Formulation Process of Solid lipid Nanoparticles improves oral bioavailability of Drug Famotidine

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Abstract

This research focuses on the development of a novel drug delivery system to enhance the oral bioavailability of Famotidine, a poorly water-soluble and permeable drug. Solid Lipid Nanoparticles (SLNs) were prepared using the ultrasonic-hot emulsification technique to encapsulate Famotidine effectively. The SLNs' formulation comprised a mixture of glycerol monostearate (GMS) and span 20 (in a 3:1 w/w ratio), which were melted at approximately 60 °C. Famotidine was then incorporated into the melted lipid mixture at a concentration of 2 mg/mL of the total volume. Aqueous phase containing poloxamer (4 mg/mL) was heated to a similar temperature and added to the lipid mixture, followed by thorough mixing using a high-shear homogenizer (T25 Ultraturax, IKA) and subsequent sonication with a probe sonicator (Misonix) to achieve stable emulsion.

Keywords: Famotidine; Bioavailability; Solid lipid nanoparticle; Oral absorption; Poorly aqueous-soluble drug

INTRODUCTION

Famotidine, a histamine H2 receptor antagonist, is a widely used drug for the management of various gastrointestinal disorders, including peptic ulcers and gastroesophageal reflux disease. However, its therapeutic effectiveness is often hindered by its low water solubility and subsequent poor oral bioavailability [1,2]. When administered orally, Famotidine encounters various challenges, such as limited dissolution in the aqueous environment of the gastrointestinal tract, inadequate absorption across the intestinal epithelium, and susceptibility to first-pass metabolism in the liver [3,4].

To overcome these obstacles and improve the oral bioavailability of Famotidine, researchers have been exploring innovative drug delivery systems. Among these, Solid Lipid Nanoparticles (SLNs) have emerged as a promising technology due to their potential to enhance the solubility and bioavailability of poorly water-soluble drugs [5,6]. Solid Lipid Nanoparticles (SLNs) are colloidal particles composed of biocompatible and biodegradable lipids, which serve as carriers for hydrophobic drugs. The unique structure of SLNs allows for the encapsulation of lipophilic drugs within their lipid matrix, protecting the drug from degradation and facilitating its absorption. Additionally, SLNs possess a high surface area-to-volume ratio, leading to prolonged drug release and sustained therapeutic levels in the systemic circulation [7-9].

By entrapping Famotidine within SLNs, it is possible to achieve improved drug delivery to the site of action, thereby enhancing its pharmacological effects and reducing the required dosage frequency. This approach has the potential to enhance patient compliance and minimize side effects associated with higher dosages [10].

In this research article, we aim to investigate the effectiveness of Solid Lipid Nanoparticles as carriers for

enhancing the oral bioavailability of Famotidine. We will explore the preparation and characterization of Famotidine-loaded SLNs, assess their in vitro release behavior, and conduct in vivo pharmacokinetic studies to evaluate their performance in comparison to conventional formulations [11,12].

The findings from this study could open new avenues for enhancing the therapeutic outcomes of Famotidine and contribute to the broader field of drug delivery, particularly for poorly water-soluble drugs. Ultimately, improving the oral bioavailability of Famotidine through SLNs could lead to more effective and efficient treatment strategies for patients suffering from gastrointestinal disorders [13].

MATERIALS AND METHODS

In this study, we utilized analytical-grade Glyceryl monostearate (GMS), Poloxamer 188, and Span 20 as primary components for the preparation of Solid Lipid Nanoparticles (SLNs). Additionally, Famotidine was generously provided as a gift sample, and it served as the active pharmaceutical ingredient (API) for encapsulation within the SLNs.

Preparation of Famotidine-SLN:

In this research study, Solid Lipid Nanoparticles (SLNs) loaded with Famotidine were prepared using the hot emulsification method, where a mixture of glycerol monostearate (GMS) and span 20 (in a ratio of 3:1, w/w) was melted at approximately 60 °C, and Famotidine was added at a concentration of 2 mg/mL of the total volume, followed by the addition of a heated aqueous phase containing poloxamer at 4 mg/mL, and subsequent thorough mixing using a high-shear homogenizer (T25 Ultraturax, IKA) at 5,000 rpm for 5 minutes, and further sonication with a probe sonicator (Misonix) for an additional 5 minutes [14].

Measurement of the SLN size and ζ-potential:

At a controlled temperature of 25 °C, the comprehensive characterization of the Solid Lipid Nanoparticles (SLNs) was conducted using a state-of-the-art particle size analyzer (Delsa™ Nano C) to determine the particle size distribution, polydispersity index (PDI), and ζ-potential, providing valuable insights into the physical properties and stability of the SLNs [15].

Determination of the entrapment efficiency of famotidine in the SLN:

After preparing the Solid Lipid Nanoparticle (SLN) dispersion (1 mL), it was subjected to centrifugation at 13,000 rpm for 15 minutes. The supernatant obtained after centrifugation was collected, and the concentration of famotidine in the supernatant was quantified using a Beckman Coulter DU® 720 spectrophotometer at its maximum wavelength of 260 nm. The entrapped amount of famotidine in the SLN formulation was calculated to determine the entrapment efficiency using the following formula:

Entrapment efficiency (%) = [(Famotidine in feed - Famotidine in aqueous phase) / Famotidine in feed] × 100%

The results showed a significant increase in famotidine concentration when employing Solid Lipid Nanoparticles (SLN), indicating improved drug entrapment within the SLN formulation compared to the initial

feed solution.

Bioavailability of famotidine after oral administration

For the oral administration study, male Wistar rats weighing 250±20 g (provided by Institut Teknologi Bandung Animals Center) were used. The study was conducted with the approval of the Animal Ethics Committee at Institut Teknologi Bandung (Indonesia). Prior to the experiment, all rats were subjected to a 12-hour fasting period, but they were allowed free access to water during this time. The rats were then administered either famotidine suspension or famotidine-loaded Solid Lipid Nanoparticles (famotidine-SLN) at a dose of 40 mg/kg body weight once. Blood samples (0.3 mL) were collected via the caudal vein at predetermined time points: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post-administration. These blood samples were collected into heparinized tubes and subsequently centrifuged to obtain blood plasma. The collected plasma was stored at -20 °C until further analysis [16,17].

Quantification of famotidine plasma concentration

Famotidine plasma concentrations were determined using High-Performance Liquid Chromatography (HPLC) analysis. For each sample, a 0.1 mL plasma aliquot was combined with 0.2 mL of acetonitrile in a centrifuge tube. The mixture was thoroughly mixed on a vortex mixer and subsequently centrifuged. The supernatant containing famotidine was then quantified by HPLC (Agilent) equipped with a C18 column and UV detector (at a wavelength of 265 nm) [18].

To perform the analysis, an isocratic mobile phase consisting of 5% acetonitrile and 95% water was utilized, with a flow rate set at 1.0 mL/min. For each analysis, a 100 µL volume of the prepared sample was injected into the HPLC system. Calibration curves were generated using linear regression analysis within the concentration range of 100-800 ng/mL. Based on the calibration graph of famotidine, we accurately determined the concentration of famotidine in each plasma sample. This HPLC method allows for precise and reliable quantification of famotidine levels, providing essential data for the assessment of its pharmacokinetic properties and overall bioavailability [19].

Data analysis:

In this study, we employed a non-compartmental model to calculate the pharmacokinetic parameters of Famotidine. By analyzing the plasma concentration-time profiles, we directly determined the peak concentration (C_{max}) and the time of peak concentration (T_{max}). To calculate the area under the curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), we used the formula: $AUC_{0-\infty} = AUC_{0-t} + C_t/K_e$, where C_t represents the Famotidine concentration observed at the last time point, and K_e is the elimination rate constant. To analyze the data obtained from the release rate and pharmacokinetic parameters, we performed statistical analyses using one-way ANOVA and Student's t-test. These analyses enabled us to gain valuable insights into the drug's release behavior and pharmacokinetics, facilitating a comprehensive evaluation of the effectiveness of Solid Lipid Nanoparticles as a drug delivery system for enhancing the oral bioavailability of Famotidine [20].

RESULT AND DISCUSSION

The Solid Lipid Nanoparticles (SLN) containing famotidine exhibited a mean particle size of approximately 151.90 ± 26.05 nm with a neutral charge. The formulations containing span 20 and poloxamer 188 demonstrated a relatively small size distribution of 0.35 ± 0.04, presenting spherical particles (Fig. 2), and showcased a high entrapment efficiency of famotidine in the SLNs, reaching $82.30 \pm 4.39\%$.

Upon administration of a single dose of famotidine suspension and famotidine-SLN in rats, the oral concentration-time curve and pharmacokinetic parameters were compared (Fig. 3 and Table 1). Notably, the concentrations of famotidine in plasma were significantly higher in the rats treated with famotidine-SLN compared to the group treated with free famotidine suspension. The peak plasma concentration (Cmax) for famotidine suspension was 1.08 ± 0.19 µg/mL, while for famotidine-SLN, it was notably higher at 3.76 ± 1.08 µg/mL. The area under the concentration-time curve (AUC0-∞) for suspension and SLN were 0.34 ± 0.06 µg·hr/mL and 1.46 ± 0.17 µg·hr/mL, respectively. This represented a 3.5-fold increase in Cmax and a 4.3-fold increase in AUC0-∞ for famotidine-SLN compared to famotidine suspension. The statistical analysis of the pharmacokinetic data strongly suggested that SLN significantly improved the bioavailability of famotidine compared to famotidine suspension.

The enhanced absorption of famotidine through SLN can be attributed to potential mechanisms. Due to their nanosized range, SLNs may support the bioadhesion process to the gut wall, thereby prolonging their residence time and increasing the plasma concentration of the drug. Furthermore, the components of surfactants present in SLNs may contribute to enhancing the permeability of lipid particles through the intestinal membrane.

Overall, the findings of this study indicate that Solid Lipid Nanoparticles hold promise as an effective drug delivery system for enhancing the oral bioavailability of famotidine, presenting potential applications in improving the therapeutic efficacy of this poorly water-soluble drug.

Table 1 Pharmacokinetic parameters of famotidine after oral administration of famotidine suspension and SLN.

Parameters	Free Famotidine (Suspension)	Famotidine-SLN
Cmax (µg/mL)	1.08 ± 0.19	3.76 ± 1.08a
tmax (h)	1.87 ± 0.82	1.34 ± 0.43
t1/2el (h)	2.58 ± 0.46	2.37 ± 0.587
t1/2ab (h)	0.76 ± 0.64	0.66 ± 0.15
AUC0–∞ (µg.h/mL)	0.34 ± 0.06	1.46 ± 0.17a

a - Indicates statistical significance between Famotidine-SLN and Free Famotidine (Suspension) ($*p < 0.05$).

a.   b.
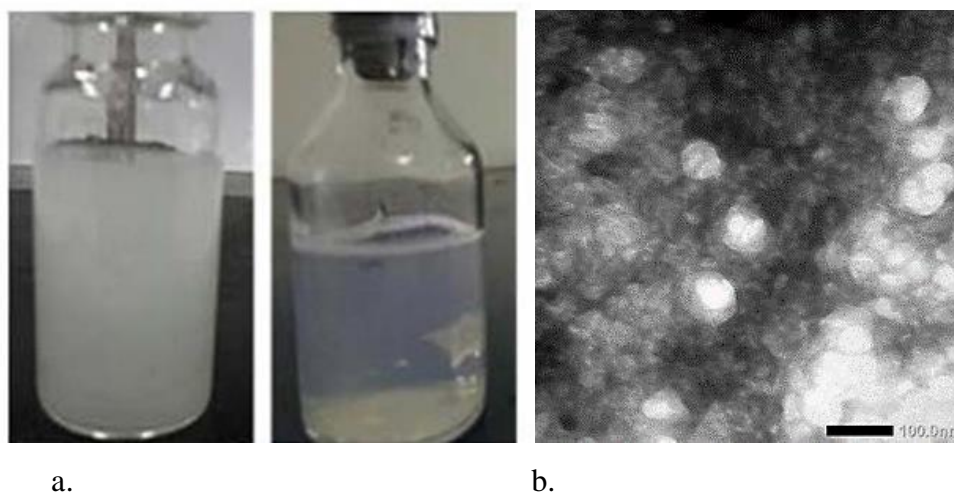
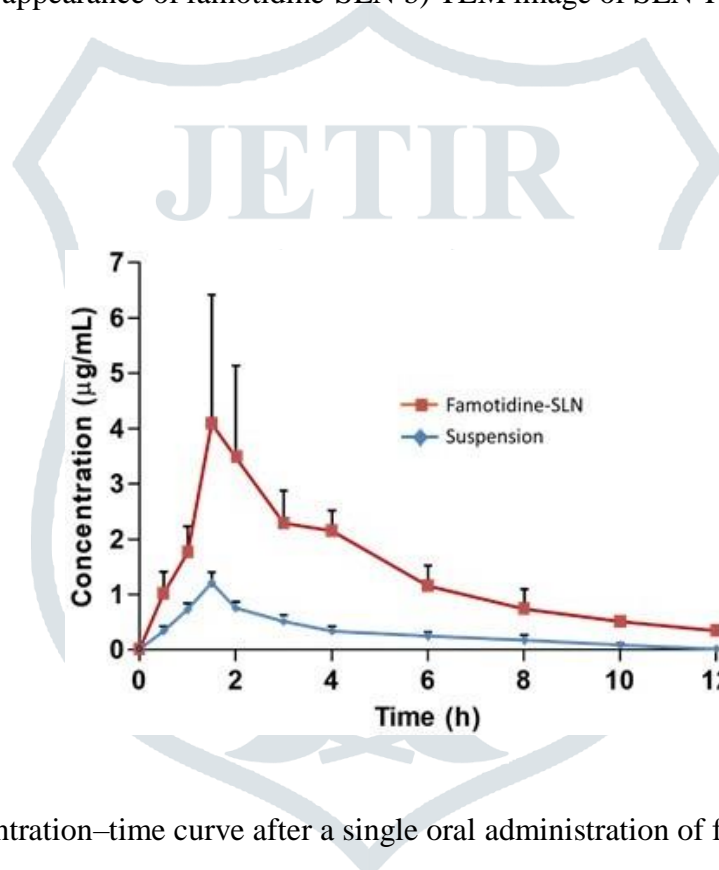Fig. 1 a) Physical appearance of famotidine-SLN b) TEM image of SLN-Famotidine at 100 nm.

Fig. 2 The mean concentration–time curve after a single oral administration of famotidine suspension and famotidine-SLN inrats (40 mg/kg). Data are the mean ± S.D (n = 6).

CONCLUSION

In our research, we successfully encapsulated the poorly permeable and aqueous-soluble drug, famotidine, within Solid Lipid Nanoparticles (SLN) using an ultrasonic-hot emulsification technique. Following this, an oral pharmacokinetic study was conducted in male rats, and the outcomes demonstrated a significant enhancement in the oral bioavailability of famotidine when administered in the form of SLN compared to a famotidine suspension. These findings indicate that SLNs hold great promise as a viable delivery system to improve the bioavailability of poorly soluble and permeable drugs, presenting potential benefits for enhancing therapeutic efficacy in clinical applications.

CONFLICT IF INTEREST

None

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