

Formulation, Development and Evaluation of Etoricoxib Nanosize Microemulsion Based Gel for Topical Drug Delivery

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ABSTRACT

Introduction: Etoricoxib is a poorly water-soluble oral NSAID and is associated with a number of complications such as bleeding, ulcers and dyspepsia but these can be overcome by delivering the drug topically. **Objectives:** Microemulgel for the topical delivery of etoricoxib was formulated to increase its solubility and thus improve the skin permeability. **Methods:** The solubility of etoricoxib was studied in various oils, surfactants and cosurfactants. Pseudo-ternary phase diagrams were constructed by varying the surfactant to cosurfactant (Smix) ratio. Microemulsions with different compositions were formulated and optimized. Selected o/w microemulsions contained 1% etoricoxib and were evaluated for pH, rheology, drug content, particle size and *in vitro* drug release. Optimized microemulsion was incorporated in 1% Carbopol® 934 and was evaluated for rheological properties, spreadability, *in vitro* permeation, skin irritation and stability. **Results:** Capryol™ 90, Tween 80 and Transcutol® P exhibited the highest solubility. Maximum microemulsion region was observed when the Smix ratio was 3:1. The average particle size of the optimized microemulsion was 37.61 nm, zeta potential was -2.88 mV and permeability of the drug from the microemulsion was 66.8% after 8 h. The prepared gel showed 57.8% drug release after 8 hr. Skin irritation studies indicated that the optimized formulation was safe for topical application. Stability studies indicated that the formulation remained unaffected at accelerated storage conditions. **Conclusion:** Results indicated that the micro-emulgel has potential for sustained action of drug release and may act as a promising tool to enhance percutaneous delivery of etoricoxib.

Key words: Etoricoxib, Microemulsion, Topical gel, *in vitro* release, Particle size, Skin irritation.

INTRODUCTION

Rheumatoid arthritis is a chronic, systemic inflammatory disease that affects nearly 1% of the world's adult population and results in the destruction of the joints thereby significantly impairing the quality of life of the patient.¹ This disease is two to three times more likely to affect women than men and can occur at any age, but mostly it starts at middle age.² Osteoarthritis, a chronic disease involves both cartilage and bone and results from an imbalance in erosive and reparative processes. Gout represents a heterogeneous group of diseases that are caused by an inflammatory response to the formation of

monosodium urate crystals which develop secondary to hyperuricemia.³

Etoricoxib (ETO) is a non-steroidal anti-inflammatory drug indicated for the symptomatic relief of rheumatoid arthritis, osteoarthritis and gout.⁴ It belongs to Class II category under the Biopharmaceutical Classification System.⁵ It is available in the form of oral tablets. Major side-effects include: gastrointestinal ulcers, bleeding on chronic use and possibly anemia.⁶

The use of microemulsions as potential drug delivery vehicles has attracted considerable interest due to their ease of prepara-

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tion, clarity, thermodynamic stability, low viscosity, small droplet size and the ability to incorporate hydrophilic as well as hydrophobic drugs.⁷ Most of the drugs, when given by oral route, have side effects such as gastric irritation, nausea, bleeding in the gastrointestinal tract, etc. The topical route of administering such drugs is a substitute, thereby reducing their side effects.⁸

Many of the widely used topical agents such as ointments, creams and lotions are associated with a number of disadvantages. They cause uneasiness to the patient when applied due to their sticky nature and need to be applied with rubbing as they have a lower spreading coefficient.

They also exhibit the problem of stability. Due to these limitations, the use of transparent gels in pharmaceutical preparations has increased. The major disadvantage of gels is their inability to deliver water-insoluble drugs. A hydrophobic drug cannot be directly incorporated into a gel base therefore microemulsion based approach is used so that the drug can be successfully incorporated into a gel-based system. The oil-in-water microemulsion is first prepared and evaluated and then incorporated into a gel base and this dosage form is referred to a microemulsion based gel. It is more advantageous as compared to conventional topical formulations.⁹

In the literature, cream and gel of etoricoxib were developed in order to overcome the toxicities associated with oral administration of the drug.^{10,11} Polymeric nanoparticles, ethosomes and poly (caprolactone) microparticles (MPs) loaded composite injectable chitosan gel were formulated for the topical delivery of etoricoxib.¹²⁻¹⁴ Mouth dissolving films of etoricoxib as an alternative to oral disintegrating tablets due to its ease of administration and better patient compliance.¹⁵ Lala and Awari developed nanoemulsion-based gel improved transdermal delivery of etoricoxib.¹⁶

In this study, a topical microemulsion based gel of etoricoxib was formulated in order to minimize the side effects associated with the oral delivery of the drug. The formulated microemulsion based gel was then evaluated.

MATERIALS AND METHODS

Materials

Etoricoxib was obtained as a gift sample from Sanofi India Limited (Verna, Goa, India). Capryol™ 90 and Transcutol® P were gifted by Gatefosse' (India). Cremophor® RH 40 was received as a gift sample from Centaur Pharmaceuticals Ltd., (Goa, India). Oleic acid, castor oil, isopropyl myristate, olive oil, Tween 20, Tween 80, polyethylene glycol 600, polyethylene glycol 400, isopro-

pyl alcohol, ethanol and propylene glycol were obtained from standard sources. The dialysis membrane was purchased from Himedia (India). All the other chemicals used were of analytical grade.

Screening of oils, surfactants and cosurfactants on the basis of solubility study

The components selected for the formulation of the microemulsions were of pharmaceutical grade, non-irritating and non-sensitizing to the skin and fall under the Generally Recognized as Safe (GRAS) category. The surfactants were chosen based on their Hydrophilic Lipophilic Balance (HLB) value and were non-toxic in nature. The cosurfactant forms a stable microemulsion with the surfactant at a minimum concentration.¹⁷ Screening of the oils, surfactants and co-surfactants was done for etoricoxib solubility using the shake flask method.¹⁸ An excess amount of drug was added to 5 mL of each of the oil, surfactant and cosurfactant in conical flasks and was placed on a mechanical shaker (Orbitek, India) at ambient temperature and humidity for 48 h at 100 rpm. The suspensions were filtered through 0.45 µm membrane filters, diluted appropriately with methanol and the amount of drug dissolved was quantified using a UV-visible spectrophotometer (UV 3092, Labindia, India) against methanol as the blank at 235 nm. The oil, surfactant and cosurfactant that showed the maximum solubility of etoricoxib (ETO) were selected for the formulation of the microemulsions.¹⁹

Screening of the selected surfactant and cosurfactant for emulsification ability

The efficacy of the surfactant and cosurfactant was assessed by the turbidimetric method¹⁹ to improve the ability of micro-emulsification. For screening of the surfactant, 300 mg of surfactant was added to 300 mg of the selected oil phase and heated at 45-60°C to aid in the homogenization of the components. For screening of the cosurfactant, 200 mg of the surfactant and 100 mg of the cosurfactant was added to 300 mg of the oil phase. This mixture was heated at 45-60°C to aid in homogenization. Then, 50 mg of each of the isotropic mixture was diluted to 50 mL with distilled water in a volumetric flask to form a fine emulsion. The emulsions were allowed to stand for 2 hr and their transmittance was measured at 650 nm using a UV-visible spectrophotometer against distilled water as the blank.²⁰

Construction of pseudo-ternary phase diagrams

Pseudo-ternary diagrams were constructed by employing the water titration method²¹ to define the extent and nature of the microemulsion region. The surfactant and cosurfactant (Smix) were mixed in different volume

ratios (K_m) i.e., 1:1, 2:1 and 3:1. The ratio of oil and Smix were varied for each phase diagram i.e., 9:1 to 1:9 (v/v). To each of the oil: Smix mixture, water was added drop-wise under magnetic stirring at ambient temperature and was examined for appearance after each addition. The point where the solution turned turbid or cloudy was the end point of the titration. The volume of water required to make the mixture turbid or cloudy was noted. Pseudo-ternary diagrams were constructed using CHEMIX School 7.00 software. The percentages of the components were calculated and plotted on the pseudo-ternary phase diagram. The points were joined and a boundary between the clear and turbid region was defined.²²

Formulation and development of blank microemulsions

The ratio of the surfactant and cosurfactant was selected from the pseudo-ternary phase diagrams and the o/w microemulsion region was identified. The microemulsions were formulated at definite component ratios i.e. 5-30% for oil, 30-65% for Smix and 35-65% for water. The surfactant, cosurfactant and oil in which the drug had maximum solubility were mixed with continuous magnetic stirring (Remi, India). Fresh deionized water was added drop wise to this uniform blend and mixed well for 30 min to form a transparent microemulsion. The formulations were then evaluated.²³

Formulation of etoricoxib loaded microemulsions

The blank microemulsions were prepared first and checked for stability. Stable blank formulations were then used to formulate microemulsions containing the drug. The drug containing microemulsions were prepared by dissolving accurately weighed etoricoxib in the oil and Smix at room temperature. Water was added dropwise to this mixture with constant stirring at ambient temperature. The micro-emulsions were allowed to equilibrate for 30 min with gentle magnetic stirring. The formed microemulsions were then evaluated after 24 hr. The compositions of the microemulsions are tabulated in Table 1.

Evaluation of blank and etoricoxib loaded microemulsions

The blank and drug loaded formulations were evaluated for clarity and appearance, quantitative tests (dilution and dye test), percent transmittance, viscosity, pH and centrifugation. Drug loaded formulations were also evaluated for drug content, droplet size, polydispersity and zeta potential. In all the tests, the results were recorded in triplicate and the average was considered.

Table 1: Composition of etoricoxib loaded micro-emulsion formulations.

| Formulation | Oil (% v/v) | Smix (% v/v) | Water (% v/v) |
|-------------|-------------|--------------|---------------|
| M5 5% | 5 | 50 | 45 |
| M6 5% | 5 | 55 | 40 |
| M7 5% | 5 | 60 | 35 |
| M4 10% | 10 | 45 | 45 |
| M5 10% | 10 | 50 | 40 |
| M6 10% | 10 | 55 | 35 |

The prepared microemulsions were visually evaluated for their color, homogeneity, consistency and physical changes such as phase separation or precipitation.

Dilution test and dye test were performed to determine whether the formulated microemulsions were w/o or o/w type.

The microemulsions were diluted 10, 100 and 1000 times with distilled water and visually examined for clarity, phase separation and drug precipitation.

A water-soluble dye (methylene blue) was added to the microemulsion and was visually observed for its distribution after 5 min. A rapid dispersion of the water-soluble dye indicates that the microemulsion is o/w type whereas a w/o type of microemulsion provides microscopically visible droplets.

The optical clarity of the microemulsions was determined by measuring the percent transmittance of the formulated microemulsions using a Ultraviolet (UV) - visible spectrophotometer at 650 nm against distilled water as the blank. The percent transmittance of the diluted microemulsions at 10, 100 and 1000 times with the continuous phase was measured in the same manner.

The viscosity was measured using a Brookfield® viscometer (DVE, Brookfield, USA). The spindle number 62 was dipped in the microemulsion and was rotated at 20 rpm at ambient temperature.

The pH of the drug loaded microemulsions was measured using a calibrated digital pH (1010, Esico, India) meter at ambient temperature.

Microemulsion equivalent to 10 mg of etoricoxib was taken in a 10 mL volumetric flask and was extracted using methanol as the solvent. The volume was made up to 10 mL with methanol. The absorbance of the solution was measured after suitable dilution using a UV-visible spectrophotometer at 235 nm and the concentration of the drug was calculated.

The microemulsions were centrifuged at 5000 rpm for 10 min at ambient temperature and the systems were visually examined for creaming and phase separation.

The droplet size, polydispersity index and zeta potential of the microemulsions were measured using a particle size analyzer (Zetasizer zen 3600, Malvern, UK).

In vitro drug release

In vitro drug release study of etoricoxib was carried out using a modified Franz diffusion cell.¹⁶ The semipermeable membrane was previously soaked overnight in phosphate buffer pH 7.4 and was mounted between the donor and receptor compartment. The active diffusion area of the cell was 4.91 cm². Microemulsion equivalent to 10 mg of etoricoxib was placed in contact with the dialysis membrane of the donor compartment. The receiver compartment contained 25 mL of phosphate buffer pH 7.4 and was stirred at 100 rpm using a magnetic stirrer throughout the duration of the experiment. The temperature of the assembly was maintained at 37 ± 2°C. One mL of the fluid from the receptor compartment was periodically withdrawn every one hour up to 8 h and was immediately replaced by an equal volume of receiver fluid. The concentration of the drug in the receptor compartment was determined spectrophotometrically at 234 nm after suitable dilution with phosphate buffer pH 7.4 using the same as the blank.²⁴

Stability studies

The stability studies were performed in accordance with the ICH guidelines.²⁵ The stability of the optimized microemulsion was monitored at 40°C/75% RH for 3 months. It was inspected and evaluated for physical stability, percent transmittance, viscosity, pH, drug content and *in vitro* drug release.

Formulation and development of etoricoxib microemulsion based gel

The low viscosity of microemulsions restricts its application and this disadvantage can be overcome by incorporating them in gelling agents. The optimized drug loaded microemulsion was selected to formulate the etoricoxib microemulsion based gel. Carbopol® 934 was selected as the gelling agent based on previous studies. 1% w/w of the gelling agent was soaked in water for 24 hr. The pH of the Carbopol® 934 gel was adjusted to 6-7 by the dropwise addition of triethanolamine. The microemulsion based gel was prepared by adding the optimized microemulsion to the gel base.

Evaluation of etoricoxib microemulsion based gel

The gel was evaluated for physical appearance, viscosity, pH, spread ability and drug content, in all the tests, the results were recorded in triplicate and the average was considered.

The microemulsion based gel was visually examined for its appearance, color, consistency, homogeneity, texture, etc.

The viscosity of the microemulsion based gel was measured using a DVE, Brookfield Viscometer. The spindle number 64 was dipped in the formulation and was rotated at 20 rpm at ambient temperature.

The pH of a 1% aqueous solution of the microemulsion based gel was measured using a digital pH meter.

The spread ability of the etoricoxib microemulsion based gel was determined as per the procedure described by Bachhav, *et al.* 0.5 g of the microemulsion based gel was placed within a 1 cm diameter circle premarked glass plate over which a second glass plate was placed. A 5 g weight was allowed to rest on the upper glass plate for 5 min. The increase in diameter of the micro-emulgel due to spreading was noted.²⁶

Microemulsion based gel, equivalent to 10 mg of etoricoxib was taken in a 10 mL volumetric flask and was dissolved in methanol. The volume was made up to 10 mL with methanol. The absorbance of the solution was measured after suitable dilution using a UV-visible spectrophotometer at 235 nm and the concentration of the drug was calculated.

In vitro release study

In vitro drug release study of etoricoxib loaded microemulsion based gel was carried out using a modified Franz diffusion cell with an active diffusion area of 4.91 cm². The membrane which was previously soaked overnight in phosphate buffer pH 7.4 was mounted between the donor and receptor compartment. The 1 g of the drug loaded microemulsion based gel equivalent to 10 mg of etoricoxib was placed in contact with the dialysis membrane of the donor compartment. The receiver compartment contained 25 mL of phosphate buffer pH 7.4 and was stirred at 100 rpm using a magnetic stirrer throughout the duration of the experiment. The temperature of the assembly was maintained at 37±2°C. Then, 1 mL of the fluid from the receptor compartment was periodically withdrawn every one hour up to 8 h and was immediately replaced by an equal volume of receiver fluid. The concentration of the drug in the receptor compartment was determined spectrophotometrically at 234 nm after suitable dilution with phosphate buffer pH 7.4 using the same as the blank.

Kinetic modelling in vitro drug release results

The results of *in vitro* studies were fitted in the zero order, first order, Higuchi and Korsmeyer-peppas kinetic models.

Ex vivo permeation study

Ex vivo release studies were carried out on goat's pineal skin as the thickness of the skin over the pinna is less as compared to other parts. The hair was removed from the upper portion of the skin surface and the excised skin was thoroughly washed with distilled water and phosphate buffer pH 7.4. The permeation studies were performed using a modified Franz diffusion cell with an active diffusion area of 4.91 cm². The excised skin was mounted between the two compartments with the stratum corneum facing the donor compartment. 25 mL of phosphate buffer pH 7.4 was placed in the receiver compartment and stirred at 100 rpm. Then, 1g of microemulsion based gel containing 1% w/w etoricoxib was placed in the donor compartment on the skin surface. The temperature of the assembly was maintained at 37±2°C. One mL of the fluid from the receptor compartment was periodically withdrawn every one hour up to 8hr and was immediately replaced by an equal volume of receiver fluid. The concentration of the drug in the receptor compartment was determined spectrophotometrically at 234 nm after suitable dilution with phosphate buffer pH 7.4 using the same as the blank.²¹

Stability studies

The stability of the microemulsion based gel was monitored at 40°C/75% RH for 3 months. The formulated microemulsions were visually inspected and evaluated for physical stability, viscosity, pH, drug content and *in vitro* release.

RESULTS AND DISCUSSION

Screening of the shortlisted oils, surfactants and cosurfactants

Based on the criteria for the selection of the microemulsion components, oleic acid, isopropyl myristate, olive oil, castor oil and Capryol™ 90 was selected as oils, Tween 20, Tween 80 and Cremophor® RH as surfactants and polyethylene glycol (PEG) 400, PEG 600, propylene glycol, ethanol and Transcutol® P as cosurfactants. The saturation solubility of etoricoxib in various oils, surfactants and cosurfactants is shown in Figure 1. Among the selected oils, Capryol™ 90 showed the maximum solubility while isopropyl myristate had the lowest solubility. Thus, Capryol™ 90 was selected as the oil for further studies. The primary factor to be considered while selecting a surfactant is its safety. Ionic surfactants have been reported to be more toxic than non-ionic surfactants.²⁷ A particular balance of low and high HLB surfactants is necessary to reduce the amount of surfactant used. Solubility of etoricoxib in Tween 80

was the highest among the surfactants. Transcutol® P demonstrated highest solubility of etoricoxib as compared to the other tested cosurfactants.

Screening of the selected surfactant and cosurfactant for its emulsification ability

The percentage transmittance of the dispersions is given in Table 2. The emulsification study indicated that the surfactant Tween 80 had good ability to emulsify Capryol™ 90. The pseudo-ternary phase diagrams of Capryol™ 90 with Tween 80 and Transcutol® P at various Km ratios, i.e. 1:1, 2:1 and 3:1 is represented in Figure 2. The microemulsion area is represented by the colored portion in the phase diagram while the non-coloured portion represents the existence of a turbid and conventional emulsion. The phase diagram with the Smix ratio of 3:1 showed the highest area of emulsification and was therefore selected for further studies. It can be seen that an increase in the weight ratio of Tween 80 resulted in an expansion of the microemulsion region. This may be due to the reduction of the interfacial tension, increasing the fluidity of the interface and thereby increasing the entropy of the system.²⁸

Formulation and development of blank microemulsions

The o/w microemulsion region was identified in the pseudo-ternary phase diagram. A high concentration of

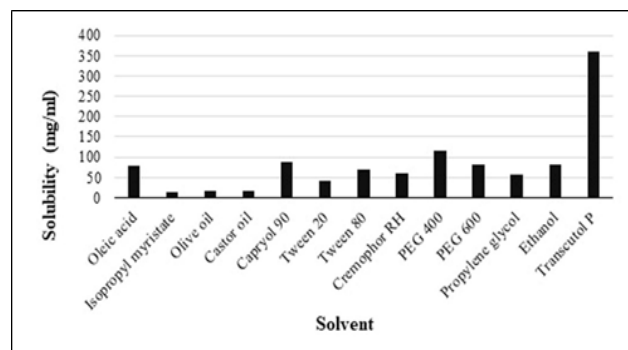


Figure 1: Bar graph indicating the solubility of ETO in various oils, surfactants and cosurfactants.

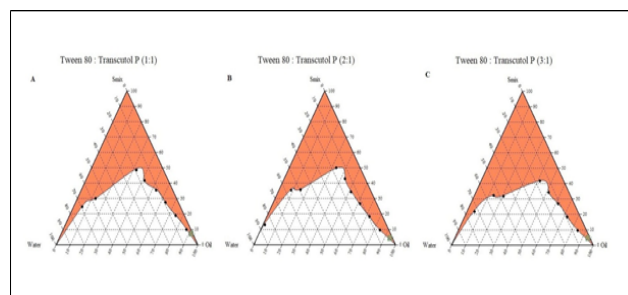


Figure 2: Pseudo-ternary phase diagrams of MEs comprising of Capryol™ 90, Smix (Tween 80: Transcutol® P) and water at various oil: Smix ratios; (A) 1:1, (B) 2:1, (C) 3:1.

oil and surfactant in the formulation can cause toxicity and skin irritation. It should be determined properly and an optimum concentration should be used. The maximum safe concentration of Smix was selected as 60%. In the present study, blank microemulsions were prepared at 5-30% oil, 30-60% Smix and 35-65% water by water titration method.

Evaluation of the microemulsions

Among the formulated blank microemulsions the microemulsions M5 5%, M6 5%, M7 5%, M4 10%, M5 10% and M6 10% were found to be clear, stable and had appreciable viscosity.

These blank microemulsion formulae were formulated into drug loaded microemulsions and were further evaluated.

Evaluation of etoricoxib loaded microemulsions

The drug loaded microemulsions did not show any physical changes such as phase separation or precipitation. They were clear transparent liquids with a homogeneous appearance and a yellow tinge.

Qualitative test

Upon dilution microemulsions were clear and did not show phase separation or precipitation indicating that the microemulsions were o/w type.

In dye test, the water-soluble dye (methylene blue) that was added to the microemulsions got rapidly dispersed throughout the microemulsions indicating that they were o/w type of microemulsions.

The percent transmittance of the drug loaded microemulsions and the microemulsions after dilution were close to 100% indicating that the microemulsions were clear and transparent.

The viscosity of the microemulsions was found to be in the range of 72 ± 0.577 cps and 127 ± 1.000 cps and increased with the increase in concentration of the surfactant and cosurfactant.

The pH range accepted for dermal preparations is 4-7 i.e. close to the pH of the skin. The pH of all the systems lied within the limit.

The drug content of the formulations was found to be in the range of 90.43 ± 0.907 to 98.03 ± 0.611 with formulation M7 5% having the highest amount of drug content.

When subjected to centrifugation, drug loaded microemulsions did not show any signs of phase separation or precipitation thereby confirming the stability of the microemulsions.

Droplet size, polydispersity index and zeta potential measurement

The concentration of the oil phase in the formulated microemulsion affected the globule size. The average globule size increased with the increase in the concentration of the oil. The smaller globule size of microemulsion was obtained due to the higher concentration of surfactant and cosurfactant in microemulsion system. The decrease in the globule size can be attributed to the solubilization of internal phase within a larger number of surfactant micelles, which are consequently swollen to a lesser extent. PDI varies from 0.0 to 1.0 and is a measure of particle homogeneity. The particles are more homogenous if the PDI value is closer to zero. The PDI of the formulations was found to be less than 1 and indicated acceptable homogeneity. The zeta potential of the formulations was found to have a negative charge. Due to the slight negative charge of the droplets, aggregation is less likely to happen. The results

Table 2: Emulsification study on surfactant and cosurfactant.

| Sr. No. | Dispersion | Percent transmittance (Mean \pm SD, $n=3$) |
|---------|------------------|---|
| 1. | For surfactant | 99.8 \pm 0.058 |
| 2. | For cosurfactant | 99.8 \pm 0.115 |

Table 3: Results of particle size, zeta potential and polydispersity index.

| Formulation | Particle size (nm) | Zeta potential (mV) | Polydispersity index |
|-------------|--------------------|---------------------|----------------------|
| M5 5% | 35.14 \pm 0.3 | -0.187 \pm 0.012 | 0.327 \pm 0.006 |
| M6 5% | 17.78 \pm 0.5 | -1.11 \pm 0.04 | 0.250 \pm 0.002 |
| M7 5% | 37.61 \pm 0.2 | -2.88 \pm 0.03 | 0.162 \pm 0.005 |
| M4 10% | 178.7 \pm 0.1 | -1.20 \pm 0.24 | 0.521 \pm 0.014 |
| M5 10% | 161.0 \pm 0.4 | -1.70 \pm 0.011 | 0.312 \pm 0.001 |
| M6 10% | 128.0 \pm 0.1 | -2.03 \pm 0.19 | 0.301 \pm 0.008 |

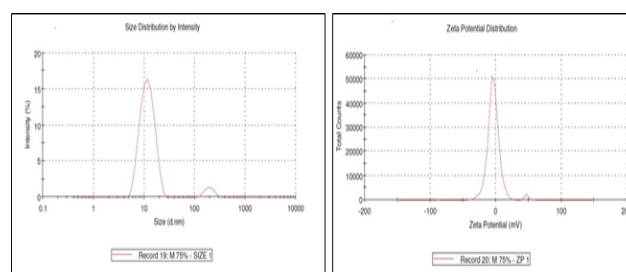


Figure 3: Graph of (A) particle size and (B) zeta potential of formulation M7 5%.

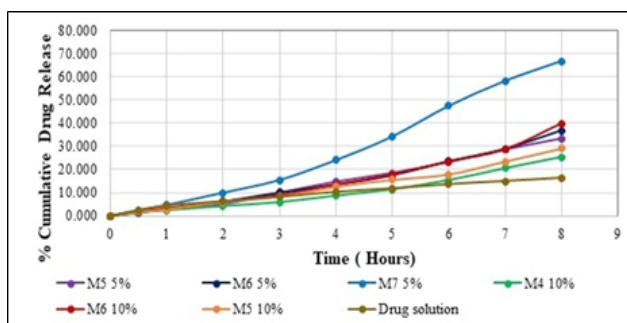


Figure 4: Graph of cumulative drug release vs time of selected microemulsion formulations and drug solution.

of particle size, zeta potential and polydispersity index are depicted in Table 3. Formulation M7 5% was found to have satisfactory results and is depicted in Figure 3 (A) and 3 (B).

In vitro drug release

The *in vitro* release profile of the drug from the selected microemulsions and drug solution is depicted in Figure 4. This study was performed to find out the amount of drug released by the formulation and the results were compared with that of the pure drug solution. The optimum formulation M7 5%, showed a release of 66.82% in 8 hr indicating that the diffusion was increased with the use of a higher ratio of surfactant mixture. The formulated microemulsions showed a higher release as compared to the drug solution. This may be due to the solubility enhancing capacity of the surfactant and cosurfactant.

From the above tests carried out on the ETO microemulsions formulation M7 5% was found to exhibit superior results and was therefore selected as the optimized formulation.

Stability studies

The optimized microemulsion were found to be stable. No significant deviations were observed at 40°C/75% RH in 3 months' time.

Formulation and development of etoricoxib microemulsion based gel

The optimized microemulsion M7 5% was incorporated into the gel base to form a microemulsion based gel.

Evaluation of etoricoxib microemulsion based gel

The prepared microemulsion based gel was found to have a glossy appearance with a smooth and homogeneous texture. The gel was clear with a gel consistency and no phase separation was observed.

The viscosity of the etoricoxib loaded microemulsion based gel was found to be 9742 ± 63.592 cps.

The pH of the microemulsion based gel of etoricoxib was found to be 6.75 ± 0.015 which is equivalent to the pH of the skin and is therefore suitable for topical application.

In spreadability test, the diameter was found to be 6.8 ± 0.021 cm which is indicative of good spreadability.

The etoricoxib content of the microemulsion based gel was found to be $97.6 \pm 0.458\%$ of the theoretical value. The amount of drug released after 8 h from the microemulsion based gel was found to be $57.804 \pm 0.561\%$ indicating slow release

Kinetic modelling of *in vitro* release results

The regression coefficient for zero order, first order and Higuchi model was found to be 0.9327, 0.8384 and 0.8404. It can be deduced that the microemulsion based gel follows zero order kinetics due to the higher correlation coefficient of the zero-order plot as compared to that of the first order plot. The correlation coefficient is close to 1 indicating that the formulations exhibit diffusion mechanism in drug release and is suitable for modified release formulations. The data was subjected to Korsmeyer-peppas plot and the '*n*' value was found to be higher than 0.89 indicating that the formulation exhibits super case II transport type of diffusion.

Ex vivo permeation studies

The *ex vivo* permeation studies was carried out on the microemulsion based gel and was found to be $49.191 \pm 0.622\%$ which is comparable with earlier results of *in vitro* studies.

Stability studies

The results of the stability studies of the microemulsion based gel showed no significant change in physical appearance, viscosity, pH, drug content and *in vitro* release after 3 months of storage at accelerated conditions of temperature and humidity.

CONCLUSION

The microemulsion based drug delivery system of ETO was successfully prepared by initially formulating a microemulsion comprising of Capryol™ 90, Tween 80 and Transcutol® P as the oil, surfactant and cosurfactant respectively. The microemulsion was then incorporated into a 1% Carbopol® 934 gel base. The formulated microemulsion based gel of ETO has a potential for the transdermal delivery of the drug thereby overcoming the complications associated with the oral administration of the drug. The *in vitro* release of the drug from the microemulsion based gel was much higher than that of the drug solution. Thus, this study demonstrated

that the microemulsion based gel formulation can be employed to improve the solubility and skin permeability of etoricoxib.

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CONFLICT OF INTEREST

The authors have no conflict of interest

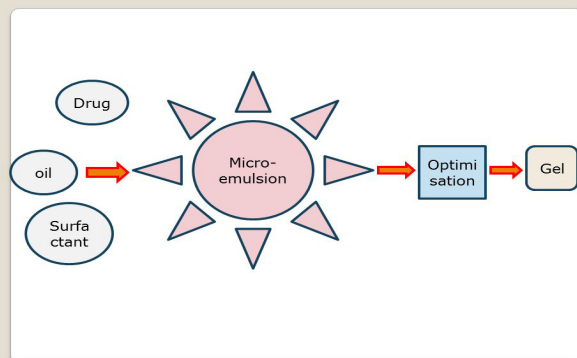
ABBREVIATIONS

NSAID: Non steroidal antiinflammatory drug; **MP'S:** Microparticles; **v/v:** Volume/volume; **UV:** Ultraviolet; **UK:** United Kingdom; **RH:** Relative Humidity; **IAEC:** Institutional Animal Ethics Committee; **PDI:** Polydispersity Index; **ETO:** Etoricoxib; **o/w:** Oil in water.

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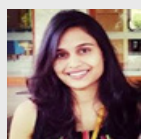
PICTORIAL ABSTRACT



SUMMARY

Microemulsion based gel for the topical delivery of etoricoxib was formulated to avoid complications associated with oral administration and to increase its solubility and thus improve the skin permeability. Formulations were prepared by testing solubility of etoricoxib in various oils, surfactants and cosurfactants with different compositions and optimized. Optimized 1% etoricoxib microemulsion was evaluated for pH, rheology, drug content, particle size and *in vitro* drug release. Gel was then prepared using 1% Carbopol® 934 and was evaluated for rheological properties, spreadability, *in vitro* permeation, skin irritation and stability. The optimized formulations showed 57.8% drug release after 8 hours. The formulation was also found to be stable. Etoricoxib microemulgel can be used for sustained action of drug release and to enhance percutaneous delivery.

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