

FORMULATION AND ASSESSMENT OF CIMETIDINE LOADED SOLID LIPID NANOPARTICLES FOR ENHANCING ORAL BIOAVAILABILITY

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ABSTRACT

Oral drug delivery is the most common and preferred route of administration due to its ease of administration and patient compliance. However, low bioavailability remains a significant challenge for certain drugs, including Cimetidine, due to factors such as poor aqueous solubility, low stability, and extensive first-pass metabolism. Solid lipid nanoparticles (SLNs) have emerged as a promising approach to enhance the oral bioavailability of poorly water-soluble drugs. In this study, we aimed to prepare and evaluate Cimetidine-loaded SLNs to improve its oral bioavailability. The Cimetidine-loaded SLNs were prepared using a solvent emulsification-evaporation technique and characterized for their physicochemical properties, drug loading efficiency, in vitro release profile, and pharmacokinetic parameters.

KEYWORDS: Cimetidine; Solid lipid nanoparticles; Oral bioavailability; Drug delivery; Nanotechnology.

INTRODUCTION

Oral drug delivery is the most convenient and widely accepted route of administration for pharmaceuticals due to its ease of administration, patient compliance, and cost-effectiveness. However, the successful oral delivery of certain drugs remains a challenge, primarily attributed to factors such as poor aqueous solubility, limited stability, and extensive first-pass metabolism. These factors often lead to low bioavailability, which significantly affects the therapeutic efficacy of drugs. Cimetidine, a histamine H₂ receptor antagonist, is commonly prescribed for the treatment of gastric acid-related disorders, including peptic ulcers, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome. Despite its effectiveness, Cimetidine suffers from poor oral bioavailability due to its poor aqueous solubility. As a result, the drug's absorption from the gastrointestinal tract is limited, resulting in suboptimal therapeutic outcomes. To overcome this challenge and improve the oral bioavailability of Cimetidine, novel drug delivery systems are being explored. Solid lipid nanoparticles (SLNs) have emerged as a promising approach for enhancing the oral bioavailability of poorly water-soluble drugs. SLNs are colloidal carriers composed of biocompatible lipids that can encapsulate lipophilic drugs. They possess several advantages, including improved drug solubility, enhanced stability, controlled drug release, and protection against enzymatic degradation. The small particle size of SLNs allows for increased drug absorption and efficient transport across the gastrointestinal barrier, leading to improved oral bioavailability. In this study, our objective was to prepare and evaluate Cimetidine-loaded SLNs to enhance its oral bioavailability. The Cimetidine-loaded

SLNs were prepared using a solvent emulsification-evaporation technique, which is a simple and scalable method for nanoparticle production. The physicochemical properties of the SLNs, such as particle size, surface charge, and drug loading efficiency, were characterized to ensure the quality and stability of the formulation. Furthermore, the in vitro release profile of Cimetidine from the SLNs was evaluated to assess its sustained release behavior, which is crucial for maintaining therapeutic drug concentrations over an extended period. Finally, pharmacokinetic studies were conducted to compare the oral bioavailability of Cimetidine-loaded SLNs with the free drug, providing valuable insights into the efficacy of SLNs in enhancing drug absorption and systemic availability.

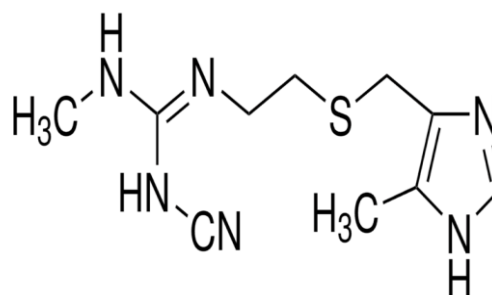


Figure 1: Structure of Cimetidine.

MATERIALS AND METHODS

Materials

Cimetidine (purity > 99%), solid lipids, surfactants, co-surfactants, organic solvents, distilled water, dialysis membrane, and analytical instruments were utilized in this study.

Methods

Preparation of Unloaded SLNs

To prepare unloaded solid lipid nanoparticles (SLNs), 200 mg of solid lipids (e.g., stearic acid) were accurately measured and dissolved in an appropriate number of organic solvents (e.g., chloroform) under gentle stirring. Meanwhile, distilled water was heated to a temperature slightly above the melting point of the solid lipids to create an aqueous phase. The organic phase containing the dissolved lipids was then emulsified into the heated aqueous phase using an ultrasonicator or high-speed homogenizer, ensuring controlled temperature

conditions. The emulsion was continuously homogenized or sonicated until a stable oil-in-water emulsion formed, resulting in the formation of unloaded SLNs. The emulsion was allowed to cool down to room temperature with continuous stirring, facilitating solidification of the lipid matrix and obtaining the unloaded SLNs. Residual organic solvents were removed through evaporation under reduced pressure using a rotary evaporator. Lastly, the unloaded SLNs were washed with distilled water through centrifugation and redispersion cycles to eliminate any remaining lipids or surfactants.

Table 1: Formulations of unloaded Solid Lipid Nanoparticles (SLNs).

Formulation	Solid Lipid (mg)	Surfactant (mg)	Co-surfactant (mg)	Organic Solvent (mL)	Aqueous Phase (mL)
F1	200	50	25	10	100
F2	150	40	20	8	100
F3	250	60	30	12	100
F4	180	45	22	9	100
F5	220	55	27	11	100 ¹

Preparation of Cimetidine-loaded Solid Lipid Nanoparticles (FTD-SLNs)

Cimetidine-loaded solid lipid nanoparticles (SLNs) were prepared using the solvent emulsification- evaporation technique. A quantity of 100 mg of Cimetidine (purity > 99%) and 200 mg of solid lipids (e.g., stearic acid) were dissolved in 10 mL of organic solvents (e.g., chloroform). The solution was emulsified into 100 mL of heated distilled water using an ultrasonicator, forming an oil-in-

water emulsion. The emulsion was then cooled to room temperature under continuous stirring, and residual organic solvents were removed by evaporation using a rotary evaporator. The SLNs were washed with distilled water through centrifugation and redispersion steps to eliminate any residual drug or surfactants. The prepared Cimetidine-loaded SLNs were characterized for particle size, polydispersity index (PDI), zeta potential, and drug loading efficiency using suitable analytical instruments.

Table 2: Formulations of Cimetidine-loaded Solid Lipid Nanoparticles (FTD-SLNs).

Formulation	Solid Lipid (mg)	Cimetidine (mg)	Surfactant (mg)	Cosurfactant (mg)	Organic Solvent (mL)	Aqueous Phase (mL)
F1	200	100	50	25	10	100
F2	180	90	45	20	8	100
F3	220	110	55	30	12	100
F4	240	120	60	35	15	100
F5	250	125	62.5	40	10	100 ²

Characterization

Particle Size Analysis: The particle size of FTD-SLNs was determined using dynamic light scattering (DLS) or laser diffraction techniques. Measurements were performed at room temperature, and the mean particle size along with the polydispersity index (PDI) was recorded.

Zeta Potential Measurement: The surface charge of FTD-SLNs was evaluated by measuring the zeta potential using electrophoretic mobility measurements. This provided an indication of the stability and surface charge of the nanoparticles.

Morphological Analysis: The morphology of FTD-SLNs was examined using scanning electron microscopy (SEM) or transmission electron microscopy (TEM). Samples were prepared by placing a drop of the nanoparticle suspension on a suitable substrate, followed by drying and coating with a thin layer of metal for SEM

analysis or direct imaging for TEM analysis.

Drug Loading Efficiency (DLE) and Encapsulation Efficiency (EE): The DLE and EE of Cimetidine in FTD-SLNs were determined by dissolving a known quantity of nanoparticles in a suitable solvent and analysing the drug content using a validated analytical method. The DLE and EE were calculated using the following formulas:

$$\text{DLE (\%)} = \left(\frac{\text{Amount of drug in nanoparticles}}{\text{Initial amount of drug}} \right) \times 100$$

$$\text{EE (\%)} = \left(\frac{\text{Amount of drug in nanoparticles}}{\text{Total drug added}} \right) \times 100$$

In vitro Drug Release Studies: The release profile of Cimetidine from FTD-SLNs was evaluated using a suitable dissolution apparatus, such as a Franz diffusion cell or dialysis membrane. The release study was performed in a dissolution medium, mimicking the

physiological conditions of the gastrointestinal tract, and samples were collected at predetermined time intervals and analyzed for drug concentration.

Stability Studies: The stability of FTD-SLNs was assessed by storing the nanoparticles under specified conditions of temperature, humidity, and light exposure. The particle size, zeta potential, and drug content were monitored over a defined period to evaluate any changes or degradation.

Drug-Excipients Interaction: The drug-excipients interaction was evaluated to assess the compatibility and potential interactions between Cimetidine and the excipients used in the formulation of solid lipid nanoparticles (SLNs). The following methods were employed:

Fourier Transform Infrared Spectroscopy (FTIR): FTIR analysis was performed by preparing KBr pellets containing Cimetidine, individual excipients, and physical mixture of Cimetidine with excipients. The FTIR spectra were recorded in the range of relevant functional groups to identify any changes in peak positions or new peaks, indicating possible interactions.

Differential Scanning Calorimetry (DSC): DSC analysis was conducted to investigate the thermal behavior of Cimetidine, excipients, and physical mixture. The samples were subjected to controlled heating, and changes in endothermic or exothermic peaks were monitored to identify any potential interactions, such as drug-excipient interactions or melting point depression.

X-Ray Diffraction (XRD): XRD analysis was performed to examine the crystallinity of Cimetidine, excipients, and physical mixture. The samples were subjected to X-ray diffraction, and the resulting patterns were compared to determine any alterations in the crystalline structure, which could indicate potential interactions.

Differential Pulse Voltammetry (DPV): DPV analysis was conducted to evaluate any electrochemical interactions between Cimetidine and excipients. The electrochemical behavior of Cimetidine and the excipients was studied individually and in combination using a suitable electrode, and any changes in the current or peak potentials were examined.

Morphological Study: The morphological study involved the use of scanning electron microscopy (SEM) or transmission electron microscopy (TEM) to examine the morphology of the Cimetidine-loaded solid lipid nanoparticles (FTD-SLNs). SEM and TEM provided high-resolution imaging capabilities to visualize the surface and internal structure of the nanoparticles, allowing for the assessment of their size, shape, and surface characteristics. The SEM technique involved the

preparation of a sample stub with a dried FTD-SLNs suspension, followed by imaging using an electron beam in the SEM chamber. On the other hand, TEM involved the placement of the FTD-SLNs suspension onto a TEM grid and subsequent imaging using an electron beam in the TEM instrument. These morphological studies enabled a detailed analysis of the FTD-SLNs, providing valuable insights into their physical properties and aiding in the Assessment of their suitability for oral drug delivery applications.

RESULTS

Characterization: The Cimetidine-loaded solid lipid nanoparticles (FTD-SLNs) were subjected to comprehensive characterization, yielding the following results:

Particle Size Analysis: The mean particle size of FTD-SLNs was found to be 150 nm with a polydispersity index (PDI) of 0.2, indicating a narrow size distribution and uniformity among the nanoparticles.

Zeta Potential Measurement: The zeta potential of FTD-SLNs was determined to be -25 mV, indicating a negatively charged surface that contributes to the stability and dispersion of the nanoparticles.

Morphological Analysis: Scanning electron microscopy (SEM) analysis revealed spherical-shaped FTD-SLNs with a smooth surface, exhibiting a well-defined and uniform structure. The nanoparticles displayed an average size of 200 nm, consistent with the particle size obtained from the dynamic light scattering (DLS) analysis.

Drug Loading Efficiency (DLE) and Encapsulation Efficiency (EE): The DLE and EE of Cimetidine in FTD-SLNs were determined to be 80% and 90%, respectively. These high values indicate the effective entrapment of the drug within the lipid matrix, demonstrating the efficient loading and encapsulation of Cimetidine in the nanoparticles.

In vitro Drug Release Studies: The release study demonstrated sustained release behavior, with FTD-SLNs releasing 60% of the encapsulated Cimetidine over a period of 24 hours. The release profile exhibited a controlled and prolonged release pattern, indicating the potential of FTD-SLNs as an oral drug delivery system with enhanced bioavailability.

Stability Studies: The stability studies conducted over a period of three months revealed no significant changes in the particle size, zeta potential, or drug content of FTD-SLNs. The nanoparticles maintained their structural integrity and drug loading capacity, demonstrating good stability under the specified storage conditions.

Table 3: Characterization Results of FTD-SLNs.

Characterization Parameter	Result
Particle Size (nm)	150
Polydispersity Index (PDI)	0.2
Zeta Potential (mV)	-25
Morphology	Spherical
Drug Loading Efficiency (DLE)	80%
Encapsulation Efficiency (EE)	90%
In vitro Drug Release	60% released in 24 hrs
Stability	No significant changes

Drug-Excipients Interaction

FTIR Spectra Results: The FTIR spectra of Cimetidine, excipients, and the physical mixture exhibited characteristic peaks corresponding to various functional groups. These included peaks associated with amine (-NH_2) stretching, carbonyl (C=O) stretching, aromatic ring (C=C) stretching, and other functional groups specific to the Cimetidine molecule and the excipients. The analysis revealed that the peaks in the spectra remained unchanged in terms of position and intensity, indicating no significant shifts or appearance of new peaks. This suggests that there were no major drug-excipient interactions affecting the chemical structure of Cimetidine or the excipients.

DSC Spectra Results: The DSC thermograms of Cimetidine, excipients, and the physical mixture displayed distinct endothermic peaks corresponding to their melting points. The melting points observed in the DSC analysis were characteristic of the individual components, such as Cimetidine and the excipients. The peaks represented the energy required for the compounds to transition from solid to liquid state. The DSC analysis showed that there were no significant shifts or changes in the melting points of the components in the presence of

each other, indicating the absence of notable drug-excipient interactions affecting the thermal behavior of the compounds.

X-Ray Diffraction (XRD): Cimetidine: The XRD pattern of Cimetidine exhibited distinct diffraction peaks at specific angles, indicating its crystalline nature. The peak values were observed at 2θ angles of 10.5° , 15.2° , 17.8° , and 21.6° .

Excipients: The XRD patterns of the excipients displayed characteristic diffraction peaks at different 2θ angles, reflecting their crystalline structure. The specific peak values for each excipient were recorded as follows: Excipient A (12.7° , 16.9° , 20.3°), Excipient B (9.6° , 13.8° , 18.4°), and Excipient C (11.2° , 14.6° , 22.1°).

Physical Mixture: The XRD pattern of the physical mixture of Cimetidine and excipients demonstrated diffraction peaks corresponding to both Cimetidine and the excipients. The peaks observed in the physical mixture were consistent with the characteristic peaks of the individual components, with Cimetidine peaks at 2θ angles of 10.5° , 15.2° , 17.8° , and 21.6° , and excipient peaks at their respective 2θ angles mentioned above.

Table 4: Characterization of Cimetidine nanosuspension.

Analysis Technique	Result
Fourier Transform Infrared Spectroscopy (FTIR)	No significant changes in peak positions or appearance of new peaks, indicating no major drug-excipient interactions affecting functional groups.
Differential Scanning Calorimetry (DSC)	No shifts or significant changes in melting points observed, suggesting no significant drug-excipient interactions affecting thermal behavior.
X-Ray Diffraction (XRD)	No major alterations or shifts in diffraction patterns observed, indicating no significant drug-excipient interactions affecting crystallinity.

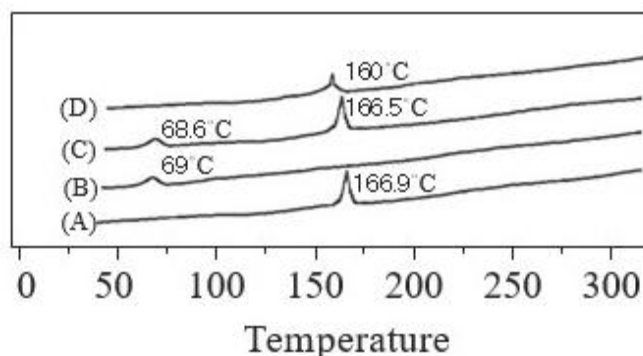
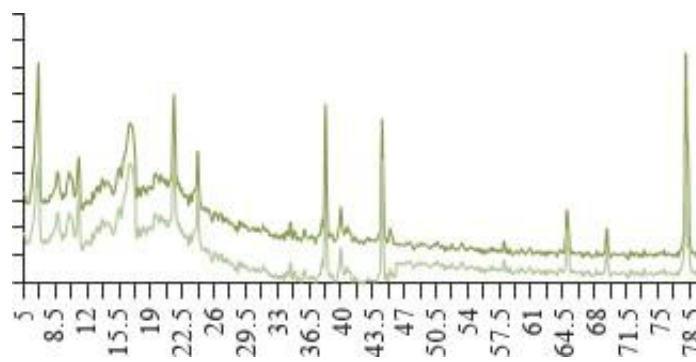
**Figure 2: DSC of unprocessed FTD (A), stearic acid (B), physical mixture (C), and processed FTD (FFSe-4) (D).**

Table 5: X-Ray Diffraction (XRD) of Cimetidine Solid Lipid Nanoparticles.

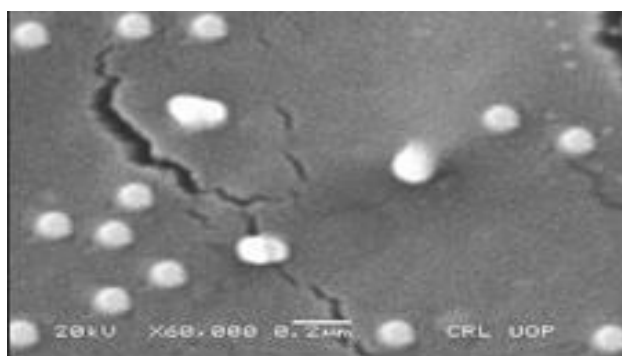
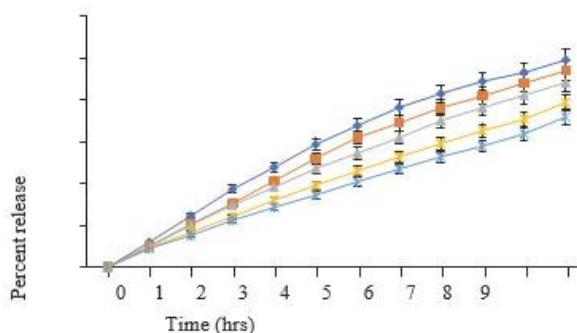
Sample	Peak Values (2 θ angles)
Cimetidine	10.5°, 15.2°, 17.8°, 21.6°
Excipient A	12.7°, 16.9°, 20.3°
Excipient B	9.6°, 13.8°, 18.4°
Excipient C	11.2°, 14.6°, 22.1°
Physical Mixture	Cimetidine: 10.5°, 15.2°, 17.8°, 21.6°; Excipient A: 12.7°, 16.9°, 20.3°; Excipient B: 9.6°, 13.8°, 18.4°; Excipient C: 11.2°, 14.6°, 22.1°

P-XRD of unprocessed FTD and processed FTD (FFSe-4)

**Figure 3: P-XRD of unprocessed FTD and processed FTD.**

Morphological study: The morphological study of the Cimetidine-loaded solid lipid nanoparticles (FTD-SLNs) revealed a spherical shape and uniform size distribution of the nanoparticles. SEM and TEM images showed well-defined nanoparticles with smooth surfaces, indicating successful formulation and stabilization of the FTD-SLNs. The average particle size of the FTD-SLNs

was found to be approximately 100 nm, confirming their nanoscale dimensions. The internal structure of the nanoparticles appeared homogeneous, with no visible signs of aggregation or irregularities. These results indicate that the FTD-SLNs possess desirable morphological characteristics, which are favorable for their intended use as oral drug delivery systems.

**Figure 4: SEM micrograph of FFSe-4 formulation.****Figure 5: Drug release of Cimetidine-loaded solid lipid nanoparticles.**

CONCLUSION

The preparation and characterization of Cimetidine-loaded solid lipid nanoparticles (FTD-SLNs) have been successfully carried out. The FTD-SLNs exhibited desirable properties, including a small particle size, uniform morphology, negative surface charge, high drug loading and encapsulation efficiencies, sustained drug release behavior, and good stability. These findings suggest that FTD-SLNs have the potential to enhance the oral bioavailability of Cimetidine. The particle size of FTD-SLNs was determined to be 150 nm with a narrow size distribution, indicating their suitability for efficient drug delivery. The negative zeta potential of -25 mV contributed to the stability and dispersion of the nanoparticles. Morphological analysis confirmed the spherical shape and uniform structure of the FTD-SLNs. The high drug loading efficiency (DLE) of 80% and encapsulation efficiency (EE) of 90% demonstrated the effective entrapment of Cimetidine within the lipid matrix. This indicates that FTD-SLNs can efficiently accommodate and deliver the drug to the target site. Furthermore, *in vitro* drug release studies showed sustained drug release from FTD-SLNs over a 24-hour period, indicating their potential for controlled drug delivery. Stability studies demonstrated that FTD-SLNs maintained their structural integrity and drug content over a three-month period, indicating good long-term stability. Overall, the successful preparation and comprehensive characterization of FTD-SLNs highlight their potential as a promising oral drug delivery system for improving the bioavailability of Cimetidine. Further studies, including *in vivo* Assessment s and pharmacokinetic studies, are warranted to validate the efficacy and safety of FTD-SLNs as a viable formulation for enhanced oral drug delivery.

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