30.12

LOADING EFFICIENCY

LOADING EFFICIENCY

Formulation F3 showed highest dug loading capacity due to increasing polymer concentration.

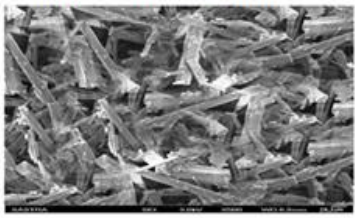
DRUG CONTENT



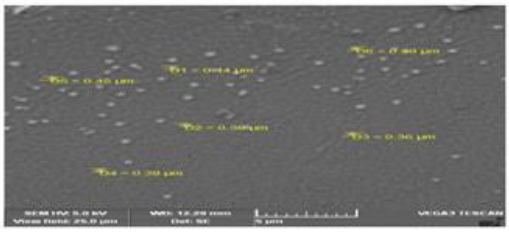
Particle size and Zeta potential

S.No	Batch.code	Polydispersity index	Average size (nm)	Zeta potential (mv)
1	F1	0.324±0.017	200±1.18	+16.3±1.6
2	F2	0.286±0.02	257±2.27	+17.6±1.8
3	F3	0.241±0.016	398±1.13	+19.8±2.2
4	F4	0.232±0.012	360±1.24	+20.5±1.6

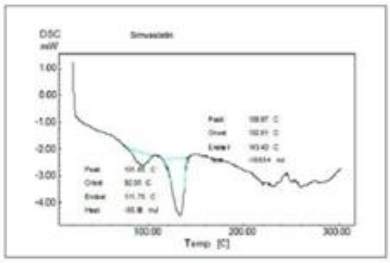
SEM image of pure Simvastatin



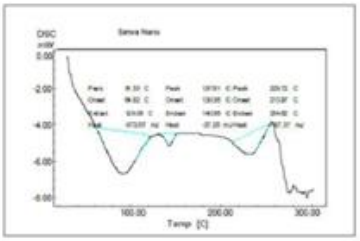
SEM image of Simvastatin nanoparticle- Fig.25: SEM image of Simvastatin Nano



Differential Scanning Colorimetry

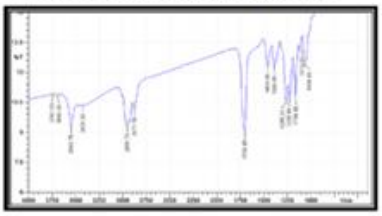


DSC Thermogram of pure drug (Simvastatin)

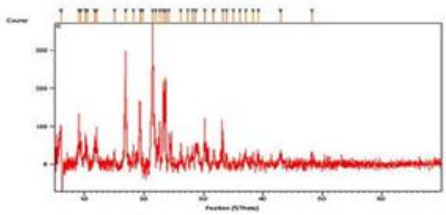


DSC Thermogram of Simvastatin Nanoparticles

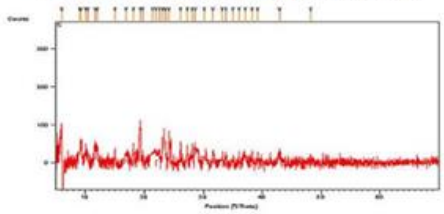
FTIR of Simvastatin nanoparticle



X-RAY DIFFRACTION STUDY



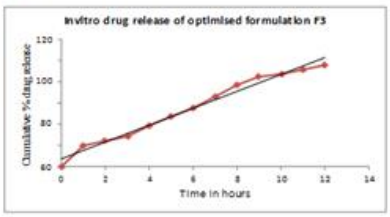
XRD Pattern of Pure Drug (Simvastatin)



In-vitro* drug release of optimised formulation

S.No	Time(hours)	% cumulative drug release
1.	0	0
2.	1	19.71±0.61
3	2	24.28±0.42
4.	3	28.50±0.20
5.	4	38.56±0.81
6.	5	47.27±1.22
7.	6	55.26±1.34
8.	7	65.90±1.82
9.	8	76.94±1.13
10.	9	84.79±1.55
11.	10	87.12±1.51
12.	11	91.34±1.28
13.	12	95.66±0.73

***In-vitro* drug release of the optimised formulation**



4. Conclusion

The present work involves the formulation development, optimization, and in-vitro evaluation of Simvastatin-loaded Chitosan nanoparticles for sustained release. Compatibility studies using FTIR and DSC confirmed that Simvastatin and Chitosan are compatible. The nanoparticles were prepared via the nanoprecipitation method, utilizing various concentrations of Chitosan, with formulation F3 achieving the highest drug loading. SEM analysis revealed that the nanoparticles were spherical with smooth surfaces, and their particle sizes ranged between 360 nm and 480 nm. In-vitro drug release studies demonstrated that the optimized formulation released 95.66% of the drug over 12 hours. The release kinetics indicated a zero-order release, governed by diffusion and non-Fickian mechanisms. Stability studies conducted per ICH guidelines confirmed that the nanoparticles remained stable without significant changes in physical characteristics, drug content, or dissolution properties. Overall, formulation F3, with a 1:3 drug to polymer ratio, was identified as the optimal formulation, effectively providing sustained drug release.

Future Scope:

- Scale up studies of the optimized formulation.
- In vivo – In vitro correlation studies.
- Pharmacokinetic and toxicity study.

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