Research Article

Pharmacodynamics and Pharmacokinetics Evaluation of Ranitidine Microemulsion on Experimental Animals

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Ranitidine microemulsion was investigated for its pharmacodynamic and pharmacokinetic evaluation to find out the suitability of microemulsion as a potential drug delivery system in the treatment of ulcer. The bioavailability of ranitidine after oral administration is about 50% and is absorbed *via* the small intestine; this may be due to low intestinal permeability. Hence the aim of present investigation was to maximize the therapeutic efficacy of ranitidine by developing microemulsion to increase the intestinal permeability as well as bioavailability. A ground nut oil based microemulsion formulation with Tween-80 as surfactant and PEG-400 as cosurfactant was developed for oral delivery of ranitidine and characterized for physicochemical parameters. In pharmacodynamic studies, significant ($P < 0.05$) variation in parameters estimated was found between the treated and control groups. Ranitidine microemulsion exhibited higher absorption and $C_{\max}$ (863.20 ng-h/mL) than the standard (442.20 ng/mL). It was found that AUC_{0-24} hr obtained from the optimized ranitidine test formulation (5426.5 ng-h/mL) was significantly higher than the standard ranitidine (3920.4 ng-h/mL). The bioavailability of optimized formulation was about 1.4-fold higher than that of standard drug. This enhanced bioavailability of ranitidine microemulsion may be used as an effective and alternative drug delivery system for the antiulcer therapy.

1. Introduction

Gastric ulcer is said to occur due to an imbalance between luminal acid synthesis and mucosal defense. Acid and pepsin components constitute the aggressive factors, and the mucous layer of mucin-bicarbonate secretion, prostaglandins, and other healing factors constitute the defensive factors [1]. The mucosal defense against these aggressive factors includes the function of the mucus-bicarbonate barrier, surface active phospholipids, prostaglandin, mucosal blood flow, cell renewal and migration, antioxidative enzymes, and some growth factors.

Even though wide range of drugs available for the treatment of ulcer may do not fulfill the requirements and have many side effects such as arrhythmias, impotence and

hemopoietic changes are noted. H_2 antagonists, unlike anticholinergics, do not delay gastric emptying time which may reflexly stimulate gastric secretion because of food remaining in the stomach for long time. Also it does not cause abdominal colic and diarrhoea caused by proton pump inhibitors. In recent years large advance in chemical and pharmacological studies has contributed to the knowledge about new therapeutically active compounds and control drug delivery systems for peptic ulcer. Out of the available category of drugs for the treatment of ulcer, H_2 antagonist's class of drugs like famotidine and ranitidine is considered to be the safest drugs available [2].

Ranitidine (*N*-[2-[[5-[(dimethylamino)methyl]-2-furyl]methyl]thio]ethyl)-*N*-methyl-2-nitro-1,1-ethylenediamine) is a selective and competitive histamine H_2 -receptor

antagonist with an extensive clinical history in the treatment of gastric and duodenal ulcers, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome.

The bioavailability of ranitidine after oral administration is about 50% and is absorbed *via* the small intestine [3]; this may be due to low intestinal permeability. The extent of drug release is also shorter which requires repeated dose administration that leads to increased adverse effect. In order to overcome these problems an attempt was made to develop microemulsion drug delivery system for ranitidine.

2. Materials and Methods

2.1. Chemicals. Ranitidine USP was obtained from SMS Pharmaceuticals Pvt. Ltd. (Hyderabad, India) as free gift sample. PEG-400 was purchased from BD Pharmaceuticals Ltd. (Kolkata, India), and Tween-80 was purchased from Merck Specialties Pvt. Ltd. (Mumbai, India). All other chemicals used in this study were obtained commercially and were of analytical (AR) grade.

2.2. Preparation and Characterization of Formulations. A ground nut oil based microemulsion formulation was developed with Tween-80 as surfactant and PEG-400 as cosurfactant. Microemulsion was prepared by using phase titration method keeping constant weight ratio of surfactant/cosurfactant (i.e., $K_m = 2:1$). Drug loaded microemulsion system (R-1) was prepared by dissolving ranitidine (150 mg/mL) in water by gentle heating and drug solution (1.4 mL) was precisely added drop by drop to the oily phases with magnetic stirring at ambient temperature. After the resulting systems were equilibrated with gentle magnetic stirring, they were ultrasonicated.

Droplet size distribution of optimized microemulsion was determined by photon correlation spectroscopy, using a Delsa Nano-C (Beckman Coulter Instruments) based on light scattering phenomenon, which analyzes the fluctuations in light scattering. Light scattering was monitored at 25°C at a scattering angle of 90°. Electrophoretic mobility ($\mu\text{m/s}$) was measured using small volume disposable zeta cell and converted to zeta potential by in-built software using Helmholtz-Smoluchowski equation. The percentage transmittance of samples was measured at 650 and 400 nm with distilled water taken as blank and three replicates were performed for each sample. The pH values of the microemulsion were measured by a pH meter (Digital Systronics, Mumbai, India) at ambient temperature with glass electrode. The viscosity measurement of the prepared microemulsion was performed using Brookfield's viscometer (Brookfield LVDV-II + pro viscometer) at single mode using spindle # CPE41 at $32 \pm 0.5^\circ\text{C}$. All aspects of testing were controlled using Rheocalc Software.

2.3. Thermodynamic Stability Studies. To overcome the problem of metastable formulation, thermodynamic stability tests were performed. Selected formulations were centrifuged at 3000 rpm for 30 min. Those formulations that did not show any phase separation were taken for the heating and cooling

cycle at temperature of 2°C, 25°C, and 50°C for 3 months as well as for 6 months. After 6 months of storage, the formulation (R-1) was subjected to test for phase separation, percentage transmittance, % cumulative drug release, and drug precipitation.

2.4. Animals. Swiss albino rats weighing 150–200 g of either sex were used for this experiment and were selected at random from animal house of the Pinnacle Biomedical Research Institute (PBRI), Bhopal. Institutional animal ethics committee approved the experimental protocol; animals were maintained under standard conditions in an animal house approved by committee for the purpose of control and supervision on experiments on animals (CPCSEA). All animal experiments were approved by Institutional Animal Ethics Committee (IAEC) of PBRI (Regd. no. 1283/C/09/CPCSEA) with protocol approval reference number PBRI/IAEC/11/PN-144. The animals were housed in polypropylene cages and maintained at $24^\circ\text{C} \pm 2^\circ\text{C}$ under 12 h light/dark cycle, were feed *ad libitum* with standard pellet diet (Golden Feed, New Delhi), and had free access to water.

2.5. Ethanol-Induced Ulcer Model. Swiss Albino rats of either sex weighing 150–200 g were divided into three groups with each group consisting of six animals. The animals were fasted for 24 h with free access water. Group I served as normal control, in which normal saline was administered orally; Group II received ranitidine 20 mg/kg orally and it was considered as standard; Group III served as ranitidine formulation group and the dose equivalent to ranitidine 20 mg/kg was administered. Animals were given test drugs or standard drug. One hour later, 1 mL/200 g of 99.80% alcohol was administered orally to each animal. The animals were anaesthetized 1 h later with ether, the stomach was incised along the greater curvature, and ulceration was scored. The number of ulcers and the length of each ulcer were measured. Ulcer index was calculated using severity scores and average number of ulcers per animal [4].

2.6. Statistical Analysis. Data are presented as mean $\pm$ SEM (standard error of the mean) and n represents the number of rats used for a particular experiment. Comparisons were made between treated and control groups using one-way analysis of variance (ANOVA) followed by Dunnett's test and significance of difference was accepted at $P < 0.05$.

2.7. Pharmacokinetics Study. All animal procedures were performed in accordance with protocols reviewed and approved by the Committee for the Purpose of Control and Supervision on Experimental Animals (CPCSEA).

The pharmacokinetic study of the microemulsion containing ranitidine was conducted in New Zealand rabbits weighing 2.5–3.0 Kg. The rabbits have been chosen as the model for study because there have been many bioavailability studies done using this animal model. The rabbits were housed individually with free access to food and water. A 12 h light/12 h dark cycle was held to keep a normal circadian rhythm in the animals.

Six rabbits were divided into three groups and fasted for 24 hours. Control batch was fed with normal saline, test batch was fed with 20 mg/kg ranitidine (pure drug), and the test batch was given the formulation equivalent to 20 mg/kg of drug. Water was given *ad libitum* during fasting and throughout the experiment. The blood samples (approximately 300–400 μ L) were collected from the marginal ear vein of the rabbits using heparinized needle (20–24 in size) at predetermined time intervals, specifically at 0.5, 2, 6, 8, 10, 12, and 24 hours after oral administration.

The heparinized blood samples were immediately collected in centrifugation tubes (5 mL) and centrifuged at 20000 rpm at 0°C for 15 minutes. Supernatant layer of plasma was separated into another centrifugation tube and stored at –20°C until analysis [5].

2.8. LC-MS/MS Instrument. The 1200 Series HPLC system (Agilent Technologies, Waldbronn, Germany) was used. Mass spectrometric detection was performed on an API 3200 triple-quadrupole instrument (Applied Biosystems/MDS SCIEX, Toronto, Canada). Data processing was performed on Analyst 1.4.2 software package (SCIEX) [6].

2.9. Chromatographic Method Conditions. Agilent Zorbax SB-CN (50 mm $\times$ 2.1 mm I.D., 5 microns) was selected as the analytical column. The mobile phase was composed of methanol : 20 mM ammonium acetate (55 : 45, v/v). The flow rate of the mobile phase was set at 0.6 mL/min and the injection volume was 10 μ L. The column temperature was set at 20°C. The retention times of ranitidine were found to be approximately 0.91 $\pm$ 0.12 min.

2.10. Sample Preparation/Extraction Procedure. An aliquot 50 μ L plasma was used for analysis. All samples and standards were made slightly acidic by addition of 10 μ L of 0.1 M aqueous ammonium acetate (pH 6) and were extracted into 3 mL of ethyl acetate. The extraction tubes were shaken at high speed for 5 min followed by centrifugation at 6000 rpm for 5 min. The organic phase was transferred to clean glass tubes and evaporated to dryness in a 45°C water bath under a nitrogen stream. The samples were reconstituted within 200 μ L of mobile phase and vortexed for 30 sec. After transfer into glass inserts of autosampler vials, an aliquot of 10 μ L of each sample was injected onto the LC-MS/MS system [7].

2.11. Pharmacokinetic Data Analysis. After oral administration of the microemulsion and standard drug, plasma samples were analyzed by LC-MS/MS for their ranitidine content. A curve of cumulative drug absorbed versus time curved from 0 to 24 hours was plotted to calculate the area under curve (AUC). Other pharmacokinetic parameters, that is, peak plasma level (C_{max}) and time to reach peak plasma level (T_{max}), were obtained after analysis of the individual time-plasma concentrations.

TABLE 1: Composition of ranitidine microemulsion.

Ingredients (by wt)	Ranitidine microemulsion (R-1)
Ranitidine (mg/mL)	150
Ground nut oil	6.67
Smix (Tween-80 : PEG 400)	60.00
Water	33.33

3. Results and Discussions

3.1. Physicochemical Characterization of Formulation. Microemulsion formulations (nine batches) containing ground nut oil as an oil phase were prepared at Tween-80 and PEG 400 fixed Smix ratios of 2:1 (Table 1). All formulations were prepared and characterized for the various physicochemical parameters (Table 2). The narrow globule size range of 16.2 ± 1 nm and polydispersity index 0.135 ± 0.017 for R-1 indicated that the microemulsion approached a monodispersed stable system and could deliver the drug effectively owing to larger surface area. The presence of zeta potential to the tune of -3.02 ± 0.18 mV on the globules of R-1 conferred physical stability to the system. The microemulsions were expected to have good physical stability (phase separation) as zeta potential is less than –30 to –40 mV [8–10]. A percentage transmittance of 98.2% for R-1 indicated clear dispersion. The pH of the optimized ranitidine microemulsion was found to be 7.32 ± 1.12 , approximating the normal blood pH (7.4).

It was observed that the viscosity of the microemulsion formulation generally was very low (65.38 ± 0.982 cp). This was expected, because one of the characteristics of microemulsion formulations is of lower viscosity [11–13]. Low viscosity value of R-1 ensures easy handling, packing, and hassle-free oral administration of formulations.

In stability studies, formulation R-1 was found to be stable for 3 months at intermediate and accelerated conditions and 6 months at long-term conditions. There was no significant change in % transmittance, % cumulative drug release of the resultant microemulsions. Furthermore, the formulations were found to show no phase separation, drug precipitation, thus substantiating the stability of formulations for 6 months (Table 3).

3.2. Antiulcer Activity. Ethanol is considered a risk factor for developing gastric ulcers. It readily penetrates the gastric mucosa due to its ability to solubilize the protective mucous and expose the mucosa to the proteolytic and hydrolytic actions of hydrochloric acid and pepsin, causing damage to the membrane [14]. The ulcer index in ethanol-induced control animals was $UI = 13 \pm 1.0$. The reduction in ulcer index was observed in standard ($UI = 5 \pm 0.63$) and in test formulation ($UI = 2.5 \pm 0.92$) was significant ($P < 0.05$) when compared to control. Similarly, ranitidine formulation has significantly reduced mucosal damage (80.77%) as compared to standard ranitidine (61.54%) induced by ethanol, which suggests that ranitidine formulation strengthens and protects the gastric mucosal barrier (Table 4, Figures 1 and 2).

TABLE 2: Characterization parameters of optimized microemulsion ($n = 3$).

Formulation	pH	Globule size (nm) $\pm$ SEM	PDI $\pm$ SEM	Zeta potential (mV) $\pm$ SEM	Viscosity (cp)	Percentage transmittance
R-1	7.32 $\pm$ 1.12	16.2 $\pm$ 1	0.135 $\pm$ 0.017	-3.02 $\pm$ 0.18	65.38 $\pm$ 0.982	98.2

TABLE 3: Thermodynamic stability studies of selected ranitidine microemulsion.

Formulation	Variables	Phase separation		% transmittance		% CDR		Drug precipitation	
		After 3 months	After 6 months	After 3 months	After 6 months	After 3 months	After 6 months	After 3 months	After 6 months
R-1	2-8°C	No	No	87.4	87.2	94.40 $\pm$ 1.32	94.37 $\pm$ 1.24	Absent	Absent
	25 $\pm$ 2°C	No	No	88.6	88.1	94.35 $\pm$ 1.45	94.32 $\pm$ 1.62	Absent	Absent
	50 $\pm$ 2°C	No	No	88.4	88.7	94.19 $\pm$ 1.29	94.12 $\pm$ 1.34	Absent	Absent

FIGURE 1: Percentage ulcer protection by standard drug and microemulsion formulation in ethanol-induced gastric ulcer.

TABLE 4: Antiulcer activity of ranitidine formulation on ethanol induced gastric ulcer in rats.

Groups	Induction	Dose [#]	Ulcer index	% protection
Group I	Normal saline	10	13 $\pm$ 1.0	—
Group II	Ranitidine	20	5 $\pm$ 0.63	61.54***
Group III	Formulation	20	2.5 $\pm$ 0.92	80.77***

[#] mL/kg or mg/kg; values are mean $\pm$ SEM; $n = 6$; *** $P < 0.05$ versus control.

3.3. Pharmacokinetic Studies. The pharmacokinetic study was performed to quantify ranitidine, after oral administration of test formulation (R-1). The plasma concentration-time profiles of the drug in male New Zealand albino rabbits following oral administration of the microemulsion formulation and standard drugs were compared.

Figure 3 shows mean plasma concentration-time curve of ranitidine after a single oral administration of standard drug and test formulation. The results of pharmacokinetic study are presented in Tables 5 and 6. The microemulsion (R-1) demonstrated a longer T_{max} (4.5 hr) compared with standard drugs (1.8 hr) and sustained the release of drugs over 24 hrs because the drug needs to be released out from the oil phase thereby resulting in a delayed T_{max} [15]. Ranitidine microemulsion exhibited the higher absorption and C_{max} achieved from the optimized ranitidine

Control treated

(a)

Standard treated

(b)

Formulation treated

(c)

FIGURE 2: Photographs of stomach: ethanol-induced gastric ulcers in different groups of treated rats.

formulation (863.20 ng·h/mL) was higher than the standard (442.20 ng/mL).

Area under the curve (AUC) for microemulsion showed almost a 1.4-fold increment from AUC generated after administering standard ranitidine solution indicating a significant enhancement of ranitidine's bioavailability when given orally as microemulsions [16]. It was found that AUC_{0-24} hr obtained from the optimized ranitidine test formulation (5426.5 ng·h/mL) was significantly higher than the standard

FIGURE 3: Comparison of pharmacokinetic profiles of standard drug and oral microemulsion of ranitidine (R-1).

TABLE 5: Results of pharmacokinetics study on standard ranitidine and test formulation.

Time (hr)	Plasma concentration (ng/mL)	
	Ranitidine standard	Ranitidine test (R-1)
0.00	0.000	0.000
0.50	66.20	74.30
2.00	442.20	863.20
6.00	326.00	638.60
8.00	223.40	196.80
10.00	106.40	106.20
12.00	89.70	49.20
24.00	62.10	18.70

TABLE 6: Pharmacokinetic data of standard ranitidine and test formulation.

Pharmacokinetic parameters	Ranitidine standard	Ranitidine test (R-1)
AUC ₍₀₋₂₄₎ (ng·h/mL)	3920.4	5426.50
C _{max} (ng/mL)	442.20	863.20
T _{max} (hr)	1.800	4.500

ranitidine (3920.4 ng·h/mL). The significant differences of the factors leading to drug absorption in vivo between the microemulsion preparation and standard drug were probably attributed to the following.

Ranitidine belongs to BCS class III drug; the oral absorption as well as the bioavailability of the drug is mainly limited due to low intestinal permeability. The surfactant and cosurfactant (Tween-80 and PEG 400) may have contributed to an increase in the permeability of the intestinal membrane or improved the affinity between lipid particles and the intestinal membrane. Further, due to small particle size, microemulsions may adhere to the gut membrane or enter the intervillar spaces thus extending gastrointestinal residence time in the gastrointestinal tract [17]. Moreover, micro-sized preparation ensures greater surface area and also the presence

of Tween-80 as a surfactant in the microemulsion formulation might modulate the intestinal membrane permeability through apically polarized efflux system leading to enhanced oral bioavailability [18].

4. Conclusion

In the present investigation, the utility of microemulsion as carrier for oral delivery of ranitidine was studied. The pharmacodynamic study (ethanol-induced ulcer model) revealed that ranitidine microemulsion showed lower incidence of mucosal damage when compared with standard drug, both administered orally, indicating the superiority of oral ranitidine microemulsion over standard ranitidine. The pharmacokinetic studies reveal that the oral administration of ranitidine microemulsion sustained the release of drugs over 24 hrs. As a consequence of this, decrease in the dose and frequency of administration for drugs is possible to achieve the desired therapeutic activity.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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