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Characterization of Olive Oil based Microemulsion Drug Delivery System for Oral delivery of Antiulcer agent

Sajal Kumar Jha [*1], Roopa Karki[2], Venkatesh D P[2], B Sajeev[3], Geethalakshmi A[4]

1 Department of Pharmaceutics, Bengal College of Pharmaceutical Sciences and Research, Durgapur, India.

2 Department of Pharmaceutics, Acharya & B M Reddy College of Pharmacy, Bangalore, India.

3 Asian Institute of Medicine Science and Technology, Semeling, Bedong, Malaysia.

4 Department of Pharmaceutics, Oxford College of Pharmacy, Bangalore, India.

ABSTRACT

The objective of the present research was to develop and characterize an olive oil based oral microemulsion systems for 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 co-surfactant, was developed for oral delivery of famotidine. Pseudoternary phase diagram was constructed to determine the microemulsion existing zone. Optimized microemulsion was evaluated for its transparency, droplet size, polydispersity index, zeta potential, viscosity, conductivity, DSC studies, SANS studies. The results showed that maximum oil was incorporated in microemulsion system that was contained surfactant to co-surfactant ratio (Km) of 2:1. The optimized microemulsion formulation containing olive oil (7.14%), Tween-80 & PEG-400 [Smix=64.29% (2:1 ratio)], and distilled water (28.57%), had a droplet size (10 times diluted) and zeta potential (10 times diluted) of 170.1 nm and -6.58 mV respectively. Particle size characterization of the resulting microemulsion is essential in ensuring stability and efficient dosage. FTIR and DSC studies revealed the compatibility among the famotidine and microemulsion components. The experimental SANS data of optimized formulation fit well by spherical micelles interacting with hard sphere potential. These results demonstrate microemulsion formulation may be used as an effective and alternative drug delivery system for the antiulcer oral therapy with famotidine.

Keywords: Famotidine; BCS class III drugs; Olive oil; Pseudoternary phase diagram; Microemulsion

*Corresponding Author Email: sajal.kumar.jha@gmail.com

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INTRODUCTION

Famotidine is *N*'-(amino sulfonyl)- 3-[[[2-[(diaminomethylene) amino]-4-thiazolyl] methyl] thio] propanimidamide a model BCS Class-III drug. It is a potent H2 receptor antagonist used to treat peptic ulcer and hence effectively heals gastric and duodenal ulcers and is also effective in Zollinger-Ellison Syndrome. Famotidine is absorbed only in the initial part of GI tract and has less absolute bioavailability (40-45%) after oral administration, with the peak serum level occurring at approximately 1-3hrs[1]. The BCS classification of drugs provided new quantitative data of importance for modern drug development, especially within the area of drug permeability. It gives clear and easy applied rules for determining the rate limiting factors of GI absorption process. 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. 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 100-2000À (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[2].

MATERIALS AND METHOD

Famotidine was obtained from Micro Labs (Bangalore, India) as free gift sample. PEG-400 was purchased from B.D Pharmaceuticals Ltd. (Kolkata, India), Tween-80 was purchased from Merck Specialties Pvt. Ltd.(Mumbai, India), Disodium hydrogen orthophosphate, sodium citrate and sodium chloride were purchased from SD Fine Chemicals (Mumbai, India). All other reagents were of analytical grade.

Methods:

Determination of drug solubility in microemulsion components

The solubility of famotidine in various oils (olive oil, ground nut oil, coconut oil, castor oil), surfactants (tween 20,40,60,80) and co-surfactant (polyethylene glycol400 & propylene glycol) was determined by dissolving an excess amount of drug 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 co surfactants by UV spectrophotometer at λmax 265nm [3].

Drug-excipients incompatibility studies

The infra red spectra (IR) of pure famotidine and with olive oil, Tween-80, PEG-400 and optimized formulation were obtained using FTIR Shimadzu, Japan.

Development of Pseudoternary Phase Diagram

Surfactant (Tween 80) and cosurfactant (PEG 400) were mixed (Smix) in different volume ratios (1:1, 2:1, 3:1, 4:1) etc. These Smix ratios were chosen to reflect increasing concentrations of co-surfactant with respect to surfactant and increasing concentrations of surfactant with respect to cosurfactant for detailed study of the phase diagrams in the microemulsion formation[4].

Preparation of drug loaded microemulsion

Drug loaded microemulsion systems were prepared by dispersing famotidine in the mixture olive oil & Smix (Tween 80 & PEG 400) followed by water addition drop by drop to the oily phase with magnetic stirring at ambient temperature. After the resulting systems were equilibrated with gentle magnetic stirring, they were ultrasonicated[4].

CHARACTERIZATION OF DEVELOPED MICROEMULSION FORMULATION

Conductivity values

Electrical conductivity of ME was measured using a conductivity meter [(CM 180 conductivity meter (Elico, India)] at ambient temperature. 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 determination

Viscosity of sample was measured at 32 ± 0.5°C with a Brookfield viscometer (DV-II+Pro Brookfield., USA) using spindle no. 41. with shear rate of 5 rpm. Each measurement was performed in triplicate [6-7].

Particle size, polydispersity index & zeta potential measurements

Droplet size distribution of optimized microemulsion was determined by photon correlation spectroscopy, using a Delsa Nano-C (Beckman Coulter Instruments). Light scattering was monitored at 25°C at a scattering angle of 90°. The sample of optimized microemulsion was suitably diluted with distilled water and filtered through 0.22 µm membrane filter to eliminate multi scattering phenomena. The diluted sample was then placed in quartz couvette and subjected to droplet size analysis [8].

Differential Scanning Calorimetry (DSC) Studies

DSC measurements were carried out by means of a Metller Toldo DSC1 STARe SW 8.10 system equipped with refrigerated cooling system (Hubert Tc45). Approximately 5-10 mg of famotidine microemulsion samples were weighted into hermetic aluminium pans and quickly sealed to prevent water evaporation from microemulsion samples. Simultaneously an empty hermetically sealed pan was used as a reference. Microemulsion samples were exposed in a temperature ranging from 25.0-250.0°C (scan rate: 10 ºC/min) [6].

Small-angle neutron scattering analysis (SANS)

Small-angle neutron scattering experiments were performed at the SANS diffractometer at Guide Tube Laboratory, Dhruva Reactor, Bhabha Atomic Research Centre, Mumbai, India. The mean wavelength of the monochromatized beam is 5.2 $Å^0$ with a spread of $\Delta\lambda/\lambda \sim 15\%$. The angular distribution of neutrons scattered by the sample is recorded using a 1 m long one-dimensional He^3 position sensitive detector. The instrument covers a *Q*-range of 0.015–0.35 $Å^{-1}$. The temperature in all the measurements was kept fixed at 30 ^oC [9].

RESULTS AND DISCUSSION:

The solubility of famotidine in different oils was determined. The solubility was found to be highest in Olive oil (6.9±0.282 mg/ml), lowest solubility in castor oil (0.95±0.238mg/ml). Among the surfactants, solubility of famotidine was found to be highest in tween 80 (8.85±0.264 mg/ml), lowest solubility in tween 20(2.35±0.191mg/ml). Among the cosurfactants, the solubility of famotidine was found to be highest in polyethylene glycol-400 is (14.7±0.416 mg/ml), lowest solubility in span-80(4.95±0.173 mg/ml) (Figure 1).

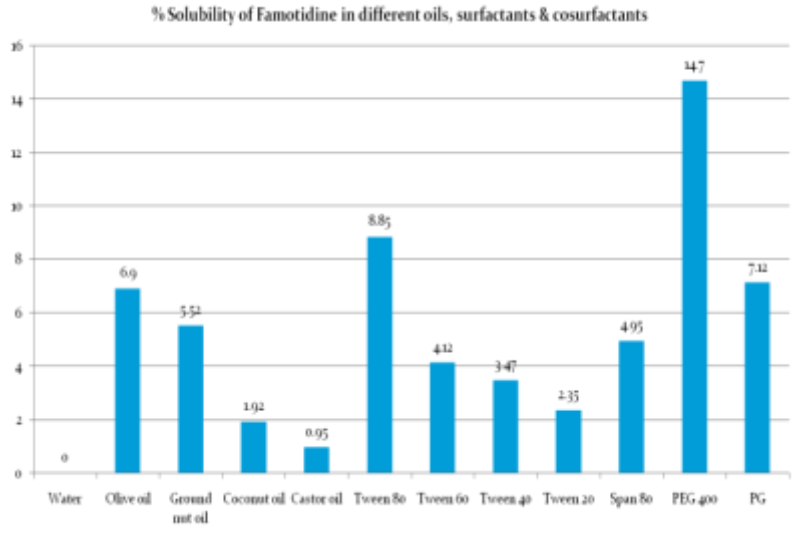

Figure 1: Solubility profiles of famotidine in different microemulsion components

Drug-excipients incompatibility studies

In the first mixture of famotidine and olive oil, the peaks related to famotidine like, 3440 cm^{-1} for N-H stretch, 1216 cm^{-1} for thiazole etc, were found at their respective places, whereas for olive oil peak at 1739 cm^{-1} was of C=O group in the form of an ester, present in olive oil, which suggest no cross reaction with the excipients (Figure 2 & 3).

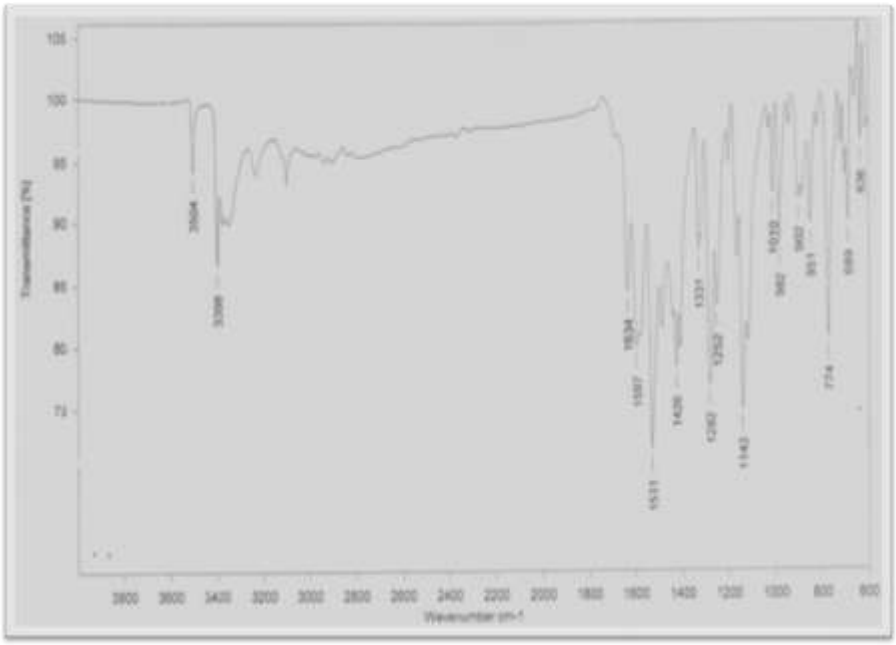

Figure 2: I R Spectra of pure Famotidine

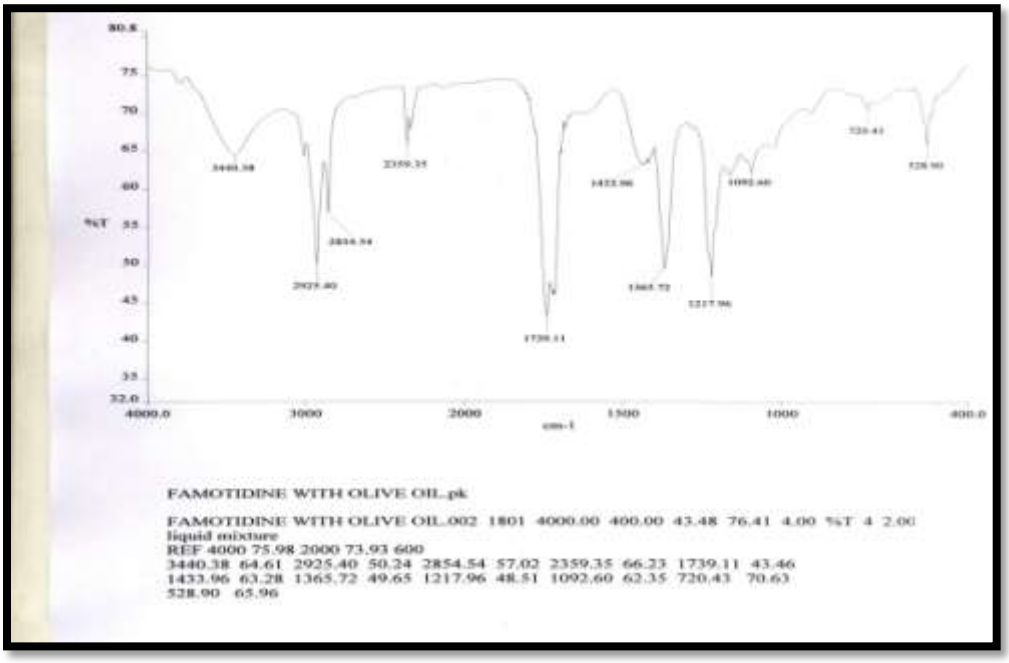

Figure 3: I R Spectra of famotidine with olive oil

Similar features were observed when famotidine was mixed with PEG-400(Figure 4). No cross reaction was observed as the characteristic peak for PEG, i.e; OH stretching at 3390 cm^{-1} was unaltered.

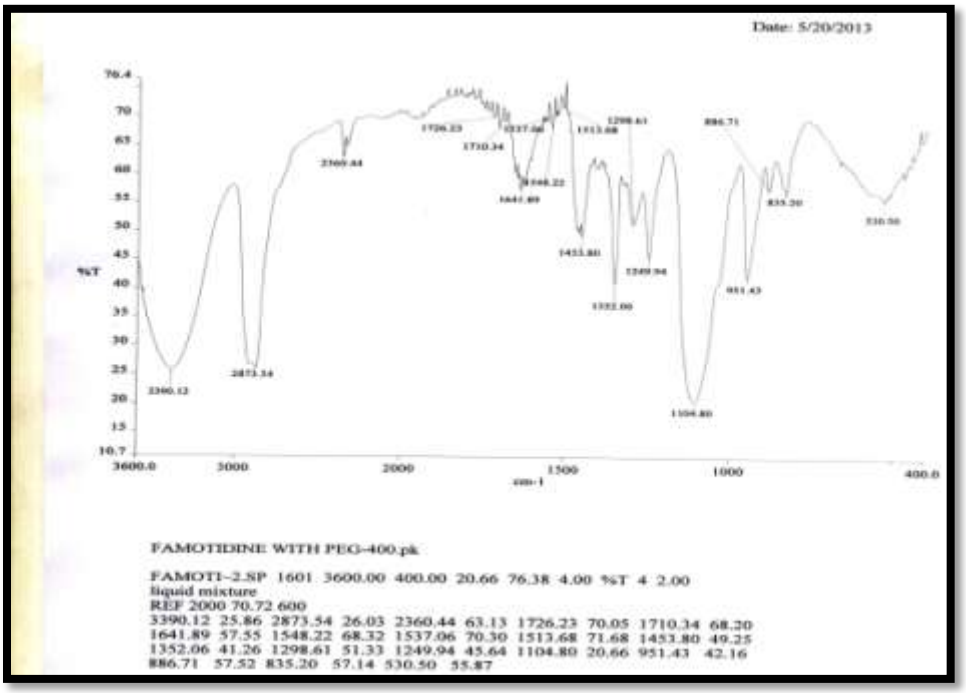

Figure 4: I R Spectra of famotidine with PEG-400

Later mixing Tween-80 with famotidine (Figure 5) left no traces of cross reaction. The C=O group present in Tween-80 showed a definite peak at 1738 cm^{-1} and ethereal stretch at 1096 cm^{-1}.On the other hand the peaks for famotidine remained same.

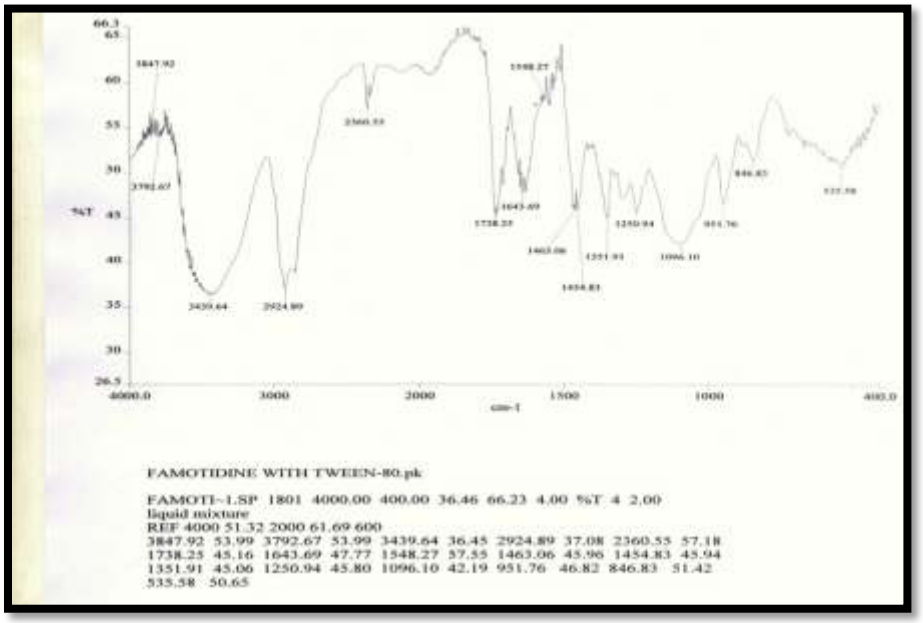

Figure 5: I R Spectra of famotidine with TWEEN-80

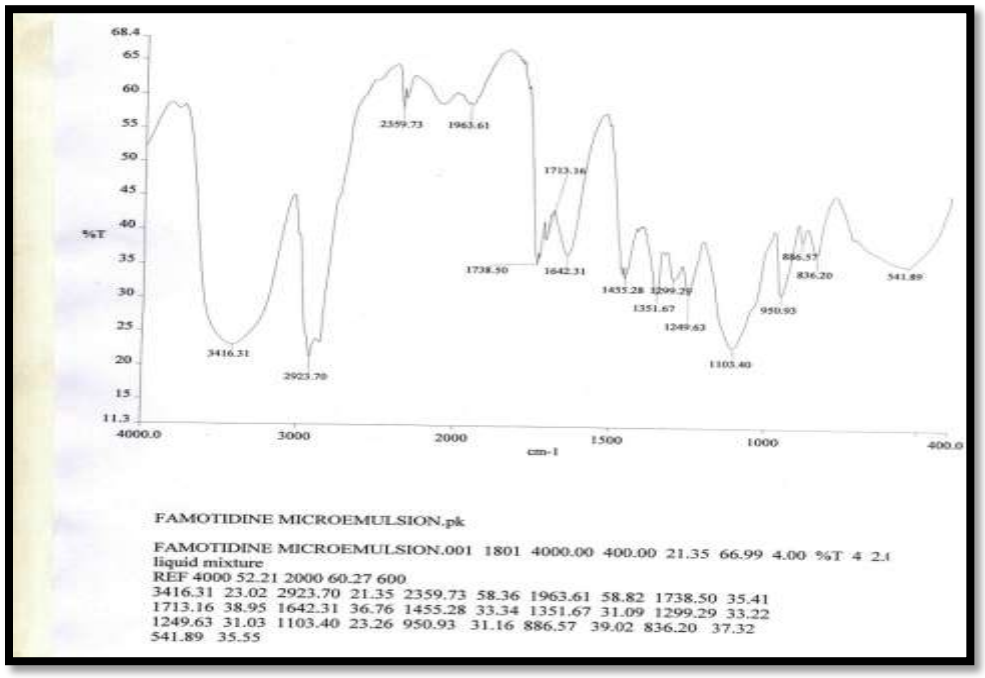

Figure 6: I R Spectra of famotidine microemulsion

Finally in famotidine microemulsion peaks at 3416 cm^{-1}, 1642 cm^{-1} remain unchanged despite being formulated with other excipients (Figure 6). Presence of thiazole can be attributed to the peak at 1249 cm^{-1}. With this supportive information the conclusion which can be drawn is that, as such there is no cross reaction that has been found in the formulation.

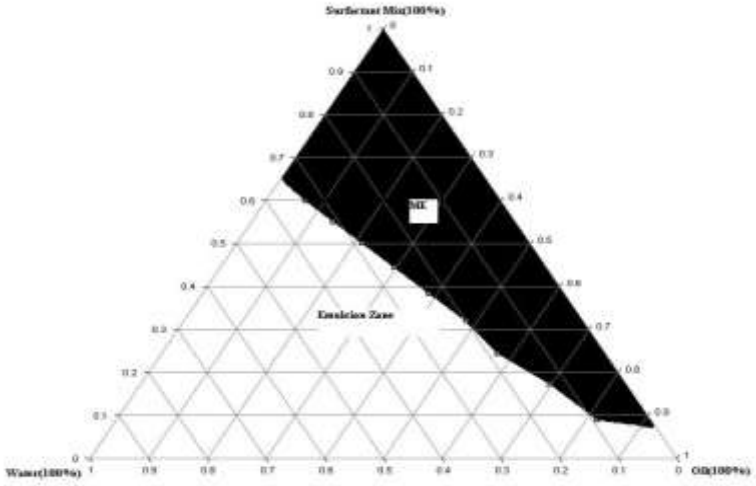

Figure 7: Pseudoternary phase diagram of system with the following components: oil = Olive Oil, surfactant = Tween-80, cosurfactant = PEG-400, using Smix ratio of 2:1.

The pseudoternary phase diagram study revealed that the maximum proportion of oil was incorporated in microemulsion systems when the surfactant to cosurfactant ratio (Km) of 2:1.

From a formulation viewpoint, the increased oil content in microemulsion may provide a greater opportunity for the solubilization of famotidine (Figure 7).

Table 1 Composition of Famotidine Microemulsion formulations

Formulation Code	Oil: Smix	Olive Oil(%w/w)	Smix(%w/w)	Water(%w/w)
F-1	1:9	7.14	64.29	28.57
F-2	1:8	8.16	65.86	25.97
F-3	1:7	9.43	66.04	24.53
F-4	1:6	10.96	65.96	23.08
F-5	1:5	13.14	65.29	21.57
F-6	1:4	15.69	62.75	21.57
F-7	1:3	20.83	62.5	16.67
F-8	1:2	28.98	57.95	13.07
F-9	1:1	45.45	45.45	9.09

Table 2 Composition of optimized microemulsion formulation

Optimized ME	Oil (%)	Surfactant & cosurfactant mixture (%)	Water (%)	Drug (mg)
F1	7.14	64.29	28.57	40

After the development of each phase diagram, different formulations has been selected by keeping the total quantity of the formulation constant as 100% and varying all components of the system. Famotidine was added to the oil and S/ CoS mixture and the microemulsions containing famotidine were obtained by water titration method followed by stirring the mixtures at ambient temperature. The composition (%w/w) of famotidine microemulsion & optimized famotidine microemulsion were shown in Table 1 Table 2.

Table 3 Characterization parameters of optimized microemulsion

	Characterization Parameters				
Optimized ME	Conductivity (µs/cm)	Viscosity (cp)	Particle Size (nm)	Polydispersity index	Zeta potential (mV)
Value obtained	89.61±3.12	138.5±0.96	170.1±1	0.415	-6.58

There was a strong correlation between the specific structure of the microemulsion systems and their electrical conductive behavior. Conductivity values the optimized microemulsion formulation of famotidine was found to be 89.61±3.12µs/cm (Table 3). Viscosity studies are necessary determinations for microemulsions to characterize the system physically and to control its physical stability. The viscosity of optimized microemulsion formulation was show in Table 3.

It is known that particle size distribution is one of the most important characteristics of an emulsion for evaluation of its stability and the bioavailability of drug from an emulsion. Various parameters which can affect globule size of a microemulsion include the type of surfactants and

co-surfactants, amount of dispersed phase and rate of stirring (Table 2). Particle size characterization of the resulting microemulsion is essential in ensuring stability and efficient dosage. The average diameter of optimized formulation is shown in Figure 8, as observed the mean diameter was found to be 170.1 nm. The polydispersity index was found to be 0.415. The zeta potential of prepared microemulsion was measured using Delsa Nano-C (Beckman Coulter Instruments) was found to be -6.58 mV (Figure 9).

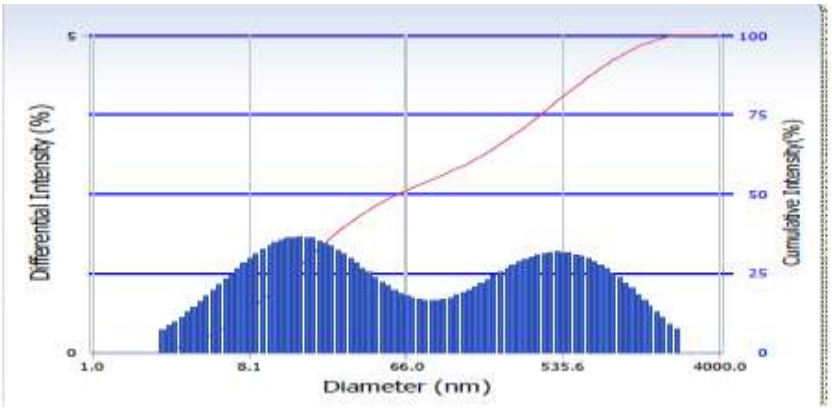

Figure 8: Droplet size distribution of optimized famotidine microemulsion

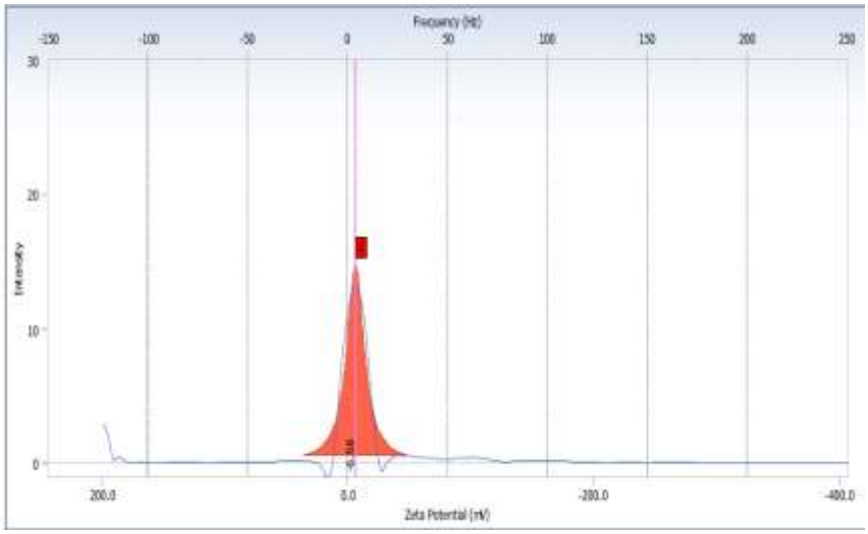

Figure 9: Zeta potential determination of optimized famotidine microemulsion

The DSC thermogram of pure drug famotidine showed a characteristic endothermic peak at 164.66 ^{0}C showed in (Figure 10), which is in the range of melting point of famotidine. The peak disappeared for the drug loaded microemulsion, which indicated that the drug was molecularly dispersed with the aid of surfactant & cosurfactant combination. In this context, a small broadened peak at very low temperatures has been suggested to be either internal water or water that is interacting strongly with the surfactants. DSC thermogram showed one exothermic peak at around 0 to -4 ºC that indicate the freezing of bulk water in the formulation and also one

endothermic peak at around 97.54 ºC indicates the water must be strongly bound or interacts with surfactants & cosurfactants(Figure 11).

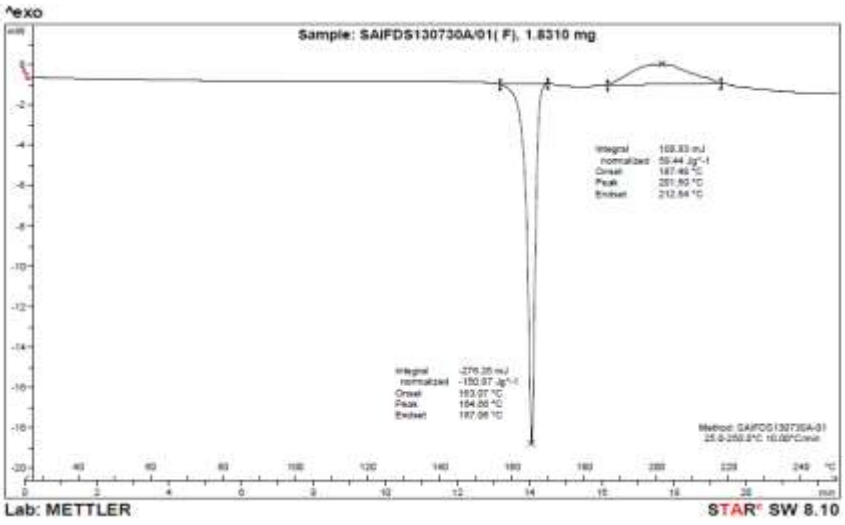

Figure 10: DSC thermogram of pure famotidine

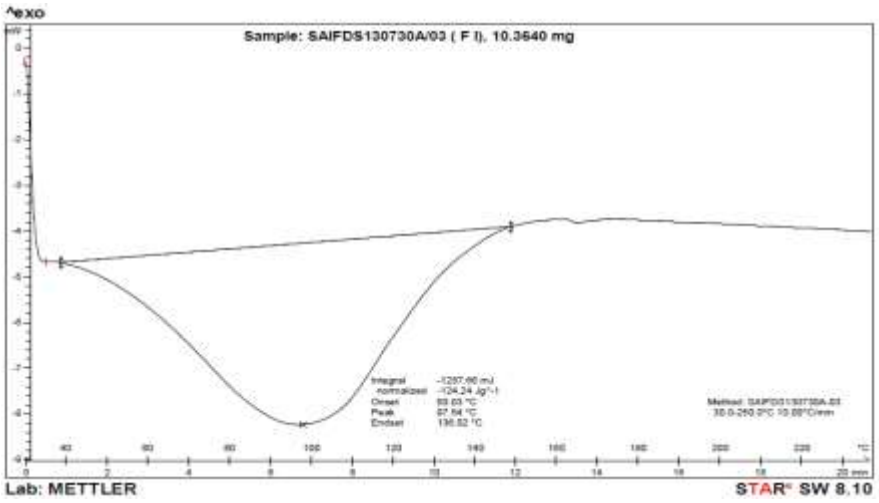

Figure 11: DSC thermogram of optimized famotidine Microemulsion

SANS Analysis

The data has been fitted for spherical particle form factor with structure factor for hard sphere potential (spherical micelles interacting with hard sphere potential). In the case of non-ionic micelles, the interparticle interaction is obtained using the Percus-Yevick approximation & employing the hard sphere potential between micelles. Fitted data are shown in (Figure 12). Structural parameters of the formed micelles were obtained by fitting the micellar volume fraction, core radius, hard sphere radius as shown in Table 4. It seems to be microemulsion system.

Table 4 Structural parameters of the formed micelles during SANS

Optimized ME	Core radius R_c (Å)	Polydispersity σ	Hard sphere radius R_{HS} (Å)	Volume fraction
F1	31.1 ± 1.8	0.415	51.7 ± 2.3	0.26

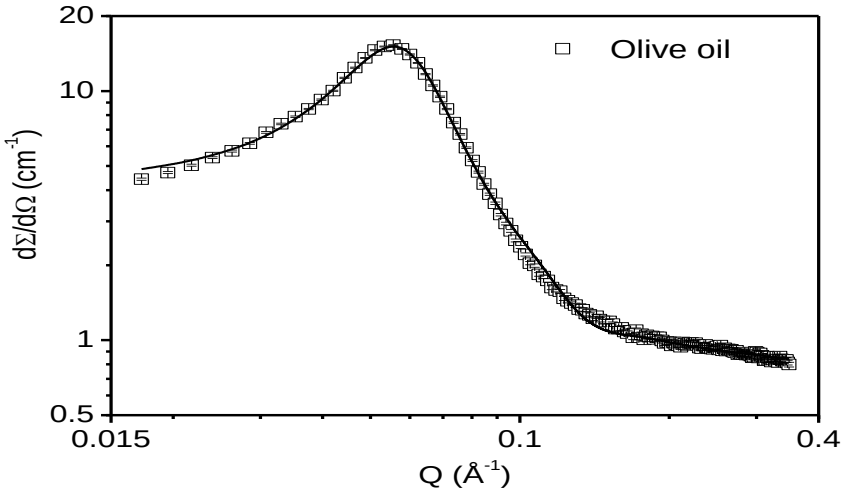

Figure 12 SANS study of optimized famotidine microemulsion

CONCLUSION

Microemulsions are fascinating systems, in that nature prefers to have a dispersed system of oil, water and combination of surfactants & cosurfactants having large total interfacial area. Therefore, the elucidation of the internal structure of a microemulsion can be very complex, and sophisticated physical techniques are required. The present work describes the development and characterization of olive oil based pharmaceutical microemulsion system by using sophisticated physical techniques like differential scanning calorimetry studies & small angle neutron scattering studies which can derive multiple data on microemulsion structure, and their suitable application in pharmaceutical research.

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