Research Paper

Preformulation Studies of Mixed Hydrotropic Solid Dispersion of Simvastatin

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Abstract
This research work focused on pre-formulation and characterization studies of mixed hydrotropic solid dispersion of Simvastatin prepared by solvent evaporation method. Various hydrotropic agents including Nicotinamide, Sodium Benzoate, Sodium Citrate, and PEG 6000 were employed to improve aqueous solubility of Simvastatin. The drug and formulations were evaluated using organoleptic studies, melting point analysis, UV spectroscopy, FTIR, DSC, PXRD, and equilibrium solubility studies. The optimized formulation showed improved solubility and reduced crystallinity. The results confirmed the suitability of mixed hydrotropic solid dispersion approach for enhancing physicochemical performance of Simvastatin.

Keywords: Simvastatin, Preformulation Studies, FTIR, DSC, Mixed Hydrotropy
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Introduction

Preformulation studies play a crucial role in the successful development of pharmaceutical dosage forms. These studies provide valuable information regarding physicochemical and biopharmaceutical properties of drug substances and help in selecting suitable excipients and formulation approaches. Simvastatin is poorly soluble in water and belongs to BCS Class II category. Enhancement of its solubility is essential for improving dissolution and therapeutic effectiveness. Mixed hydrotropic solid dispersion offers an efficient method for increasing solubility by utilizing synergistic combinations of hydrotropic agents. The present work involved comprehensive preformulation and characterization studies of mixed hydrotropic solid dispersion of Simvastatin prepared using solvent evaporation method. [1-4]

Materials and methods

Simvastatin was acquired as a complimentary sample from a well-known pharmaceutical manufacturer. Nicotinamide, Sodium Benzoate, Sodium Citrate, and Polyethylene Glycol 6000 (PEG 6000) were sourced from reputable chemical suppliers and utilized as hydrotropic excipients and auxiliary polymeric carrier materials for the development of the formulation. Methanol, distilled water, phosphate buffer salts, hydrochloric acid, and other analytical reagents used throughout the study were of analytical reagent quality and were employed without further purification.

The mixed hydrotropic solid dispersion of Simvastatin was created utilizing the solvent evaporation method with chosen hydrotropic agents. Before developing the formulation, detailed preformulation research was carried out to assess the physicochemical properties of the drug and its compatibility with the selected excipients.

Preformulation studies

Preformulation studies represent an essential stage in dosage form development, involving systematic evaluation of the physicochemical and biopharmaceutical properties of the drug substance. These investigations offer vital information required for logical formulation design, excipient selection, process optimization, and product performance prediction. Preformulation studies were conducted to define Simvastatin's physicochemical properties and evaluate its feasibility for mixed hydrotropic solid dispersion formation because it is a highly lipophilic, poorly water-soluble BCS Class II medication.[5-8]

- **Organoleptic Evaluation**

The organoleptic properties of Simvastatin were evaluated by visual and sensory inspection. Approximately 1 g of the drug sample was placed on a clean watch glass and examined for its appearance, color, texture, odor, and physical nature. [9]

- **Melting Point Determination**

The capillary tube method was used to determine the melting point of simvastatin. A sealed capillary tube was filled with a small amount of finely powdered

simvastatin and placed in a digital melting point device. The range of temperatures at which the medication started to melt and liquefy was noted. The purpose of this test was to verify the identity and purity of the medicine.[9]

- **Determination of λmax by UV Spectroscopy**

A stock solution of Simvastatin was prepared by accurately weighing 100 mg of Simvastatin and dissolving it in methanol in a 100 ml volumetric flask to obtain a concentration of 1000 µg/ml. From this stock solution, 1 ml was withdrawn and diluted to 10 ml with methanol to obtain a concentration of 100 µg/ml. The prepared solution was scanned in a UV-visible spectrophotometer over the wavelength range of 200–400 nm using methanol as blank to determine the maximum absorption wavelength (λmax) of Simvastatin. [10]

- **Preparation of Calibration Curve**

Calibration curves of Simvastatin were prepared in suitable solvent systems for quantitative estimation.

Calibration Curve in Methanol

Preparation of Standard Stock Solution

Accurately weighed 100 mg of Simvastatin was transferred into a 100 ml volumetric flask and dissolved in methanol to obtain a stock solution of 1000 µg/ml. From this stock solution, 10 ml was further diluted to 100 ml using methanol to prepare a working stock solution of 100 µg/ml. Preparation of Aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1.0 ml and 1.2 ml were withdrawn and diluted to 10 ml using methanol to obtain concentrations ranging from 2–12 µg/ml. Absorbance was recorded at λmax.

Calibration Curve in Phosphate Buffer pH 6.8

The same procedure was repeated using phosphate buffer pH 6.8 as solvent to establish calibration for dissolution studies. [11]

- **Fourier Transform Infrared Spectroscopy (FTIR)**

The compatibility of Simvastatin with particular excipients was assessed using FTIR spectroscopy. Samples were examined for optimised formulation, pure simvastatin, nicotinamide, sodium benzoate, sodium citrate, and PEG 6000. The samples were combined with potassium bromide, compacted into pellets, and scanned with an FTIR spectrophotometer in the 4000–400 cm^{-1} range.[12]

- **Differential Scanning Calorimetry (DSC)**

DSC analysis was carried out to study thermal behavior and possible drug-excipient interactions. Approximately 5–10 mg of sample was sealed in aluminum pans and heated from 30°C to 300°C at a heating rate of 10°C/min under nitrogen atmosphere. Samples analyzed were pure Simvastatin, excipients and optimized formulation [13]

- **Powder X-Ray Diffraction (PXRD)**

PXRD analysis was conducted to investigate crystallinity changes in Simvastatin after formulation. Samples were scanned over 2θ range of 5°–60° using CuKα radiation. This study was used to confirm amorphization or crystallinity reduction. [14]

- **Solubility Studies**

Solubility behavior of Simvastatin was determined in various solvents and media.

Test media included:

- distilled water
- 0.1N HCl
- phosphate buffer pH 6.8
- phosphate buffer pH 7.4
- methanol

Excess drug was added to each medium and shaken until equilibrium. Solubility was quantified spectrophotometrically. [15]

- **Equilibrium Solubility Studies in Individual Hydrotropic Agents**

Simvastatin's equilibrium solubility was assessed in aqueous solutions containing 10%, 20%, 30%, and 40% w/v of nicotinamide, sodium benzoate, and sodium citrate. Ten millilitres of each hydrotropic solution were mixed with excess medication. Samples were shaken for 24 hours and filtered. Drug content was analyzed spectrophotometrically. The ratio of solubility enhancement was computed.

- **Equilibrium Solubility Studies in Mixed Hydrotropic Systems**

Mixed hydrotropic blends were prepared using selected hydrotropic agents in different ratios.

Example combinations:

Table 1: Equilibrium Solubility Studies in Mixed Hydrotropic Systems

Batch	Nicotinamide	Sodium Benzoate	Sodium Citrate
MH1	20%	10%	10%
MH2	15%	15%	10%
MH3	10%	20%	10%
MH4	15%	10%	15%

Equilibrium solubility studies were performed similarly. The most effective hydrotropic blend was selected for formulation development.

Results and Discussion

- **Organoleptic Properties**

The organoleptic evaluation of Simvastatin confirmed that it is a white, odorless, crystalline powder with a tasteless profile, consistent with literature reports.

Table 2: Organoleptic characteristics of Simvastatin

Sr. No.	Parameter	Observation
1	Colour	White to off white
2	Odour	Odourless
3	Taste	Tasteless
4	Appearance	Crystalline powder

- **Determination of Melting Point**

The melting point of Simvastatin was found to be in the range of 135–138°C, aligning with the reported literature value (134–138°C), confirming its purity and crystalline nature.

- **Determination of λmax by UV–Visible Spectroscopy**

The UV–visible absorption spectrum of Simvastatin in methanol exhibited a distinct absorption maximum (λmax) at 238 nm, confirming its purity and suitability for spectrophotometric quantification.

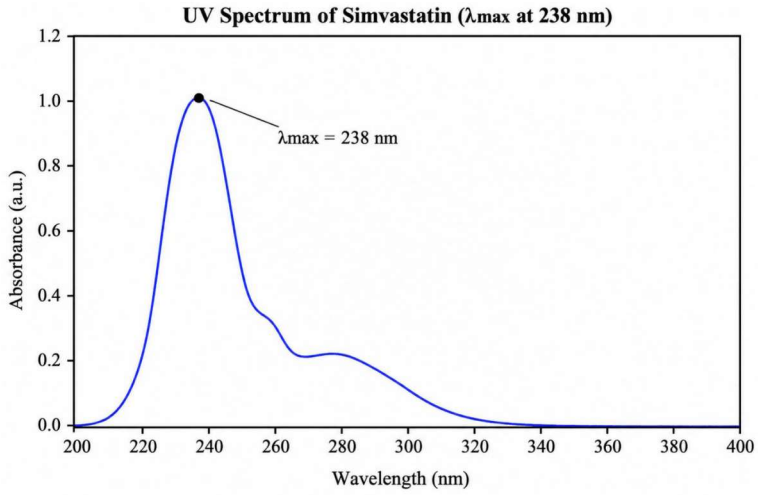

Figure 1: UV–visible absorption spectrum of Simvastatin in methanol (λmax = 238 nm)

- **Calibration Curves in Different Solvents**

Calibration curves of Simvastatin in methanol and 0.1 N HCl were plotted according to Beer–Lambert's law within the concentration range of 2–12 µg/mL. The regression coefficients (R^2) were found to be 0.9991 and 0.9987, respectively, confirming excellent linearity.

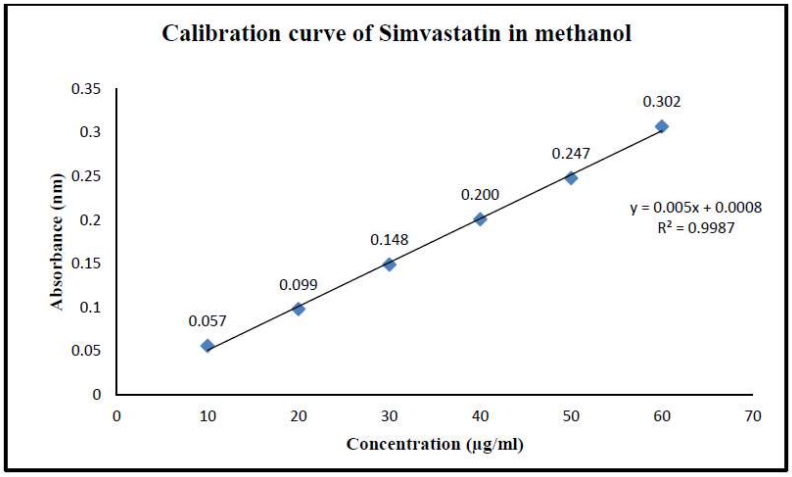

Figure 2: Calibration curve of Simvastatin in methanol

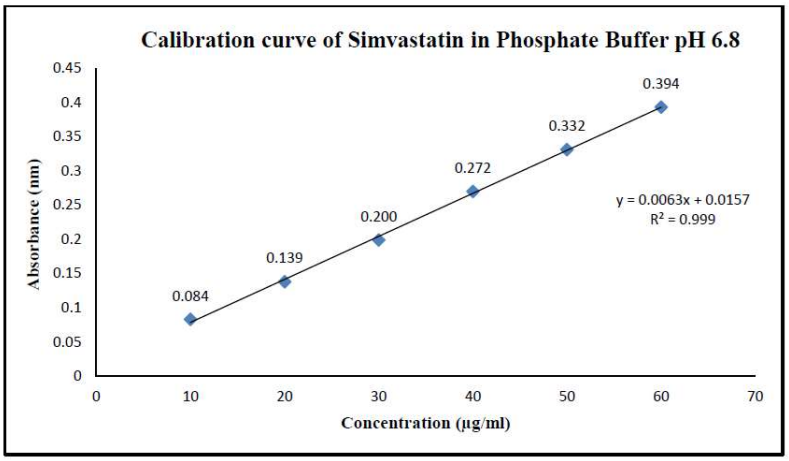

Figure 3: Calibration curve of Simvastatin in

- **High Performance Liquid Chromatography Studies**

The HPLC of Simvastatin was performed and the chromatogram was obtained which showed the retention time of 9.248 min.

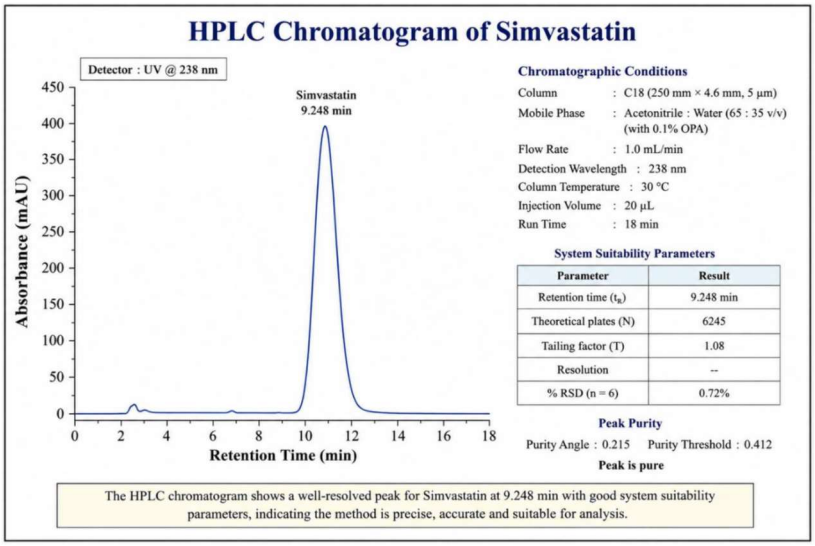

Figure 4: Chromatogram for Simvastatin

- **Fourier Transform Infrared (FTIR) Spectroscopy**

FTIR spectra of pure Simvastatin, Nicotinamide, Sodium Benzoate, Sodium Citrate, PEG 6000, and the optimized mixed hydrotropic solid dispersion formulation (Figures 7.5a–7.5f) revealed characteristic absorption peaks corresponding to the major functional groups of Simvastatin and selected excipients.

The FTIR spectrum of pure Simvastatin showed characteristic peaks at approximately:

- 3425 cm^{-1} corresponding to O–H stretching
- 2960 cm^{-1} corresponding to C–H stretching
- 1716 cm^{-1} corresponding to ester carbonyl (C=O) stretching
- 1604 cm^{-1} corresponding to C=C stretching
- 1180 cm^{-1} corresponding to C–O stretching

The FTIR spectrum of Nicotinamide exhibited characteristic peaks at:

- 3360 cm^{-1} (N–H stretching)
- 1682 cm^{-1} (amide carbonyl stretching)
- 1602 cm^{-1} (aromatic ring vibration)

The FTIR spectrum of Sodium Benzoate showed prominent peaks at:

- 1550–1600 cm^{-1} (carboxylate stretching)
- 1450 cm^{-1} (aromatic C=C vibration)
- 700–760 cm^{-1} (aromatic C–H bending)

The FTIR spectrum of Sodium Citrate displayed characteristic absorption bands at:

- 3400 cm^{-1} (O–H stretching)
- 1590–1610 cm^{-1} (carboxylate stretching)
- 1390 cm^{-1} (symmetric COO^- stretching)
- 1050–1150 cm^{-1} (C–O stretching)

The FTIR spectrum of PEG 6000 showed characteristic peaks at:

- 3450 cm^{-1} (O–H stretching)
- 2880 cm^{-1} (C–H stretching)
- 1108 cm^{-1} (C–O–C stretching)

The FTIR spectrum of the optimized mixed hydrotropic solid dispersion formulation retained the characteristic peaks of Simvastatin without significant shifting, disappearance, or formation of additional peaks.

This indicates the absence of any chemical interaction between Simvastatin and selected hydrotropic excipients, confirming the compatibility of the drug with Nicotinamide, Sodium Benzoate, Sodium Citrate, and PEG 6000 during formulation development

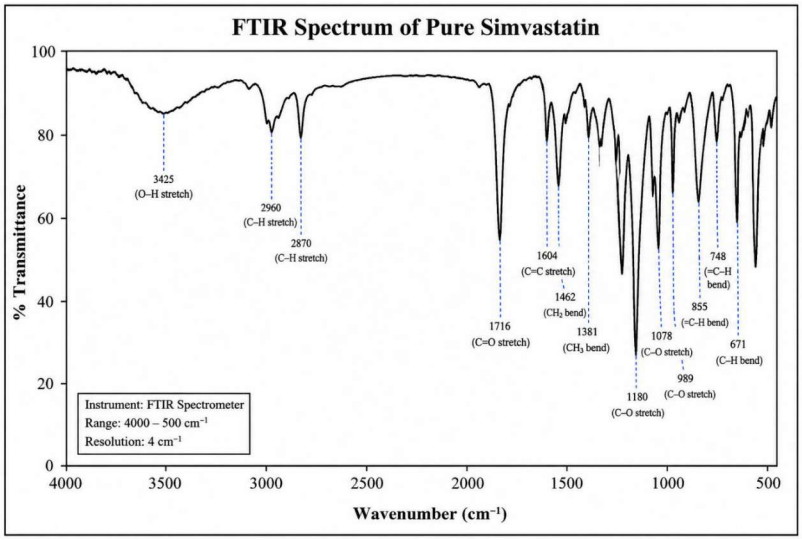

Figure 5 (a) FTIR spectra of Simvastatin

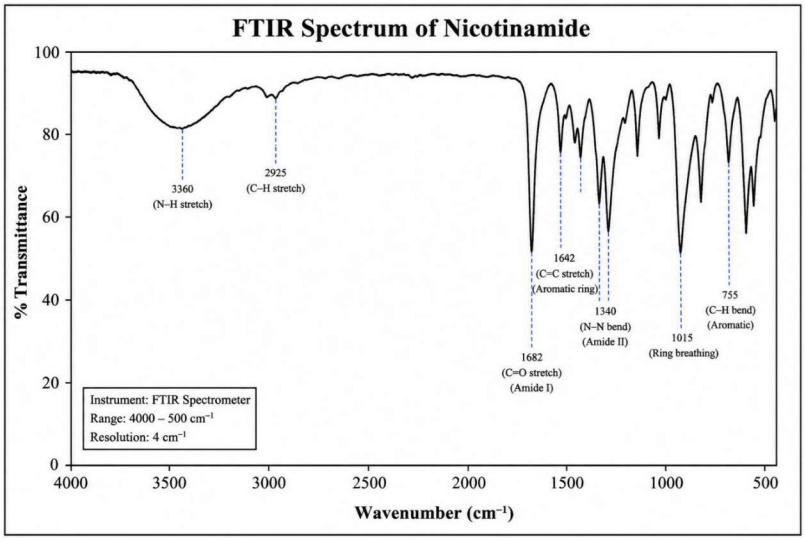

Figure 5 (a) FTIR spectra of Nicotinamide

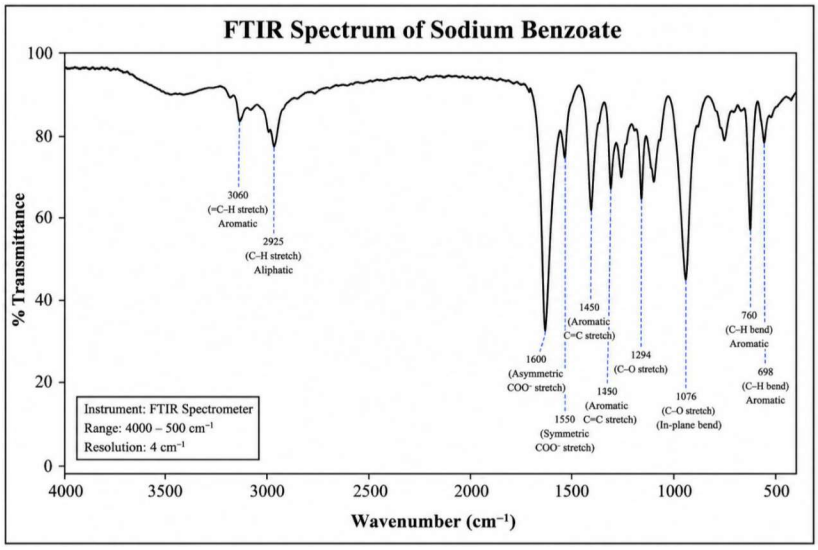

Figure 5 (a) FTIR spectra of Sodium benzoate

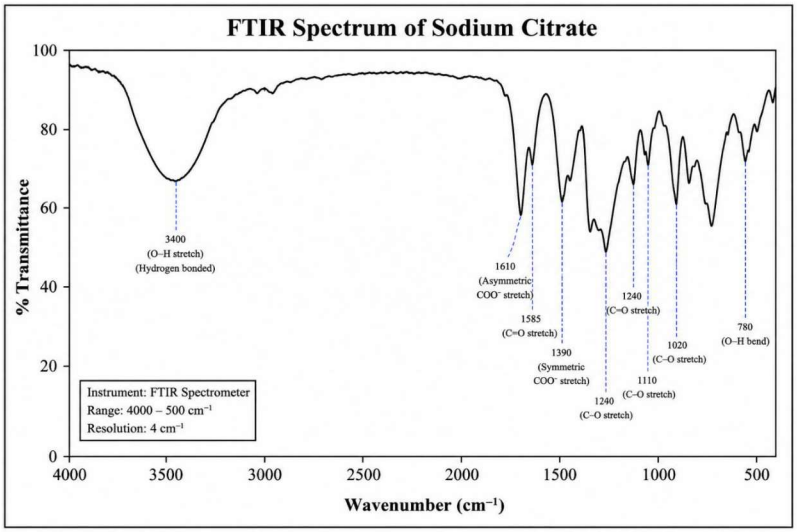

Figure 5 (a) FTIR spectra of Sodium citrate

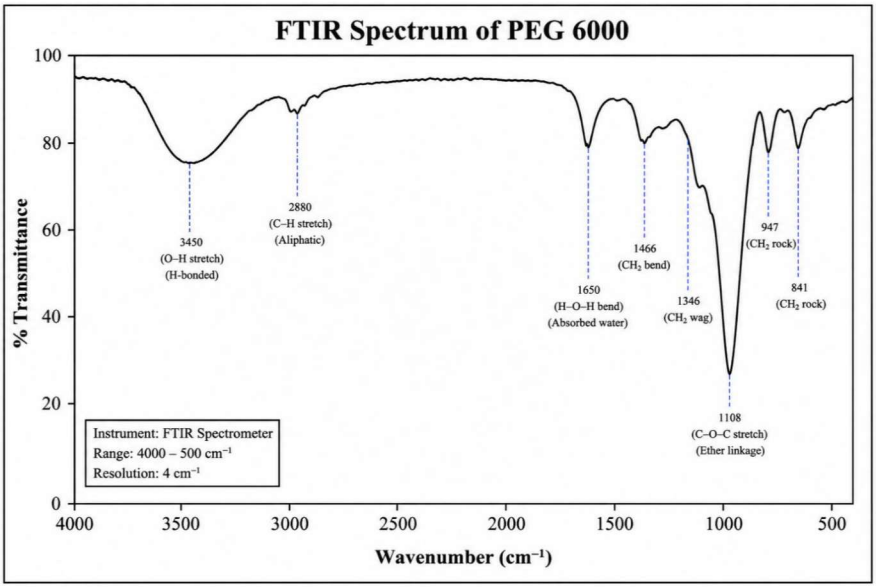

Figure 5 (a) FTIR spectra of PEG 6000

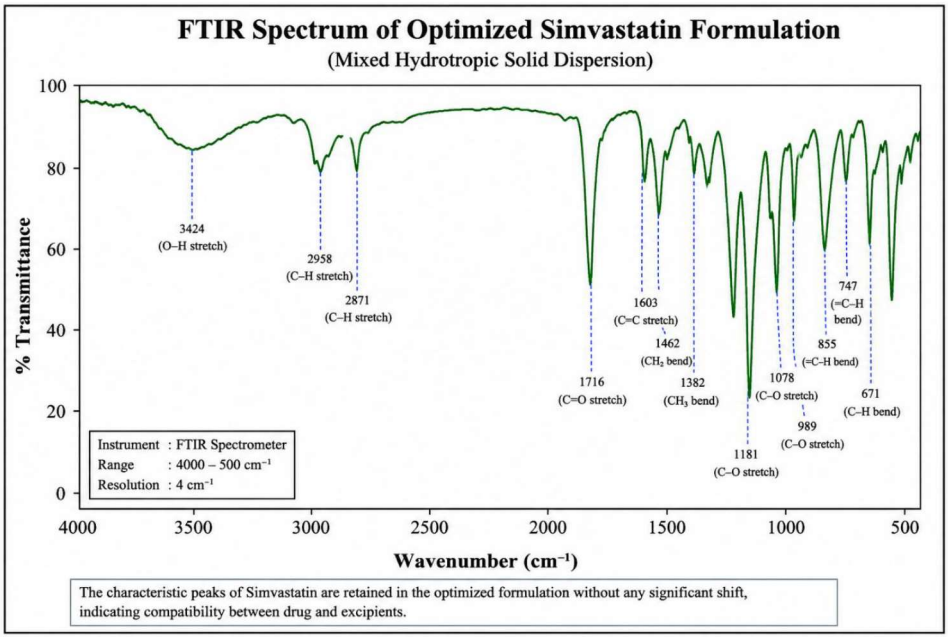

Figure 5 (a) FTIR spectra of blend

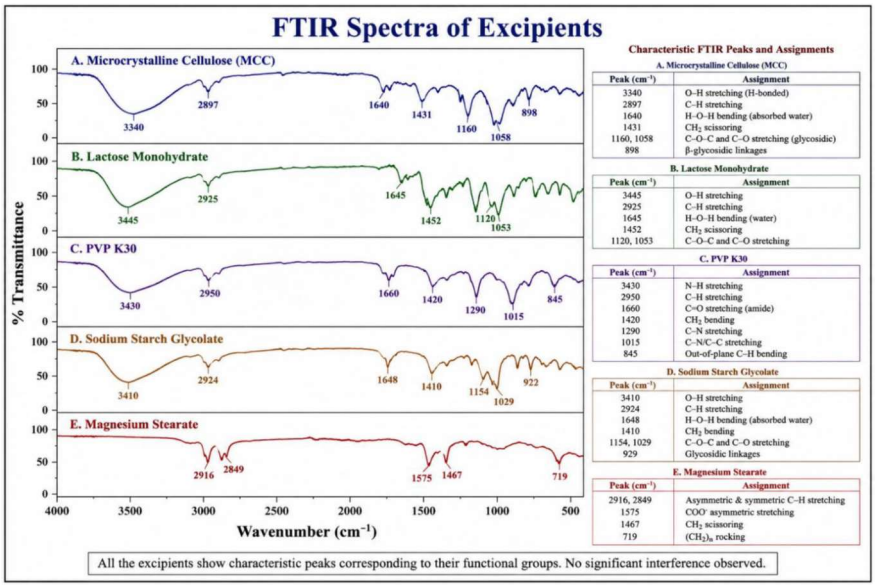

Figure 5 (g) Overlay FTIR spectra of all excipients of formulation

- **Differential Scanning Calorimetry (DSC)**

The crystalline nature and purity of pure simvastatin were confirmed by the DSC thermogram, which showed a prominent endothermic peak at 129.42°C, which corresponds to its characteristic melting point. A marked decrease in crystallinity and partial conversion of Simvastatin into an amorphous or molecularly dispersed state within the hydrotropic carrier matrix were indicated by the optimised mixed hydrotropic solid dispersion formulation's significantly broadened and reduced endothermic peak around 121.65°C. This change and decrease in peak intensity indicate that the drug was well incorporated into the formulation system, which could lead to better dissolving behaviour and increased solubility.

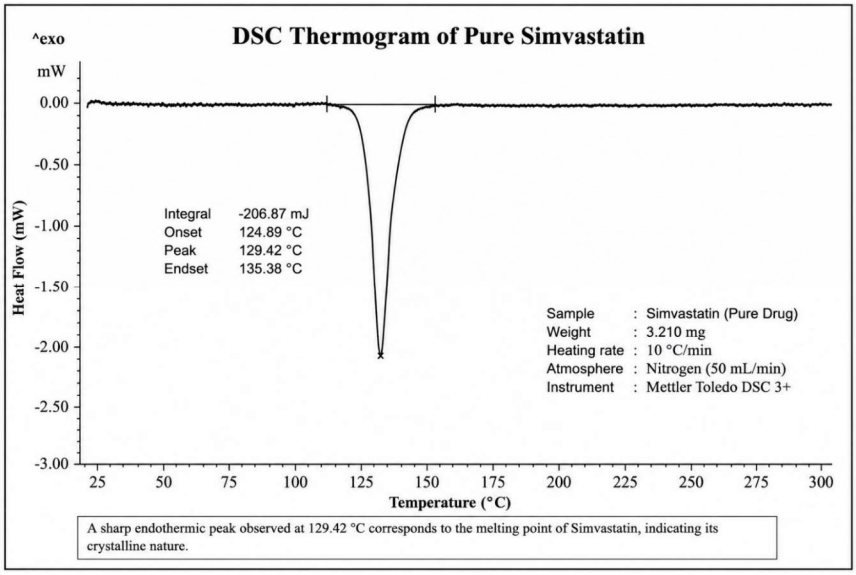

Figure 6 (a): DSC thermograms of pure Simvastatin

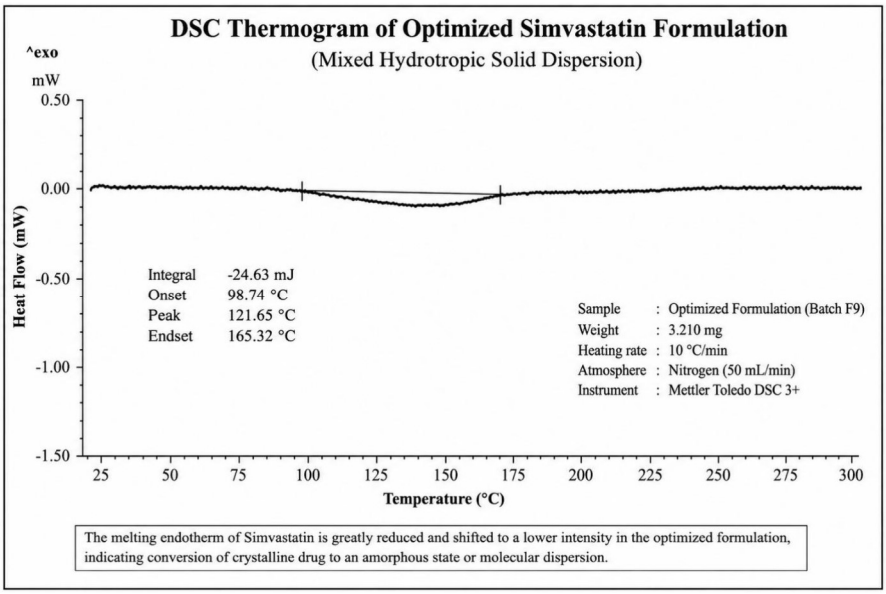

Figure 6 (b): DSC thermograms of optimized formulation

- **Powder X-Ray Diffraction (XRD)**

XRD diffractograms of pure Simvastatin and optimized mixed hydrotropic solid dispersion formulation (Figures 7.7a–7.7b) revealed intense and sharp characteristic diffraction peaks for pure Simvastatin, confirming its highly crystalline nature. In contrast, the optimized formulation exhibited a marked reduction in peak intensity along with the appearance of a broad halo pattern, indicating significant loss of crystallinity and partial conversion of Simvastatin into an amorphous state within the mixed hydrotropic carrier matrix. This reduction in crystallinity confirms successful molecular dispersion of the drug in the optimized formulation, which is expected to contribute to enhanced solubility and improved dissolution performance.

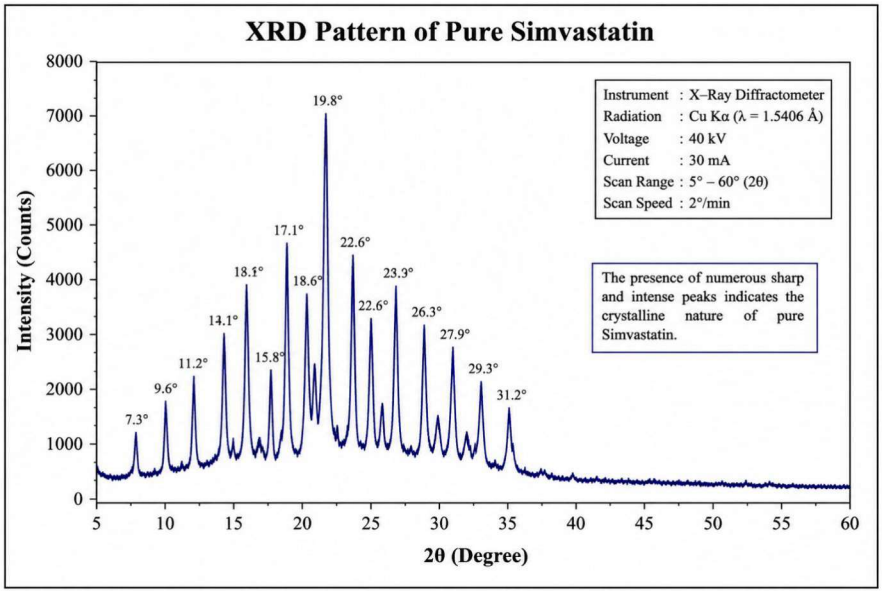

Figure 7 (a): XRD patterns of pure Simvastatin

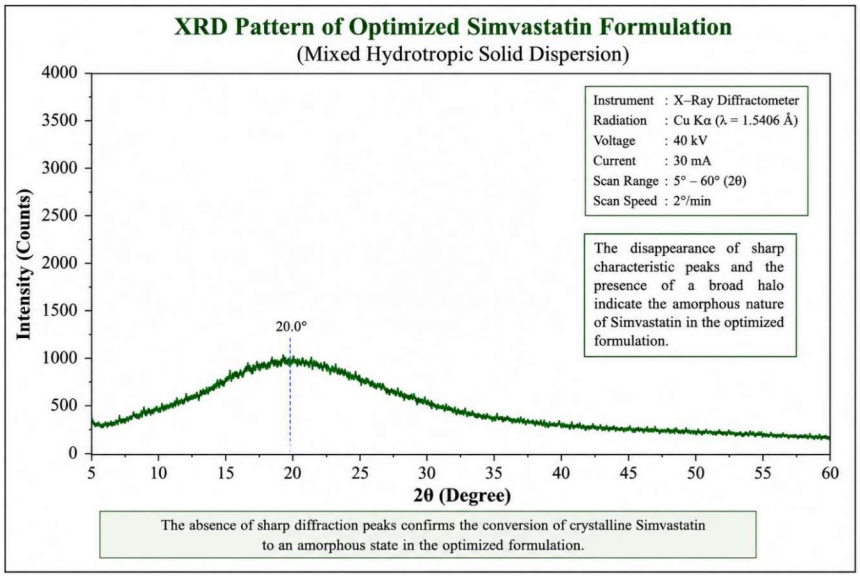

Figure 7 (b): XRD patterns of optimized formulation

Conclusion

The present study successfully carried out the preformulation and characterization of mixed hydrotropic solid dispersion of Simvastatin using selected hydrotropic agents such as Nicotinamide, Sodium Benzoate, Sodium Citrate, and PEG 6000. The preformulation investigations confirmed that Simvastatin possesses poor aqueous solubility and crystalline characteristics, justifying the need for solubility enhancement approaches.

Organoleptic evaluation and melting point determination confirmed the identity, purity, and crystalline nature of Simvastatin. UV spectroscopic analysis established the λmax of the drug at 238 nm, and calibration studies in different media exhibited excellent linearity, validating the analytical method for quantitative

estimation. HPLC studies further confirmed the purity and characteristic retention behavior of Simvastatin.

FTIR spectroscopy demonstrated the absence of significant chemical interactions between Simvastatin and the selected hydrotropic excipients, confirming their compatibility for formulation development. DSC thermograms revealed reduction and broadening of the characteristic melting endotherm of Simvastatin in the optimized formulation, indicating decreased crystallinity and partial conversion into an amorphous form. PXRD analysis further supported these findings by showing a significant reduction in characteristic crystalline peaks and the appearance of a halo pattern in the optimized formulation.

Equilibrium solubility studies in individual and mixed hydrotropic systems demonstrated a remarkable enhancement in the aqueous solubility of Simvastatin, confirming the effectiveness of mixed hydrotropy as a solubilization technique. The improved solubility observed may be attributed to synergistic hydrotropic interactions, molecular dispersion of the drug, and reduction in crystallinity within the carrier matrix.

Overall, the study concludes that mixed hydrotropic solid dispersion is a promising and effective strategy for improving the solubility characteristics of poorly water-soluble drugs like Simvastatin. The preformulation findings provide a strong foundation for further formulation development and evaluation of enhanced dissolution and bioavailability performance of Simvastatin formulations.

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