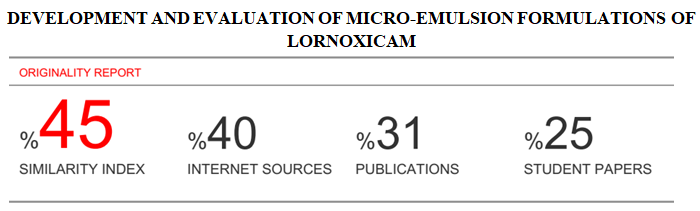
**Reviewer’s Comments**

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**DEVELOPMENT AND EVALUATION OF MICRO-EMULSION FORMULATIONS OF LORNOXICAM**

**ABSTRACT:**

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. Whenever given topically, it is used for the skin infections like jock itch, and for ringworm and Candida species.In the present study an attempt was made to increase solubility of Lornoxicam by the means of ME formulations. Prepared formulations were evaluated on different parameters.Study concluded that the means of microemulsions formulations solubility of Lornoxicam can be enhanced.  
**Keywords**: Microemulsions, Lornoxicam,Thermodynamics, Co-solvents, Transparent, Coarse.

**INTRODUCTION:**

A microemulsion is considered to be athermodynamically or kinetically stable liquid  
dispersion of an oil phase and a water phase, incombination with a surfactant. The dispersed phasetypically comprises small particles or droplets, with asize range of 5 nm-200 nm, and has very low oil/waterinterfacial tension1,2. 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 nm3. 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 ingredients4.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 wettability5-8.

Lornoxicam is a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class with analgesic (pain relieving), anti-inflammatory and antipyretic (fever reducing) properties9,10.

The aim of my present study is 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.

**MATERIALSAND METHODS:**

**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 phase10.

**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 concentration11.

**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-surfactants12-15.

**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 microemulsion16,17.

**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 sample18.

**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 meter19.

**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 slide20.

**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 viscometer21.  
**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 sample22.  
**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 ingredients23.

***In-vitro* drug release:** The diffusion study was carried out on a modified Franz diffusion cell of  
volume 20ml. 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 nm24.

**Drug release kinetic data analysis:**

Release data was evaluated through PCP disso software for the kinetic models. First, and Peppas and Korsmeyer model were studied25-27.

**Statistical analysis**

**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 |

**Table 4: Composition of batches for Lornoxicam micro emulsion.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Code** |  |  | | |
| **% Oil** |  |  |
| 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 |

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

**Table 6: Different release models for Lornoxicammicro 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 |

**RESULTSAND DISCUSSION:**

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**Solubility of the oil phase, surfactant and co-surfactant**

Solubility ofLornoxicam 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 (λmax) 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 UVspectrophotometer at 638 nm was found to be in the  
range of 98.48 ± 0.15to 99.42 ± 0.04for all which confirms goodtransparent nature of formulations.

pH determination

For the micro emulsionformulations, the pH value was found tobe in the range of 3.34 ± 0.18 to 4.22 ± 0.22.

Refractive indexThe refractive index for the micro emulsionformulationswas found to be in the range of 1.3218±0.009to 1.3720 ± 0.021.

Drug ContentThe drug content was found to be in the rangeof 98.47± 0.08 to 99.75 ± 0.21 in the micro emulsionformulations.

Viscosity

The Viscosity was found to be in the rangeof 63.13±2.1 to 70.86±4.74 in the micro emulsionformulations.The viscosity of themicro emulsion increased with increasing concentrationof the surfactant.

**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%.

**Kinetic modeling 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.

**CONCLUSION**

ME are clear systems of with a droplets diameter>500 nm1. Due to small droplets size, they may serve an excellent carrier for drugs having poor water solubility. Aqueous phaseconsists 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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