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Formulation Development & Characterization of Microemulsion Drug delivery systems Containing Antiulcer drug

Sajal Kumar Jha[1], Roopa Karki[2], Venkatesh D.P[2], Geethalakshami A[3]
[1]Department of Pharmaceutics, Bengal College of Pharmaceutical Sciences & Research, Durgapur, West Bengal.
[2]Department of Pharmaceutics, Acharya & B.M Reddy College of Pharmacy, Bangalore, Karnataka.
[3]Department of Pharmaceutics, Oxford College of Pharmacy, Bangalore, Karnataka.

Abstract

An attempt was made to develop an oral microemulsion formulation for enhancing the bioavailability of famotidine is a BCS class III drugs which are known to have high solubility but low permeability. An Olive oil based microemulsion formulation with Tween 80 as surfactant and PEG 400 as cosurfactant was developed for oral delivery of famotidine. A single isotropic region, which was considered to be a bicontinuous microemulsion, was found in the pseudoternary phase diagrams developed at various Tween80: PEG 400: oil ratios. The microemulsion system was also investigated in terms of other characteristics, such as viscosity, pH, conductivity, clarity, particle size, *in vitro* drug release, *in vitro* intestinal permeability study compared to the plain drug solution (64.18%). The developed microemulsion system improved the permeability (93.43%) by increasing the lipophillicity due to the oil phase and also by destabilizing the membrane stability due the surfactants and may be used as an enhanced delivery of BCS class III drugs.

*Corresponding author, Mailing address:
Mr. Sajal Kumar Jha
Bengal College of Pharmaceutical Sciences & Research, Durgapur, West Bengal.
Email: sajal.kumar.jha@gmail.com.

Key words:
Microemulsion; Famotidine; BCS Class III drugs; Surfactant; Cosurfactant.

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Introduction:

Microemulsion are clear, transparent, thermodynamically stable dispersions of oil and water, stabilized by an interfacial film of surfactant frequently in combination with a co-surfactant and having diameter of the droplets in the range of 100-

2000A (10-200 nm). Recently, there has been a considerable interest for the microemulsion formulation, for the delivery of hydrophilic as well as lipophilic drug as drug carriers because of its improved drug solubilization capacity, long shelf life, ease of preparation and improvement of bioavailability [1]. A microemulsion generally consists of four different components, a lipophilic phase, a hydrophilic phase, surfactant and co-surfactant [2]. The nature of the components like the oil, surfactant, co-surfactant and water, as well as temperature and pressure which affect the microemulsion systems are known as the formulation variables. The quantities of different substances present, are also likely to change the properties, and are referred to as composition variables which can be expressed as weight, percentage or proportion**.** Pharmaceutical applications of microemulsions include drug synthesis, purification and extraction as well as drug delivery vehicles and controlled drug release systems. The biopharmaceutics classification system classifies drug according to their solubility and permeability which is chosen as reference standard are categorized as permeable drugs and those drugs which have dose number of ≤ 1 are classified as soluble. For a BCS class III drug we need to increase its permeability to improve its oral bioavailability because here, in class III drugs they have high solubility but low permeability. The purpose of this work was to improve the oral bioavailability of famotidine by preparation the microemulsion. Since most of the drugs are structurally optimized during drug discovery study to increase their solubility and efficiency penetrate the biological barriers and reach their target receptors easily. While increase in the lipophillicity helps in better absorption. On the other hand, some drugs have good water solubility but lack sufficient lipophillicity to effectively penetrate the lipoidal tissues and absorption becomes rate limiting for such candidates [8].

Materials & Methods:

Famotidine was a generous gift from Microlabs (Bangalore, India);PG, PEG 400, Tween 80, Span 80 were obtained from Merc Chemicals (Mumbai, India). All other chemicals & sovents used were of analytical grade.

Selection of Oil, surfactants & cosurfactants for microemulsion:

The solubility of famotidine in various oils (Olive oil, groundnut oil, coconut oil & castor oil), surfactants (Tween 20,40,60,80 & Span 80), cosurfactants(PG,PEG 400). Was determined by dissolving an excess amount of famotidine in 2 mL of each of the selected oils, surfactants, and co-surfactants in 5 mL capacity stoppered vials separately to determination of solubility. An excess amount of famotidine was added to each 5 mL capacity stoppered vial and mixed using a vortex mixer. The mixture vials were then kept in a shaker for 72 h to get to equilibrium. The equilibrated samples were removed from the shaker and centrifuged at 3000 rpm for 30 min. The supernatant was taken and filtered through a 0.45 µm membrane filter. The concentration of famotidine was determined in each oils, surfactants, and cosurfactants by UV spectrophotometer at their respective wavelength 265nm[3].

Construction of Pseudoternary phase diagram:

Pseudo ternary phase diagram was constructed keeping the ratio of Smix (Tween 80 and PEG 400) constant and varying the remaining two components (water and oil). For convenience, the phase diagram was constructed by drawing “water dilution lines” representing increasing water content and decreasing surfactant and cosurfactant levels. Four different combinations of oil and Smix (1:9, 2:8, 3:7, 4:6) respectively were made for the study to delineate the boundaries of phases precisely formed in the phase diagrams. Water was added drop by drop while mixing on a magnetic stirrer (Remi Instruments Ltd.

Mumbai, India) at room temperature & the samples were marked as being optically clear or turbid. The microemulsion regions were identified as transparent & isotropic mixtures[4].

Preparation of microemulsion

On the basis of the solubility studies, oleic acid was selected as the oil phase. Tween 80 and PEG 400 were selected as surfactant and cosurfactant, respectively. Distilled water was used as an aqueous phase. Surfactant and cosurfactant (Smix) were mixed at different mass ratios (1:1,2:1,3:1,4:1). These ratios were chosen in increasing concentration of surfactant with respect to cosurfactant and increasing concentration of cosurfactant with respect to surfactant for a detailed study of the phase diagrams. Predetermined amounts of the drug were dissolved in the required quantity of oil. Surfactant and co-surfactant were added to the above mixture as a fixed ratio. Distilled water was added gradually with continuous stirring, which resulted in the formulation of a transparent and homogenous microemulsion. Parameters optimized for the preparation of microemulsion were the type and concentration of the oil phase, surfactant and co-surfactant [4].

Characterization of microemulsion

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 4°C and 45°C for 48 h were done. The formulations were then observed for phase separation. The formulations which were stable at these temperatures, those formulations that survived thermodynamic stability tests were selected for the further studies[3].

pH determination:

The pH of the each formulation was found before and after diluted to 10 times as well as 25 times be measured by a pH meter[5].

Conductivity:

All formulation were studies the effect of the amount of water phase of microemulsions was found before and after diluted to 10 times as well as 25 times was monitored by measuring the electrical conductivity[5].

Viscosity:

The viscosity of all formulations was determined without dilution using normal force measurements on the AR 1000-N- Rheometer[6].

Particle size measurement:

Morphology and structure of the microemulsion were studied using transmission electron microscopy (TEM), A JEOL JEM 100. CX2 is instruments and capable of point to point resolution. To perform the TEM observations, first take 2 µL of formulation (F4) and put it on formvar coated grid, wait for 2 min, add 2µL of uranyl acetate and dry it for 1h. After 1 h take the grid and look for the image [4].

***In vitro* drug release study:**

The release of famotidine crude drug powder and microemulsion was compared. Release of drugs from microemulsion employed a dialysis bag/dialysis membrane with molecular weight. It was first activated using 5% EDTA solution and release medium. Phosphate buffer of pH 4.5 has been used as release medium; the dialysis membrane was suspended with the help of glass rod in a beaker containing 200 mL of phosphate buffer solution which was kept on magnetic stirrer. The over all experiments necessary maintain the temperature of 37°C was maintained, the formulation of 5 mL was transferred to a dialysis bag. The sample of 1mL has been removed from the beaker containing phosphate

buffer at definite time intervals 5, 15, 30, 45, 60, 120, up to 180 min. and diluted to 10 mL with phosphate buffer solution. The absorbance of each sample was noted at 265 nm[7].

Results & Discussion:

The solubility of famotidine in different oils was determined. Among the oils, the solubility of famotidine was found to be highest in Olive oil 6.9%, lowest solubility in Castor oil 0.95%. Thus, Olive oil was selected as the oil phase for the development of the formulation. The solubility of famotidine in different surfactants was determined. Among the surfactants, the solubility of famotidine was found to be highest in Tween 80 8.85%, lowest solubility in Tween 20 2.35%.The solubility of famotidine in different cosurfactants was determined. Among the cosurfactants, the solubility of famotidine was found to be highest in PEG 400 is 14.7%, lowest solubility in PG is 7.12%. The phase study revealed that the maximum proportion of oil was incorporated in microemulsion systems when the surfactant to cosurfactant Smix was 4:1 ratio. From a formulation viewpoint, the increased oil content in microemulsion may provide a greater opportunity for the solubilization of famotidine. Pseudoternary phase diagram were constructed separately for Smix ratio so O/W microemulsion regions could be identified and microemulsion formulations could be optimized. To overcome this metastable formation, thermodynamic stability tests were performed. The formulations selected were centrifugation and heating cooling cycle tests, if the microemulsion are stable over these conditions. The pH of the designed formulation varied from 7.26 to 7.48 . This was ideal and near blood pH (7.4). The formulations were having conductivity between 78.3 to 88.5 µs. All four formulations had clear transparent yellowish to pale yellow colour. The viscosity of the selected formulations was determined. The viscosity of formulation F4 (08.21) was lower than that of any other formulation, and this difference was significant. The drug release after 3 h for all formulations varied from 62.45% to 74.25% as compared with 55.21% for pure drug. The formulation F4 shows highest intestinal permeation 93.43% was found to be significantly higher as compared with that of plain famotidine is 64.18% & hence bioavailability. It could be suggested that the microemulsion formulation resulted in spontaneous formation of a microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase, much faster than that of plain famotidine. Thus, this greater availability of dissolved famotidine from the microemulsion formulation could lead to higher absorption and higher oral bioavailability.

Table 1: Solubility of Famotidine in various oils and surfactants (mean±S.D., n=3)

Serial No	Excipients	Volume (ml)	Quantity (mg)	Solubility ± SD (mg/ml)
1	Water	5	100	00
2	Olive oil	5	100	6.9±0.282
3	Ground nut oil	5	100	5.52±0.298
4	Coconut oil	5	100	1.92±0.340
5	Castor oil	5	100	0.95±0.238
6	Tween 80	5	100	8.85±0.264
7	Tween 60	5	100	4.12±0.359
8	Tween 40	5	100	3.47±0.287
9	Tween 20	5	100	2.35±0.191
10	Span 80	5	100	4.95±0.173
11	PEG 400	5	100	14.7±0.416
12	PG	5	100	7.12±0.286

Table 2: Final formulation with different oil concentration

Formulation Code	Oil (%)	S mix (%)	Water (%)
F1	5	45	50
F2	5.52	44.48	50
F3	6.25	43.75	50
F4	7.12	42.84	50

Table 3: Physicochemical Parameters of developed Microemulsion

Formulation Code	Conductivity	pH	Viscosity	% Transmittance
F1	78.3	7.26	18.64	85.4
F2	86.5	7.63	15.35	89.6
F3	84.7	7.34	12.72	92.5
F4	88.5	7.48	08.21	97.6

Table 4: *In vitro* drug release studies profile of famotidine from 4 different microemulsion formulations

Formulation Code	5min	15min	30min	45min	60min	120min	180min
F1	5.12±2.8	8.36 ±1.9	17.48±3.48	30.21 ±2.31	35.38±1.56	46.58 ±2.72	62.45 ±1.76
F2	4.18±0.56	7.29 ±3.46	13.82 ±2.17	22.64 ±2.78	32.42±2.36	40.68±3.48	59.27 ±2.18
F3	6.48±2.04	12.89 ±2.63	18.32 ±2.82	24.26±2.54	34.81 ±2.60	42.49±1.92	61.38 ±1.72
F4	9.15±2.09	14.56 ±2.57	22.68±1.8	27.32±3.42	33.73 ±2.17	57.16 ±2.84	74.25 ±1.28

(Mean result (µg/mL) ± S.D; (n=3)

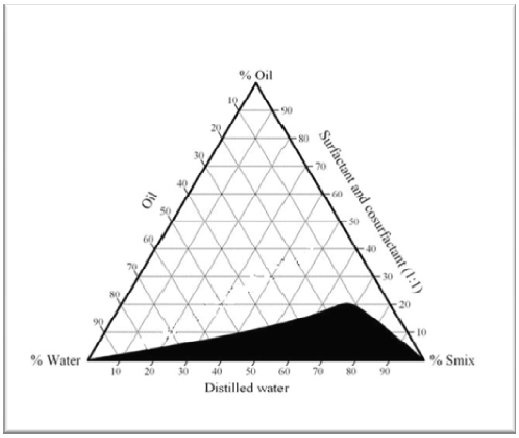
Table 5: *In vitro* intestinal permeability studies profile of famotidine from 4 Different microemulsion formulations

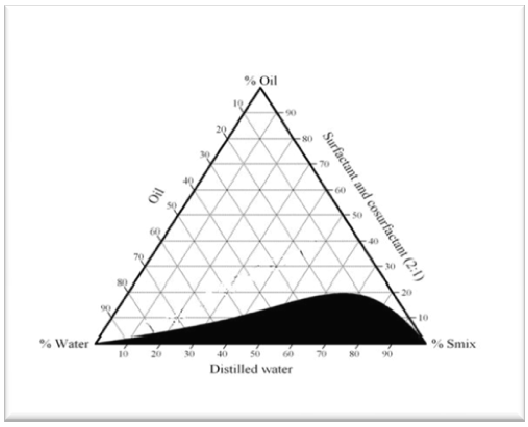
Formulation Code	5min	15min	30min	45min	60min	120min	180min
F1	12.23± 2.41	23.43±2.22	48.54±2.10	54.31±1.65	75.52±1.48	82.34±2.65	86.65±2.48
F2	16.54±2.63	27.32±3.26	51.42±1.85	56.56±1.68	78.48±2.21	84.68±2.08	88.76±1.8
F3	21.32±2.57	32.54 ±2.81	56.65±2.64	60.12±3.23	84.28±2.34	87.56±1.90	90.48±2.18
F4	26.45± 1.96	34.32±1.92	59.35±2.39	64.41±2.10	85.53±1.85	90.65±1.76	93.43±3.12

(Mean result (µg/mL) ± S.D; (n=3).

Table 6: *In vitro* stomach and intestinal permeability studies for pure drug (PD)

Time in min	% Cumulative drug release in intestine
5	17.59 ± 1.018
15	24.97 ± 2.51
30	35.32 ± 0.79
45	44.26 ± 1.82
60	51.77 ± 2.27
120	60.98 ± 1.72
180	64.18 ± 1.48





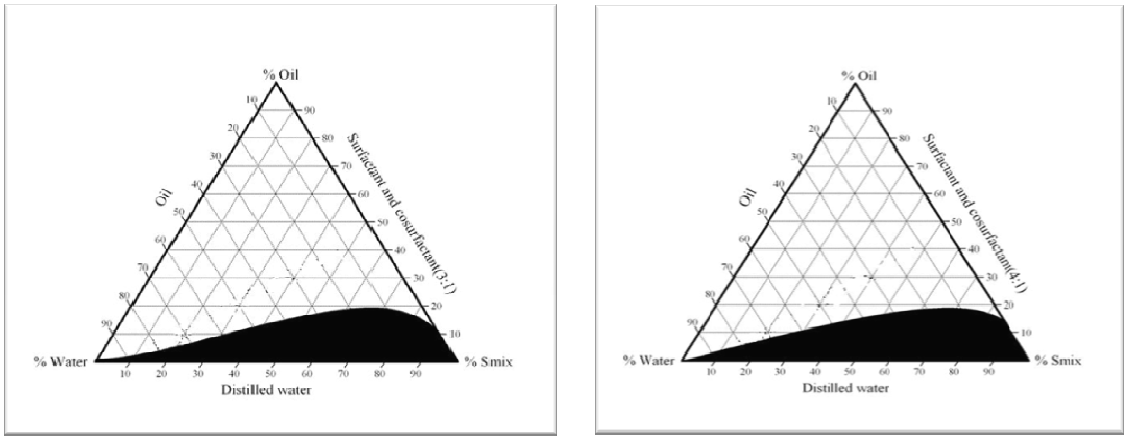


Figure 1: Pseudoternary phase diagram of system

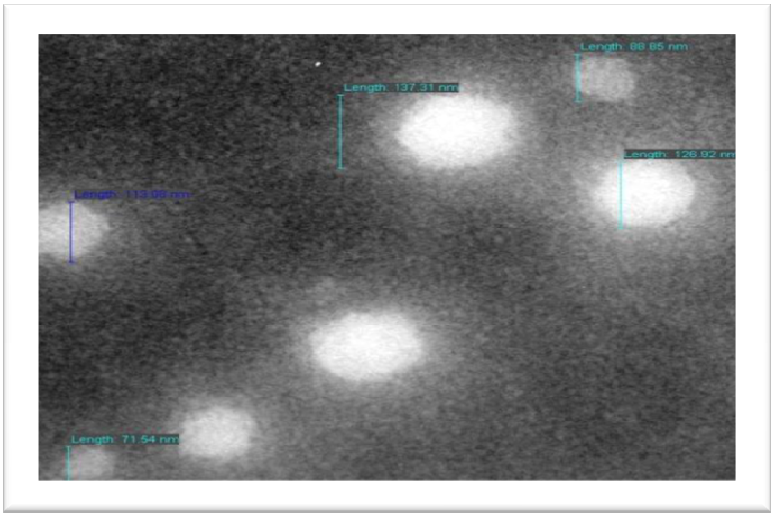


Figure 2: Transmission electron microscopic positive image of famotidine microemulsion Formulation (F 4) showing size of some oil droplets with a range of 10-200 nm.

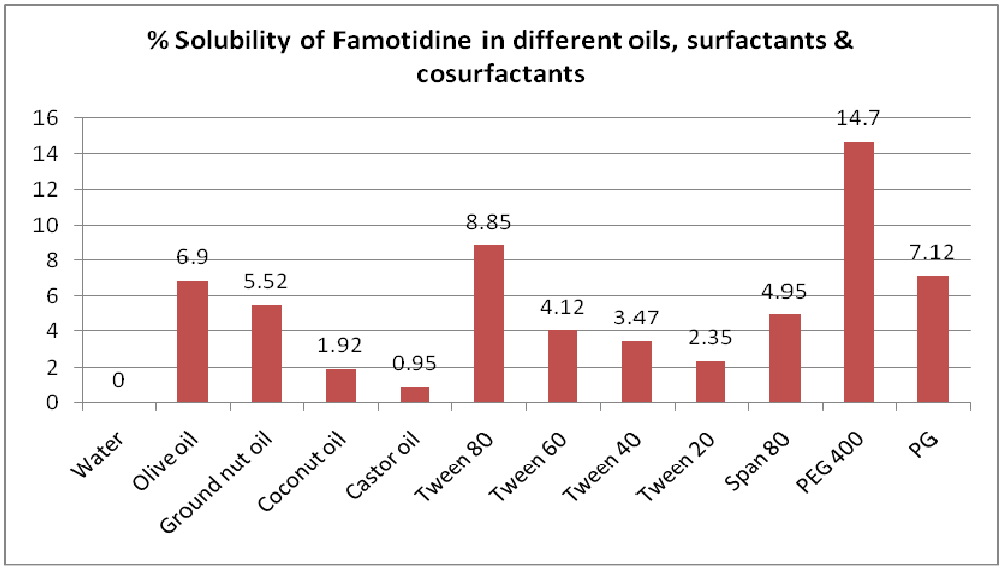


Figure 3: Solubility studies of Famotidine in various components.

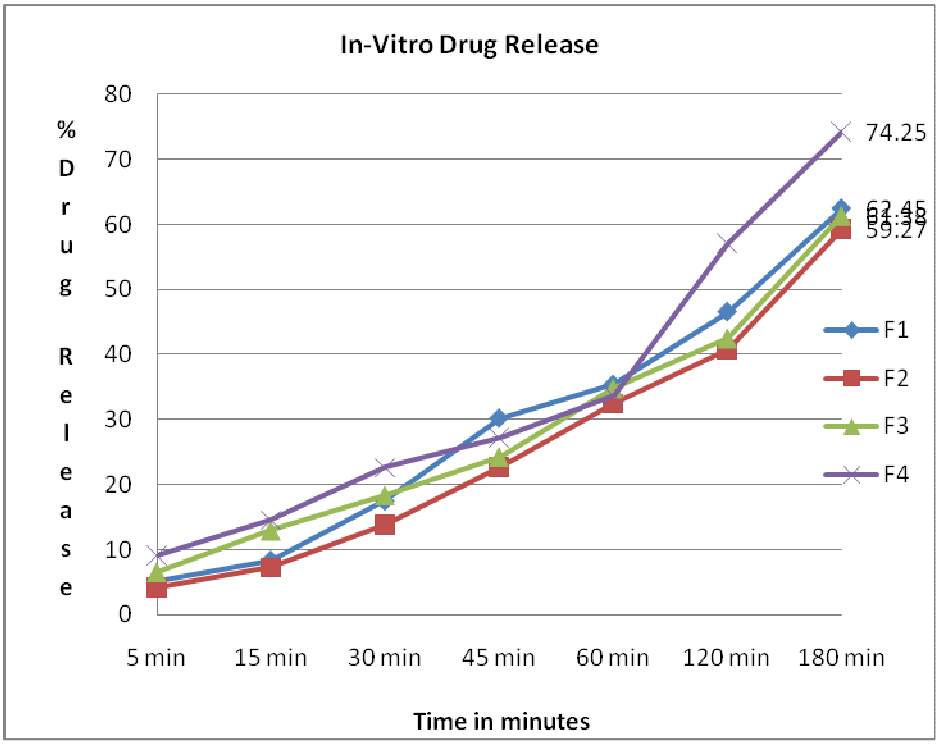


Figure 4: *In vitro* drug release studies profile of famotidine from four different microemulsion formulations.

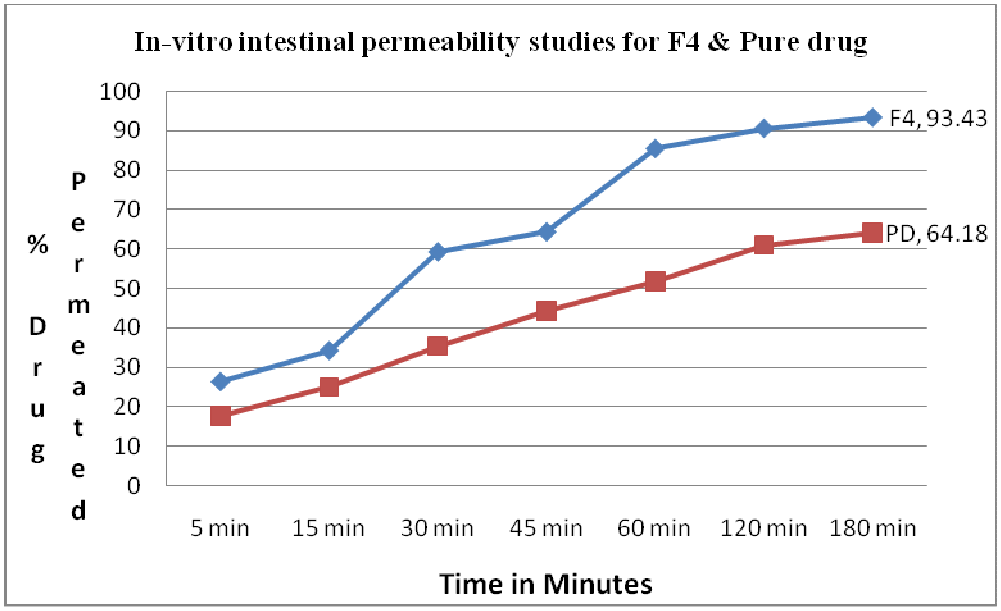


Figure 5: Comparison of % intestinal drug permeation for F4 & Pure drug

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