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Original Article

Fabrication and Characterization of Famotidine Solid Lipid Nanoparticles Using Hot Emulsification Method for Bioavailability Enhancement

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ABSTRACT

Objective: The objective of this paper was to fabricate and increase the effectiveness of the formulation of Solid lipid nanoparticle (SLN) on improving the oral bioavailability of Famotidine. **Methods:** In this study, ultrasonic-hot emulsification technology was used to manufacture Famotidine-SLN. Subsequently, the particle diameter, electrokinetic potential, and Encapsulation Efficiency of SLN were all determined during the characterization process. **Results:** The results showed that the average particle size of SLN containing Famotidine was prepared on average 151.90 ± 26.05nm and relatively small size distribution (0.35 ± 0.04). Famotidine- SLN had high entrapment efficiency in average 82.30 ± 4.39 %. Famotidine-SLN showed a 3.5-fold increase in C_{max} and a 4.3-fold increase in $AUC_{0-\infty}$ than free Famotidine suspension. **Conclusions:** SLN improved oral bioavailability of Famotidine significantly compared with Famotidine suspension. SLNs seem to offer a potential delivery strategy to increase the solubility and bioavailability and permeable medicines.

Keywords: Famotidine, Bioavailability, Solid lipid nanoparticle, Hot emulsification method, Oral absorption, Poorly aqueous-soluble drug

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INTRODUCTION

In recent years lipid-based techniques like Solid lipid nanoparticles (SLN), their capacity to carry and solubilize lipophilic medicines have attracted increased interest in therapeutic formulations.[1] SLNs have an average diameter of 50 to 1000nm, as assessed by photon correlation spectroscopy. SLNs are created from emulsions employed by substituting the lipids in liquid condition with lipids in the solid state for parenteral delivery.[2] SLNs are nerally physically stabilized by surfactants. Compared to polymeric nanoparticles, the main benefit is that SLNs may be generated utilizing High-pressure homogenization (HPH) procedures employed industrially to prepare emulsions.[3,4] Famotidine is widely used to treat active peptic or duodenal ulcer, gastroesophageal reflux, erosive esophagitis, and gastrointestinal hypersecretory.[5,6] Famotidine is a drug used primarily as a prokinetic that binds to an H2 blocker. Its molecular formula is $C_8H_{15}N_7O_2S_3$. It is a guanidine, a sulfonamide, and a component of the 1,3-thiazole family. It functions as an anti-ulcer medication, an antagonist of the H2-receptor, and a P450 antagonist.[7] Its chemical diagram is presented in Figure 1. The potential of Famotidine is known to be superior to ranitidine or cimetidine as a histamine antagonist.[8] Currently, Famotidine is available in the oral and intravenous dosage form. Regarding FDA guideline, oral Famotidine is only used for patients who suffer mild to moderate gastric acid secretion. However, patients who suffer severe gastrointestinal or ulcer hypersecretory only can be treated by intravenous Famotidine.

Famotidine given orally is unable to treat severe ulcers due to the very poor bioavailability. The poor bioavailability of Famotidine is due to some factors, such as the low Famotidine permeability on the gastrointestinal membrane and very low solubility in the intestinal pH environment.[9] To overcome these problems, some efforts have been reported, such as floating- bioadhesive tablet, cyclodextrin complexes.[10] Herein, we tried to develop a simple formulation of Solid Lipid Nanoparticle (SLN) containing Famotidine, which is expected to impact Famotidine's bioavailability substantially. We selected SLN as a carrier for Famotidine because SLN has been widely used because of their various advantages, such as the possibility of incorporation of hydrophilic or lipophilic drugs and simplicity of scale-up.[11]

MATERIALS AND METHODS

Materials

Torrent Pharma provided the Famotidine as a complimentary sample. All chemicals such as Glycerylmonostearate (GMS), Poloxamer 188, and Span 20, Tween 80 analytical grade have been used.

Methods

For the development of solid lipid nanoparticles, the hot emulsification procedure was applied. GMS and span 20 (2:1 w/w) mixtures were melted at approximately 50°C and added Famotidine (2 mg/mL of total volume). Water containing poloxamer (3 mg/mL) has been heated and added to a lipid mixture at about the same temperature. The lipid and aqueous phase were mixed by a high share homogenizer at 5,000 rpm for 5 min and then sonicated with a probe sonicator for 5 min.

Characterization of Famotidine SLN

Measuring the size of the SLN

With 25°C, a particle size analyzer evaluated the size and polydispersity index and SLN's potential.

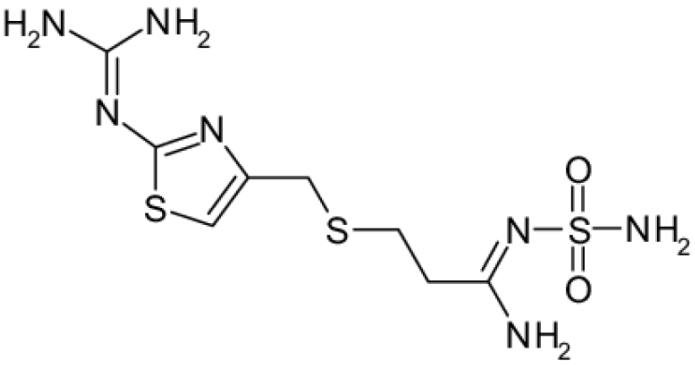

Figure 1: Chemical Structure of Famotidine.

Determination of the % Entrapment Efficacy of Famotidine in the SLN

After making the mixture of SLN, take 1mL from it and keep it to be centrifuged at 13,000 rpm for the next 15 minutes. After collecting the supernatant, the amount of Famotidine in the supernatant was quantified by Beckman Coulter spectrophotometer at the maximum wavelength (260nm). Entrapment efficiency was calculated as follows:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Famotidine in feed} - \text{Famotidine in the aqueous phase}}{\text{Famotidine increased s significantly by employing SLN}} = \text{Famotidine in feed} \times 100$$

Bioavailability of Famotidine after Oral Administration

Male Wistar rats weighing 250–200g were utilized in the oral administration trial. Animal studies were performed with the approval of the Animal Ethics Committee at OPJS University, India. Before the study, all the rats were kept without food for the next 12 hours and given water along with them continuously. Rats received Famotidine suspension or Famotidine- SLN at a dose of 40 mg/kg b.w orally once. The caudal blood (0.3 mL) was obtained at 0, 0.5, 1, 1, 5, 2, 3,4, 6, 8, 10 and 12 hours through the caudal vein. Samples of blood have been put in a heparinized microcentrifuge tube to obtain the plasma blood. After the plasma has been obtained from mice, it is kept at 20°C for centrifugation.

Quantification of the Plasma Levels of Famotidine

HPLC analysis was used to assess the plasma levels of Famotidine. A 0.1 mL plasma sample was added to a centrifuge tube, followed by 0.2 mL acetonitrile. The sample was mixed on a vortex mixer and then centrifuged. The amount of Famotidine supernatant was quantified by HPLC with a C18 column and UV detector (265nm). At a flow rate of 1.0 mL/min, we were using a mixture mobile phase consisting of 5% acetonitrile and 95% water. The ratio of mobile phase such as Acetonitrile: Methanol: Phosphoric Acid was used in 10: 10: 80. For analysis, a 100 mL aliquot of material was injected. Calibration curves in the range of 100-800 ng/mL were created using linear regression analysis. Regarding the calibration graph of Famotidine, we determined the concentration of Famotidine in the plasma sample.

Analysis of Data

For the determination of the pharmacokinetic parameters, a non-compartmental model was utilized. Plasma time profiles may be used to determine both maximum (or peak) serum concentration (C_{max}) and time of maximum concentration (T_{max}). From zero to infinity, the area under the curve (AUC) was calculated as:

$$\text{AUC} = \frac{(0)}{\lambda}$$

AUC refers to the area under the concentration-time curve, C(0) extrapolated plasma concentration at the time, λ appears to be the elimination rate constant. We used one-way ANOVA and the Student's *t*-test to analyses the overall release rate and pharmacokinetic profile data.

In vitro Drug Release of SLN

Drug releases through formulations with dialysis membrane were examined *in vitro*. For 12 hours before mounting in a spreading cell, the membrane was soaked in double-distilled water. SLN suspension (1mL) was inserted in a dialysis tube free from any unentrapped medication suspended from a 20mL phosphate buffer beaker (pH 7.4). The beaker content was swirled using a magneticstirrer at 37±20°C. To maintain a consistent volume in the receptor compartment, samples were taken and changed regularly with an equal amount of fresh elution solution. UV visible spectrometers set to 265nm were used to determine the drug content of the samples.

RESULTS

Size

The mean particle size of SLN containing Famotidine was prepared on average at 1.90 ± 26.05 nm with a neutral charge. The average size of SLN comprising Famotidine was neutrally produced at an average of 151.90 ± 26.05 nm.

Entrapment Efficiency

The SLN formulations, including span 20 with poloxamer 188, exhibited a narrow size distribution (0.35 ± 0.04), spherical particle shape shown in Figure 4, and high entrapment effectiveness Famotidine in SLN (82.30 ± 4.39 %).

Plasma Levels

Overall oral concentration-time graph and pharmacokinetic characteristics of Famotidine suspension with Famotidine-SLN in rats after a single dosage are shown in Table 1, respectively. Famotidine plasma concentrations were considerably greater at all periods in treated groups with Famotidine-SLN than in rats given with free Famotidine (suspension). Famotidine suspension had a peak plasma concentration (*Cmax*) of 1.08 ± 0.19 μg/mL and Famotidine-SLN had a peak plasma concentration (C_{max}) of 3.76 ± 1.01 μg/mL, respectively. AUC0–∞ for suspension was 0.34 ± 0.06 μg·hr/mL whereas for SLN was 1.46 ± 0.16 μg·hr/mL. Famotidine-SLN showed a 3.2-fold increase in *Cmax* and a 4.2-fold increase in $AUC_{0-\infty}$ compared to Famotidine suspension 0.32 ± 0.05.

Bioavailability

We may conclude from statistical analysis of the pharmacokinetic data that SLN considerably increased its bioavailability compared to a Famotidine suspension. There are possible mechanisms that SLN improved absorption of Famotidine. Because SLN has a nanosized range, it could support the bioadhesion process to the gut wall, increasing their residence time, thereby increasing the plasma concentration of the drug.[12] Moreover, a component of surfactants may contribute to enhancing the permeability of lipid particles into the intestinal membrane.

Drug-to-Excipient Interactions

To check out any potential drug-polymer interactions, an FTIR investigation was conducted. Pure drug and pure individual polymer peaks were compared to mixes of the same, and any substantial displacement of the band was observed as an indication of interaction. FTIR spectroscopy

Table 1: After giving Famotidine suspension and SLN by mouth its parameters[1].

Parameters	Free Famotidine (suspension)	Famotidine- SLN
C_{max} (µg/mL)	1.07 ± 0.18	3.76 ± 1.01
t_{max} (h)	1.87 ± 0.82	1.34 ± 0.41
$t_{1/2}$ (h)	2.57 ± 0.45	2.36 ± 0.585
$t_{1/2}$ (h)	0.75 ± 0.64	0.65 ± 0.16
$AUC_{0-\infty}$ (µg.h/mL)	0.32 ± 0.05	1.46 ± 0.16

The values are Mean ±SD

1 Compared with Famotidine suspension at $p < 0.001$, 'B' denotes formulation code

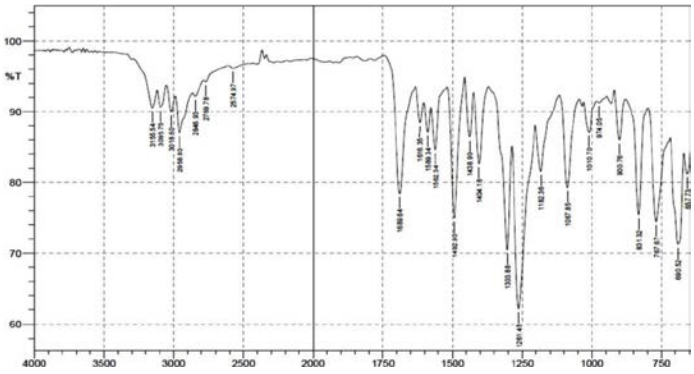

Figure 3: FTIR raw spectra of Famotidine.

Table 2: *In vitro* drug release of FTD.

		Cumulative drug released (%)				
S. No.	Time	B1	B2	B3	B4	B5
1	0	0	0	0	0	0
2	1	11.92	10.22	9.45	9.13	9.03
3	2	24.59	20.56	20.22	16.82	15.24
4	3	37.43	30.56	28.66	23.22	21.55
5	4	46.86	42.34	38.24	31.12	29.62
6	5	57.83	53.12	46.15	38.18	32.53
7	6	65.81	61.10	52.58	44.97	41.88
8	7	75.53	68.94	61.86	52.86	46.97
9	8	83.12	76.35	70.15	59.15	51.87
10	9	87.98	81.89	76.26	65.29	57.98
11	10	92.25	88.16	82.38	70.88	63.79
12	12	98.23	94.14	88.37	78.80	71.97

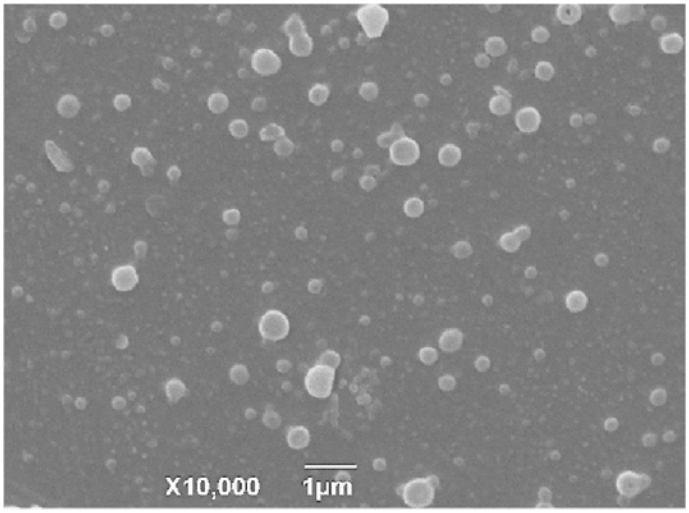

Figure 4: TEM image of SLN-Famotidine.

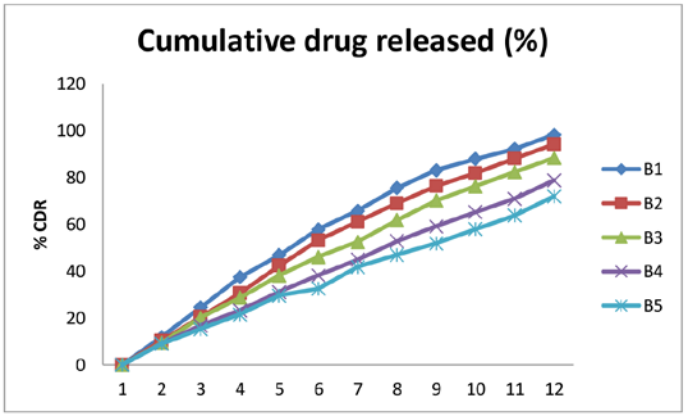

Figure 2: cumulative % drug releases B1-B5.

was used to observe the drug interaction with the excipients.[13] Figure 3 shows the prominent peaks of C=C at 1303cm^{-1}, C-H at 1261 cm^{-1}, C=S at 1142, and N-H at 982 cm^{-1} in both of the non-processed FTDs.

Surface Morphology

The formulation's structure and surface morphology were investigated using transmission electron microscopy (TEM). TEM investigation indicated that the shaped particles with well-defined perimeter were solid and reasonably spherical. Figure 4 showed the particle size in the nanometric range.

In vitro Drug Release Study

Cumulative percentage of B1-B5 drug releases indicated 98.21%, 93.13%, 86.32%, 76.86%, and 70.92% in Table 2 and Figure 2 the *in vitro* 12-hr experiment. The moment when FTD was released was directly linked to the pharmacological payload. Further examination into the utilization of the drug-releasing statistics in distinct kinetic models revealed that SLN formulations loaded via FTD were followed by 0.928–0.982 zero-order release kinetics.

DISCUSSION

For the manufacture of FTD loaded SLNs, Hot evaporation technique (HET) was utilized. All the chemicals like Stearophanic acid (1g), Polysorbate-80 (1.2 ml), Polyvinylpyrrolidone (0.3g) are mixed in a vessel and put the mixture in a magnetic stirrer for around 15 min and then optimized for the unloaded SLNs showed in Table 1. By increasing the amount of surfactant such as Tween-80 reduces the average diameter and enhanced the stability of tiny lipid droplets of Famotididne SLNs.[14]

The formulation (B4) exhibits the highest drug loading capacity and the highest encapsulation. The binding capacity of the drug with lipids plays

an essential role in encapsulation. Formulation code B4 exhibits an excellent binding capacity with lipids, thereby increasing the loading capacity of the formulation. [15]

FTIR raw FTD spectrum confirms that FTD is compatible with formulation elements shown in Figure 3. Further validated nanometric particle size FTD loaded using transmission electron microscopy. Solid, identical, and reasonably round nanoparticles with a defined diameter are seen using a TEM micrograph. Most SLNs are scattered in shape and have a homogenous distribution that displays the amorphous nature of nanoparticles created.

DSC analysis demonstrate the amorphous structure of the loaded SLNs of FTD, as the sharp peak of the melting point was 166.6°C for Famotidine without polymer, but the SLN formulation loaded for FTDs with excipients was 160°C.[16] SLNs enhances oral absorption. It also exhibits good bioavailability when given through the parenteral route, which is required additional research.

In vitro studies have shown that a higher FTD payload leads to a delayed time to release drugs. FTD releases from SLNs followed the kinetics of zero order. Significant observations from the statistically evaluated data on *in vitro* pharmacokinetics indicated increased oral bioavailability with a long-term FTD-SLN release profile (B1-B5) shown in Table 2. Results indicated that bigger particles displayed slower releases than smaller ones. The higher surface area of tiny particles might contribute to the quicker release of medicines. The medication release generally followed a consistent pattern from all formulations. Drug release may primarily be regulated via the lipid matrix via drug diffusion.[10] SLNs drug delivery system are accessible to the market in the formulation of existing medications (BCS-II and BCS-IV) that increase their oral bioavailability and provide sustainable release behaviour.

CONCLUSION

The medication Famotidine, which has low permeability and is insoluble in water, was effectively integrated into SLN using an ultrasonic-hot emulsification methodology in our investigation. An oral pharmacokinetic investigation in male rats shown that SLN increased the oral bioavailability of medicines with low solubility and permeability. Famotidine was shown to be substantially more effective than Famotidine suspension. SLNs seem to be a potential delivery strategy for increasing the bioavailability of medicines with low solubility and permeability.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

GMS: Glyceryl monostearate; **FTD:** Famotidine; **FTIR:** Fourier-transform infrared spectroscopy; **HET:** Hot evaporation technique. **PVP:** Polyvinylpyrrolidone.

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