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RESEARCH ARTICLE

DEVELOPMENT AND EVALUATION OF MICROEMULSION FORMULATIONS OF LORNOXICAM

Md. Shahidul Islam*, Md. Irfan Uddin[1]
Department of pharmacy, University of Science and Technology Chittagong (USTC), Chattogram, Bangladesh.

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***Address for Correspondence:**
Dr. Md. Shahidul Islam, Department of pharmacy, University of Science and Technology Chittagong (USTC), Chattogram, Bangladesh; Tel: +88 01815579040.
E-mail: *s_i_liton@yahoo.com*

Abstract

Background and aims: Microemulsions (ME) basically are the mixture of oil, surfactant (SA) and water, with a co surfactant (Co-SA) in different ratio. This mixture is clear and stable. The final prepared fluid possesses low viscosity. ME are isotropic, stable transparent systems of with a droplets diameter>500 nm. Due to small droplets size, they may serve an excellent carrier for drugs having poor water solubility. Lornoxicam is derivative of allylamine, and is used orally in the treatment of hepatic failure, neutropenia.
Methods: In the present study an attempt was made to increase solubility of Lornoxicam by the means of ME formulations. Oil, surfactant and co-surfactant were selected based on their solubility criteria. Total 5 formulations were developed using water titration method. Prepared formulations were evaluated on different parameters.
Results: The percent transmission was found to be in the range of 98.48±0.15 to 99.42±0.04. Refractive index for the micro emulsion formulations was found to be in the range of 1.3218±0.009 to 1.3720±0.021. Percent drug content was found to be in the range of 98.47±0.08 to 99.75±0.21. ME5 has shown faster drug release 91.2±0.06% in an *in-vitro* study of 4 hrs.
Conclusion: Study concluded that the means of microemulsions formulations solubility of Lornoxicam can be enhanced.
Keywords: Co-surfactant, Lornoxicam, microemulsions, surfactant, thermodynamics.

INTRODUCTION

A microemulsion is considered to be a thermo-dynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension[1,2]. Because the droplet size is less than 25% of the wavelength of visible light, microemulsions are transparent.
ME are clear systems of with a droplets diameter>500 nm[3]. Due to small droplets size, they may serve an excellent carrier for drugs having poor water solubility. Aqueous phase consists of salt(s), and/or other ingredients, while oil consists of hydrocarbons and olefins. There is need of high shear in the preparation of emulsions, but for ME, there is no need of high shear, they simply formulated by the mixing of different ingredients[3,4,5]. O/W microemulsion tends to increase solubility by changing in its dispersed phase and improve oral bioavailability by the means of increase in rate of absorption and its wettability[6,7,8].
Lornoxicam is a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class with analgesic (pain relieving), anti-inflammatory and antipyretic (fever reducing) properties[9,10].
The aim of present study was to develop and evaluate microemulsion formulations of Lornoxicam to avoid first pass metabolism and to minimize the adverse effect on the g.i.t like mild dyspepsia and heartburn to ulceration and hemorrhage.

MATERIALS AND METHODS

Lornoxicam was obtained as the Gift samples from Incepta Ltd. Octanol, Span 80, and Tween 80 from Merck ltd, Mumbai, India. Castor oil, soyabean oil, linseed oil was obtained from USTC, Foys lake, Chittagong, Department of pharmacy.

Selection of the oil phase

Selection of the oil phase was based upon the maximum solubility of the drug. Different oils

including castor oil, Capmul Pg-12, soyabean oil, Kollisolv GTA, MCT were taken for solubility studies. Based on the solubility Capmul Pg-12 was selected as the oil phase[11].

Selection of surfactants and co surfactant

Solubility of Lornoxicam was checked in different surfactants and co surfactants. Emulsification efficiency of surfactants and co-surfactants to check their ability to emulsify selected oil. To determine the emulsification ability, equal amount of surfactant was mixed with drug and after proper dilution, it was monitored for transmittance at 638 nm using UV-Vis spectrophotometer. The ease of formation of emulsion was monitored by the number inversions of volumetric flask required to produce uniform emulsion. Similarly co surfactant were selected based on their ability to form stable and clear micro emulsion at a minimum concentration[11].

Solubility analysis

About 10 gm of oil was accurately weighed in 25 ml glass beaker and 100 mg of Lornoxicam was added into it, followed by stirring on magnetic stirrer at moderate speed to dissolve the drug. When drug was dissolved completely another 10 mg Lornoxicam of was added and stirring was continued. Addition of drug was continued until the saturated solution is obtained. Finally, the total amount of drug consumed was determined by using UV-spectrophotometer at 250 nm. In the similar way solubility of Lornoxicam was checked in different surfactants and co-surfactants[12,13].

Preparation of drug loaded microemulsion

Formulations were developed using water titration method. Predetermined amounts of Lornoxicam (100) mg was dissolved in the required quantity of Capmul Pg-12 (oil). Tween-80**:** (surfactant) and Propylene glycol (co-surfactant) were added to the above mixture in different ratio. Distilled water was added gradually with continuous stirring, which resulted in the formulation of a transparent and homogenous microemulsion[14,15,16].

Characterization of micro emulsion

Percentage Transmittance

Transparency of micro emulsion formulation was determined by measuring percentage transmittance through U.V. Spectrophotometer at 638 nm with distilled water taken as blank and three replicates were performed for each sample[17].

pH determination

The apparent pH of all micro emulsions was determined at 25°C by immersing the electrode directly into the micro emulsion using a digital pH meter[18,19].

Refractive index

Refractive indices of the prepared micro emulsions were determined at 25°C by Abbe's refractometer by placing one drop of micro emulsion on the slide[20].

Viscosity measurement

Micro emulsions are generally low viscosity systems. The viscosity of the prepared micro emulsion was measured at 25°C at 60 rpm by LV spindle no. 63 using a Brookfield viscometer[21].

Determination of drug Content in the Lornoxicam micro emulsion formulations

The drug content of the micro emulsion formulation was determined by dissolving 1 ml (equivalent to 10 mg drug) of the formulation in 10 ml of methanol. After suitable dilutions with methanol, absorbance was determined using the UV spectrophotometer keeping blank micro emulsion as control at wavelength 250 nm and three replicates were performed for each sample[22].

Drug solubility study: Lornoxicam was added in excess to the optimized microemulsion formulation as well as each individual ingredient of the formulation. After continuous stirring for 4 hours at room temperature, samples were withdrawn and centrifuged for 10 minutes. The amount of drug soluble in optimized formulation as well as each individual ingredient of the formulation was calculated by subtracting the drug in the sediment from the total amount of drug added. The solubility of drug in microemulsion was compared with respect to its individual ingredients[22].

***In-vitro* drug release:** The diffusion study was carried out on a modified Franz diffusion cell of volume 20 ml. The receptor compartment was filled with 20 ml of Phosphate buffer (pH 7.4). The donor compartment was fixed with cellophane membrane (Cut Off weight=1000 Da) contains Lornoxicam microemulsion formulation (equivalent to 5 mg of drug) and plain drug solution separately. At predetermined time intervals samples were withdrawn from receptor compartment and analyzed for drug content by UV Spectrophotometer at 250 nm[23].

Drug release kinetic data analysis:

Release data was evaluated through PCP disso software for the kinetic models. First order, and Peppas and Korsmeyer model were studied[23].

RESULTS AND DISCUSSION

Solubility of the oil phase, surfactant and co-surfactant

Solubility of Lornoxicam was checked in different oil to select the oil for the preparation of micro emulsion formulation. On the basis of solubility Capmul Pg-12 was selected as the oil and on the basis of emulsification efficiency and solubility Tween 80 was selected as the surfactant and Propylene glycol as the co-surfactant. Given Lornoxicam sample has shown maximum absorption (λ_{max}) at 250 nm. FTIR spectroscopy was used to detect any kind of interaction between Lornoxicam and used oil (Capmul Pg-12), surfactant (Tween 80), co-surfactant (Propylene glycol). No change in peak was found, that indicate compatibility between them.

Total five formulations were developed to enhance the solubility of the Lornoxicam. Prepared formulations were further studied for different parameters including percent transmittance, drug content, pH determination, refractive index, viscosity, drug release. **Percentage Transmittance**

The percent transmission carried out on UV spectrophotometer at 638 nm was found to be in the range of 98.48±0.15 to 99.42±0.04 for all which confirms good transparent nature of formulations.

Table 1: Solubility of Lornoxicam.

Oils	Solubility	Surfactant	Solubility (mg/ml)	Cosurfactant	Solubility (mg/ml)
Castor Oil	1.42±0.08	Span 80	10.65±2.31	PEG 200	17.54±0.49
Soyabean Oil	0.47±0.06	Tween 80	13.73±0.77	PEG 400	8.45±0.09
Peanut oil	0.53±0.08	Labrasol	11.53±0.09	Propylene glycol	24.97±0.55
Capmul Pg-12	14.25±0.07	Tween-60	12.45±0.08	Iso propyl alcohol	0.93±0.09
Linseed oil	1.4453±0.07				
Cottonseed oil	0.649±0.08				

Table 2: Emulsification efficiency (selected oil and surfactant).

Surfactant	% Transmittance	HLB Value
Tween-80	89.07±0.05	14
Labrasol	74.38±0.09	13
Tween-60	83.15±0.08	13.9

Table 3:Emulsification efficiency (selected surfactant and cosurfactant).

Co-surfactant	% Transmittance	HLB Value
PEG 200	72.141±0.0138	5-6
PEG 400	74.132±0.0141	8-9
Propylene glycol	79.253±0.0231	11.6

pH determination: For the micro emulsion formulations, the pH value was found to be in the range of 3.34±0.18 to 4.22±0.22.

Refractive index: The refractive index for the micro emulsion formulations was found to be in the range of 1.3218±0.009 to 1.3720±0.021.

Drug Content: The drug content was found to be in the range of 98.47±0.08 to 99.75±0.21 in the micro emulsion formulations.

Viscosity: The viscosity was found to be in the range of 63.13±2.1 to 70.86±4.74 in the micro emulsion formulations. The viscosity of the micro emulsion increased with increasing concentration of the surfactant[18].

Drug release studies: It was seen that after 4 hours of diffusion, the drug released from the formulation ME5 faster and more than that of the other ratios i.e., 91.2±0.06%.

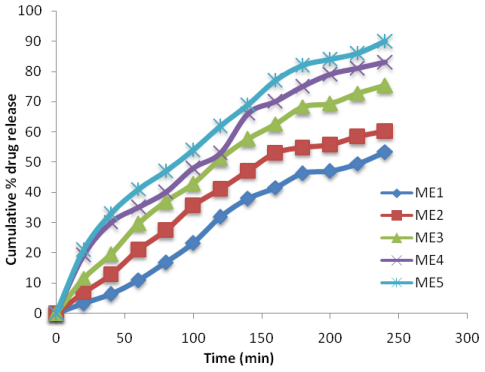

Figure 1: *In vitro* study of prepared Lornoxicam micro emulsion formulations.

Table 4: Composition of batches for Lornoxicam microemulsion.

Code	S_{mix} ratio	% w/w composition		
		Oil (%)	S_{mix}	Water (%)
ME1	1:1	30	60	10
ME2	1:2	60	35	5
ME3	1:3	35	60	10
ME4	2:1	50	40	10
ME5	3:1	40	55	5

Table 5: Evaluation parameters of prepared ME Terbinafine formulations.

Batch	Transmittance (%)	pH	Refractive index	Viscosity (cp)	Drug content (%)	Solubility mg/ml
ME1	99.42±0.04	3.46±0.06	1.3648±0.012	63.13±2.1	98.57±0.12	26.87±0.08
ME2	99.15±0.06	3.56±0.13	1.3720±0.021	66.56±3.7	98.47± 0.08	29.87±0.11
ME3	99.26±0.12	3.62±0.27	1.3618±0.031	68.66±5.77	99.36±0.09	30.87±0.08
ME4	98.37 ±0.13	3.34±0.18	1.3520±0.026	69.53±3.34	99.85±0.08	27.87±0.09
ME5	98.48±0.15	4.22±0.22	1.3218±0.009	70.86±4.74	99.75±0.21	32.87±0.13

Table 6: Different release models for Lornoxicam micro emulsion formulations.

Batch	Kinetic model	Parameters
ME1	Peppas and Korsmeyer	R=0.965, K1=4.234, n=0.750
ME2	Peppas and Korsmeyer	R=0.974, K1=3.147, n=0.854
ME3	First order	R=0.952, K1=5.61, n=0.750
ME4	Peppas and Korsmeyer	R=0.934, K1= -0.070
ME5	Peppas and Korsmeyer	R=0.963, K1=6.812, n=0.772

Kinetic modelling for micro emulsion –
In present study PCP disso Version 2 software was used in for the estimation of release pattern. Models for the release kinetic profile are shown in Table 6. *In-vitro* release data were plotted in 2 different models i.e. first, and Korsemeyer peppas. It was observed that release was governed by the diffusion process.

CONCLUSIONS

Due to small droplets size, they may serve an excellent carrier for drugs having poor water solubility. Aqueous phase consists of salt(s), and/or other ingredients, while oil consists of hydrocarbons and olefins. There is need of high shear in the preparation of emulsions, but for ME, there is no need of high shear, they simply formulated by the mixing of different ingredients. Present study concludes successful delivery of Lornoxicam by the means of micro emulsion formulations.

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AUTHOR'S CONTRIBUTION

Islam MS: Conceived idea, data collection, data analysis. **Uddin MI:** methodology, investigation. All the authors approved the finished version of the manuscript.

DATA AVAILABILITY

Data will be made available on reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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