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Formulation and Evaluation of Simvastatin loaded PLGA nanoparticles by nano-precipitation method.

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ABSTRACT: The objective of this study was to prepare a nanoparticulate formulation of simvastatin (SV) for improving oral bioavailability and sustaining the drug release while investigating the effect of various formulation parameters on characteristics of nanoparticles. Nanoparticles containing SV were prepared by a modified emulsification solvent evaporation technique using a biodegradable polymer, poly (d, l-lactide-coglycolide) (PLGA) as a sustained release carrier. The effect of various formulation parameters such as drug polymer ratios (SV: PLGA, 1:4 to 1:1), organic solvents (methanol/dichloromethane), and surfactants (PVA/polysorbate-80) in a fixed concentration (0.5%, w/v) were studied for particle size, drug loading, and entrapment efficiency. Nanoparticles were characterized by differential scanning calorimetry (DSC) and their shapes were observed by scanning electron microscopy (SEM). An aqueous solubility study indicated that the dissolution rates were remarkably increased for nanoparticles compared with the drug alone. The in vitro drug release study of the nanoparticles showed a biphasic release pattern: one initial burst release of 40.56% in the first 4 h which can be helpful to improve the penetration of drug followed by a second slow-release phase (extended release) consistent with a Higuchi diffusion mechanism.

KEYWORDS: Formulation, Evaluation, Simvastatin

INTRODUCTION

Nanotechnology involves deliberately engineering including advanced technology and particularly related to manipulating particulate matter of the substance into a physical state which is ranging from 1 nm to 100 nm and allowing for the creation of nano-based drug delivery systems with enhanced properties including functionality. This emerging field say nanotechnology, has positioned countries at the forefront of scientific research in recent years. Nanoparticles, the result of this innovative technological manipulation, exhibit special and unique properties due to their molecular modeling or molecular processing or molecular duckling, making the particles highly adaptable and suitable for special applications such as drug delivery systems with improved drug solubility, drug stability and controlled rate of drug release.

PREFORMULATION STUDIES

Calibration Curve of Simvastatin in 6.8 pH Phosphate Buffer Determination of λ max: scanning from 200 - 400 nm. The λmaxof Simvastatin was used for further quantitative analysis.

Calibration curve:

Dilution range: 2-10 µg/ml

Estimated by: UV-Visible spectrophotometer Λmax: 238 nm

Fourier Transformation Infrared Spectroscopy:

Instrument: FT-IR spectroscopy

Software: Spectrum 2000 analysis software Analyzed range: 4000 cm-1 to 400 cm-1 Pellets used: Potassium Bromide Press Pellets

Table 1: Composition for FT-IR Study

S.NO	INGREDIENTS
1.	PLGA
2.	Simvastatin
3.	PLGA and Simvastatin admixture

Preparation of PLGA nanoparticles

Nanoparticles are prepared by Nano precipitation and solvent deposition method using PLGA used as a coating material and

Simvastatin used as a core material. Drug and polymer in different ratios were weighed accurately and slowly dissolved in suitable organic solvents like acetone & 1.5% acetic acid, respectively. Both the solutions were further mixed and added drop wise into distilled water, further mixed with high speed homogenized at a speed of 3000 rpm for about 2 hrs and further observed to form a milky colloidal suspension and finally homogenized at a high speed 25000 rpm for 30 minutes. The final resultant nanoparticle suspension was recovered and recollected by centrifugation process at 12000 rpm for 30 min using lyophilized.

Photon Correlation Spectroscopy (PCS)

The particle size of obtained nanosuspension was expressed by the effective diameter of the particles and the width of size distribution range was characterized by polydispersity index (PDI). The particle size (in nm range), their range and degree of particle size distribution were studied for the best formulation.

Zeta Potential Measurements

Zeta potential (both ± values) measurements are generally performed in order to determine the drug stability in the prepared nanoparticle solution.

Scanning electron microscopic (SEM)

The prepared samples of nano-particles were metalized under an argon atmosphere with a 10- nm gold palladium.

DIFFERENTIAL SCANNING COLORIMETRY (DSC)

The samples of nano-particles were first equilibrated at 20° C for half hour and then gradually heated to 220° C at 10° C/ml in a N2 atmosphere.

FTIR of formulation F3:

The compatibility study of the optimized formulation was further carried out for the best formulation using Perkin Elmer FTIRat wavelength range of 4000 to 400 cm-1 to confirm any possible interaction between the drug (API) and polymer.

X-RAY DIFFRACTION STUDY

First, powder sample of the API was placed in a glass sample holder. Further, Cu-K radiation was generated at 30mA and 40 kV using X-ray diffracter. Finally, samples were scanned between the range of 5° to 50° with a step size of 0.02° and the scan speed was maintained 3° min-1

In-vitro drug release characteristics

Drug: Simvastatin

Membrane: Cellophane membrane

Pre-treatment: Cellophane membrane was previously soaked in the mixture of glycerol & water (1:4 ratio) for 20minutes.

Dissolution media: Phosphate buffer pH 6.8

Volume of media: 200 ml

Temperature: 37 ± 5ºC

Volume withdrawn: 10 ml

Sampling interval: 1 hr

Analyzer: UV-Vis Spectrophotometer

λmax: 238 nm

Stability studies

Stability of prepared Simvastatin nanoparticles was carried out at room temperature, refrigeration and accelerated condition at 400C/75% RH for a period of 3 months as per ICH guidelines. Then the samples were analyzed spectrophotometrically to determine the drug content.

RESULTS AND DISCUSSION

Pre-formulation Studies: Formulation optimization hinges on a deep dive into the drug's and excipient's physicochemical traits. The drug and polymer's compatibility is crucial for a successful formulation. UV-visible and FTIR spectroscopy offer key insights into the interactions between the drug and polymer.

Drug – polymer compatibility studies:

Table 2: FTIR peaks

S.No	Samples	Wave number(cm^{-1})
1.	PLGA	3384, 2933, 2875, 1640, 1579, 1429, 1370, 1329, 1062.
2.	Simvastatin	3548, 3417,2962,2877,1836, 1704, 1458, 1388, 1265, 1064.
3.	PLGA & Simvastatin	3749, 3548, 3417, 2954,2877,1828,1704, 1458,1388,1265,1064.

Formulation:

Simvastatin nanoparticles were synthesized in the laboratory via the nano precipitation method, using PLGA (a synthetic polymer) as the polymer in varying drug-to- polymer ratios. Centrifugation was used to isolate the nanoparticles from the solution.

Simvastatin loaded PLGA nanoparticles

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Differential Scanning Colorimetric

Determination of drug release mechanism of optimized nanoparticle

The drug release pattern was determined to follow zero-order kinetics which indicates concentration independent, with an R^2 value nearing 1, indicating that the formulation adheres to this kinetic model practically. Additionally, it conformed to the Higuchi release model i.e. the drug release mechanism was found to be diffusion. The n value from the Korsmeyer-Peppas equation exceeded 0.5, suggesting that the drug release mechanism operates via non-Fickian type of drug diffusion. Strong correlation coefficients were obtained for the kinetic parameters based on Higuchi's square root equation (power law), further confirming that the release process is governed by diffusion kinetics. The drug release from nanoparticles is likely driven by diffusion rather than dissolution. Further observations indicate that the release of Simvastatin from PLGA- based nanoparticles is predominantly controlled by the process of drug diffusion.

Temperature	Amount of drug retained (%) after months			
	Initial	I	II	III
Refrigeration ($4^0 \pm 1^0C$)	82.99±1.10	80.78±0.20	77.90±0.95	75.46±1.23
Room Temperature	82.99±1.50	78.34±1.76	73.88±0.10	70.66±0.56
$40^0 \pm 2^0C$ RH-70±5%	82.99±1.45	74.89±1.89	66.67±0.65	61.10±.90

Table. 3: Stability studies of optimized formulation- F3

Inference:

Stability studies on Simvastatin nanoparticles were conducted at various temperatures: refrigeration (4˚C), room temperature (25˚C), and stability chamber conditions (40˚C/75% RH) as per ICH guidelines. After 3 months, nanoparticles stored under refrigeration retained 75.46% of the drug. At room temperature, 70.66% of the drug was retained, while those stored at 40˚C/75% RH retained 61.10%, as detailed.

SUMMARY AND CONCLUSION

Compatibility between Simvastatin (API) and PLGA (polymer) was confirmed through FTIR and DSC studies. Simvastatin nanoparticles were synthesized using the nanoprecipitation method with good % entrapment efficiency. Various PLGA concentrations were tested, with the highest drug loading efficacy observed in formulation F3. SEM analysis revealed that the nanoparticles were spherical in shape with smooth surfaces, and their sizes ranged between 360 nm and 480 nm, which is an ideal. The in vitro drug release (%CDR) from the optimized formulation reached 95.66% at the 12-hour of time.

The release kinetics of the optimized nanoparticles followed zero-order kinetics which indicate drug release pattern was independent initial concentration from the device, with drug release occurring through diffusion and non-Fickian mechanisms. Stability studies, conducted per ICH guidelines, indicated that the nanoparticles remained stable without significant changes in observed physical characteristics, drug content in the formulation, or drug dissolution behavior. HDL-CH levels were notably higher (36.29±0.602 mg/dl, $p < 0.01$) in the TTG group compared to the RTG group. The TTG group demonstrated superior in vivo performance compared to the RTG group, particularly in terms of plasma lipid profile in polymer, with Simvastatin nanoparticles yielding the highest reduction in lipid levels. Overall, the results indicate that formulation F3, with a 1:3 drug-to-polymer ratio, is the optimal formulation, as it provides sustained drug release from the formulation.

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