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Solid Lipid Nanoparticle Improves Oral Bioavailability of Famotidine

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Abstract:

Objectives

The aim of this research was to investigate effectivity of our simple formulation of solid lipid nanoparticle (SLN) on improving oral bioavailability of famotidine.

***Methods*:** In this study, famotidine-SLN was prepared by combination high speed homogenization and ultrasonic-hot emulsification technique. Subsequently, characterization of SLN was determined regarding particle size, zeta potential, and entrapment efficiency analysis. Bioavailability of famotidine with doses of 40 mg/kg BW was evaluated to male Wistar rat per orally.

***Results*:** The results showed that the mean particle size of SLN containing famotidine were prepared in average 151,90 ± 26,05 nm and a relatively small size distribution (0,35 ± 0,04). Famotidine-SLN had a high entrapment efficiency in average 82,30 ± 4,39 %. Famotidine-SLN showed 3.5-fold increase in C_{max} and 4.3-fold increase in $AUC_{0-\infty}$ compared to free famotidine (suspension).

***Conclusions*:** SLN improved oral bioavailability of famotidine significantly compared with famotidine suspension. It appears that SLNs offer a promising delivery system for the improvement of bioavailability of poorly soluble and permeability drugs.

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

INTRODUCTION

Famotidine is widely used to treat active peptic or duodenal ulcer, gastroesophageal reflux, erosive esophagitis, and gastrointestinal hypersecretory [1, 2]. The potential of famotidine is known to be superior to ranitidine or cimetidine as a histamine antagonist [2, 3]. Currently, famotidine is available in 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 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 [2]. The poor bioavailability of famotidine is due some factors, such as the low famotidine permeability on the gastrointestinal membrane [4] and very low solubility in intestinal pH environment [5]. To overcome these problems, some efforts have been reported, such as floating- bioadhesive tablet [6], cyclodextrin complexes [7]. Herein, we tried to develop a simple formulation of solid lipid nanoparticle (SLN) containing famotidine which is expected stronger impact on bioavailability of famotidine. We selected SLN as a carrier for famotidine because SLN has been widely used because of their various advantages, such as possibility of incorporation of hydrophilic or lipophilic drugs and simplicity of scale-up [8]. We established preparation procedure of SLN containing famotidine (Fig. 1) and examined oral bioavailability of famotidine in male Wistar rats. Our result showed that oral bioavailability of famotidine increased significantly by employing SLN.

MATERIALS AND METHODS

Glyceryl monostearate (GMS), Poloxamer 188, and Span 20 were purchased from BASF. Famotidine was purchased from Kimia Farma (Indonesia).

Preparation of Famotidine-SLN:

Solid lipid nanoparticles (SLN) were prepared by hot emulsification method. GMS and span 20 (3:1 w/w) mixture were melted at approximately 60 °C and added famotidine (2 mg/mL of total volume). Water containing poloxamer (4 mg/mL) was heated at approximately the same temperature and transferred to melted lipid mixture. The lipid and aqueous phase were mixed by high share homogenizer (T25 Ultraturax, IKA) at 5,000 rpm for 5 min, then sonicated with a probe sonicator (Misonix) for 5 min.

Measurement of the SLN size and ζ-potential:

The size, polydispersity index, and ζ-potential of SLN were measured with a particle sizeanalyzer (Delsa™ Nano C) at 25 °C.

Determination of the entrapment efficiency of famotidine in the SLN:

SLN dispersion (1 mL) were centrifuged at 13,000 rpm for 15 min. After collecting the supernatant, the amount of famotidine in supernatant was quantified by Beckman Coulter DU® 720 spectrophotometer at maximum wavelength (260 nm). Entrapment efficiency was defined as follows:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Famotidine in feed} - \text{Famotidine in aqueous phase}}{\text{Famotidine in feed}} \times 100\%$$

Bioavailability of famotidine after oral administration:
Male Wistar rats with body 250±20 g (provided by Institut Teknologi Bandung Animals Center) were used for the oral administration study. Animal studies were performed with the approval of the Animal Ethics Committee at Institut Teknologi Bandung (Indonesia). Before the experiment, all the rats were fasted for 12 h but had free access to water. Rats received orally famotidine suspension or famotidine-SLN at a dose of 40 mg/kg b.w. once. Blood (0.3 mL) was collected via the caudal vein at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h. Blood samples were placed into heparinized tubes and centrifuged to collect blood plasma. After centrifugation, the plasma obtained was stored at -20 °C until analysis.

Quantification of famotidine plasma concentration:
Famotidine plasma concentrations were determined by HPLC analysis. A 0.1 mL plasma sample were placed into a centrifuge tube and then 0.2 mL acetonitrile was added. The sample were mixed on a vortex mixer and then centrifuged. The amount of famotidine supernatant was quantified by HPLC (Agilent) with a C18 column and UV detector (265 nm). By using an isocratic mobile phase which were consisted of 5% of acetonitrile and 95% of water with a flow rate of 1.0 mL/min. A 100 µL aliquot of sample was injected for analysis. Calibration curves were prepared by linear regression analysis in the range of 100-800 ng/mL. Regarding the calibration graph of famotidine, we determined the concentration of famotidine in plasma sample.

Data analysis:
We calculated the pharmacokinetic parameters based on a non-compartmental model. By usingplasma concentration–time profiles, we could obtain the value of peak concentration (C_{max}) and time of peak concentration (T_{max}) directly. The area under curve (AUC) from time zero to infinitywas calculated by: $AUC_{0-\infty} = AUC_{0-t} + C_t/K_e$, where C_t is the famotidine concentration observed at last time, and K_e is the elimination rate constant. The data obtained from the release rate and pharmacokinetic parameters were analyzed statistically by one-way ANOVA and Student'st-test.

RESULT AND DISCUSSION

The mean particle size of SLN containing famotidine were prepared in average 151,90 ± 26,05 nm with neutral charge. The SLN formulations containing span 20 and polaxamer 188 showed a relatively small size distribution (0,35 ± 0,04), spherical particle (Fig.2) and has a high entrapment efficiency of famotidine in SLN (82,30 ± 4,39 %).
The oral concentration–time curve and pharmacokinetic parameters after a single dose of famotidine suspension and famotidine-SLN form in rats are shown in Fig. 3 and Table 1, respectively. At all-time points, concentrations of famotidine in plasma were significantly higher in rats treated with famotidine-SLN than treated free famotidine (suspension) group. Peak plasma concentration (C_{max}) for famotidine suspension and famotidine-SLN was 1,08 ± 0,19 µg/mL and 3,76 ± 1,08 µg/mL, respectively. $AUC_{0-\infty}$ for suspension was 0,34 ± 0,06 µg·hr/mL whereas for SLN was 1,46 ± 0,17 µg·hr/mL. Famotidine-SLN showed 3.5-fold increase in C_{max} and 4.3-fold increase in $AUC_{0-\infty}$ compared to famotidine suspension. According to statistical analysis of pharmacokinetic data, we can conclude that SLN improved the bioavailability of famotidine significantly compared with a famotidine suspension.
There are possible mechanisms that SLN improved absorption of famotidine. Because SLN has nanosized range, it could support bioadhesion process to gut wall thus increasing their residence time thereby increasing plasma concentration of drug [9, 10]. Moreover, component of surfactants may have contribution to enhance permeability of lipid particles into the intestinal membrane [11, 12].

Table 1 Pharmacokinetic parameters of famotidine after oral administration of famotidine suspension and SLN. Data are the mean ± S.D (n = 6).

Parameters	Free famotidine (suspension)	Famotidine-SLN
Cmax (µg/mL)	1.08 ± 0.19	3.76 ± 1.08[a]
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
$AUC_{0-\infty}$ (µg.h/mL)	0.34 ± 0.06	1.46 ± 0.17[a]

a. ***, $p < 0.001$ compared with famotidine suspension.

Fig. 1 Physical appearance of famotidine-SLN

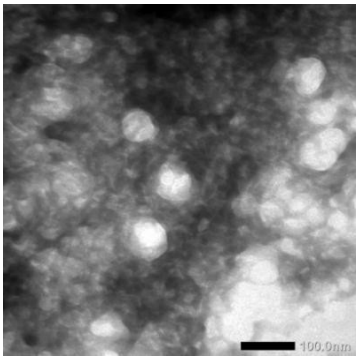

Fig. 2 TEM image of SLN-Famotidine. Scale bar: 100 nm.

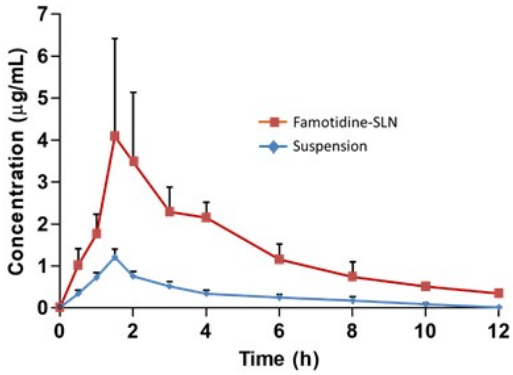

Fig. 3 The mean concentration–time curve after a single oral administration of famotidine suspension and famotidine-SLN in rats (40 mg/kg). Data are the mean ± S.D (n = 6).

CONCLUSION

In our study, a poorly permeability and aqueous-soluble drug famotidine was successfully incorporated into SLN by an ultrasonic-hot emulsification technique. An oral pharmacokinetic study was conducted in male rats and the results showed that SLN improved oral bioavailability of famotidine significantly compared with famotidine suspension. It appears that SLNs offer a promising delivery system for the improvement of bioavailability of poorly soluble and permeability drugs.

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