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Research Article

# FORMULATION AND CHARACTERIZATION OF ETORICOXIB AND METHYL SALICYLATE LOADED NANOEMULGEL

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## *ABSTRACT*

*The aim of the present work was to formulate and characterize the nanoemulsion based gel for the poorly water soluble Etoricoxib and orally toxic Methyl salicylate in order to overcome the side effects associated with its oral delivery. Pseudoternary phase diagrams were constructed using titration method. Various components of nanoemulsion were selected on the basis of compatibility study, solubility study, and emulsification ability. Nanoemulsion (NE) was formulated by low energy method and characterized for vesicle size, polydispersity index, zeta potential, TEM, % entrapment efficiency, rheological study and in-vitro skin permeation study. The optimized nanoemulsion formulation (NE1) is then converted into Nanoemulgel using 1.5% Carbopol 934. Drug loaded nanoemulgel were evaluated for viscosity, spreadability, rheological behavior, uniformity of drug content, permeation studies and stability studies. Transdermal permeation of Etoricoxib and methyl salicylate from nanoemulgel was determined by using franz diffusion cell across excised rat skin. Nanoemulgel containing 7% oleic acid as oil, 33% Tween 80, and 33% Propelyne glycol as surfactant co-surfactant mixture respectively, 27% water, 1% Etoricoxib, 2% Methyl salicylate and 1.5% carbopol 934 was concluded as optimized formulation (NG). Formulated nanoemulgel was compared with marketed gel formulation for in-vitro skin permeability. Nanoemulgel showed the two-fold increase (P<0.05) higher cumulative amount of drug permeation and flux (71.32 ±0.733 µg/cm2/hr) than marketed formulation (39.07 ± 0.52 µg/cm2/hr). Hence can be concluded that nanoemulgel formulation will treat inflammation more effectively than marketed gel.*

***KEYWORDS:*** *Anti-inflammatory, Nanoemulgel, Etoricoxib, Methyl salicylate.*

## INTRODUCTION

Nanoemulsion and nanoemulgel are promising tools for transdermal drug delivery. Nanoemulsion is an isotropic dispersion of oil, water, surfactant and co-surfactant which is thermodynamically stable and having droplet size 10µm-100µm [1].

NSAIDs are the most commonly used drugs to reduce pain and inflammation. Etoricoxib is a well-known COX-2 inhibitor. Etoricoxib recommended orally for patients with chronic inflammatory degenerative diseases such as rheumatoid arthritis and osteoarthritis, and also as anti-inflammatory agents. The chronic oral administration of Etoricoxib causes gastrointestinal ulcers, GI bleeding, high renal toxicity, and adverse cardiovascular effects. The major disadvantage of COX-2 inhibitors is it not shows significant action on COX-1 [2]. Hence when methyl salicylate used in combination with Etoricoxib. Methyl salicuylate shows significant action on COX-1 also [3]. Hence it results in increase in Anti-inflammatory activity. Therefore, an improved nanoemulsion formulation of COX inhibitors such as Etoricoxib and Methyl salicylate with a high degree of permeation could be useful in the treatment of inflammatory conditions.

Use of the transdermal route eliminates these side effects, increases patient compliance and avoids the first-pass metabolism. Nanoemulsion and Nanoemulgel are most promising techniques for enhancement of transdermal permeation. Nanoemulsions are thermodynamically stable transparent dispersions of oil and water stabilized by an interfacial film of surfactant and co-surfactant molecules having a droplet size of less than 10µm-100µm [1].

The present work describes effective use of nanoemulgel for the topical delivery of Etoricoxib and Methyl salicylate using nonirritating, pharmaceutically acceptable ingredients without using additional permeation enhancers. The objective of the research work was to investigate the potential of Etoricoxib and Methyl salicylate loaded nanoemulsion-based emulgel for topical delivery. This alternative route will help to achieve the fast effect and avoid the oral side effect of the drug.

## MATERIALS AND METHODS

### Materials:

Etoricoxib was purchased from Torent pharmaceutical. Oleic acid and Methyl salicylate perches from S d fine-chem limited. propylene glycol was purchased from Fisher scientific, tween 80 and carbopol 934 was purchased from Loba Chemie pvt ltd, triethanolamine was purchased from Qualigens, methyl Paraben and propyl Paraben was purchased from Central drug house. All other reagents used were of analytical grade. Wistar rat skin was obtained from Dr. V.V.P.F's College of Pharmacy, Ahmednagar.

### Methods:

***Determination of solubility of Etoricoxib:*** The solubility of Etoricoxib in various oils (olive oil, oleic acid, isopropyl myristate, and castor oil) was determined by dissolving an excess amount of Etoricoxib in 5 ml of each of the selected oils, surfactants, and co-surfactants in stoppered vials. The mixture was continuously stirred for 15 min and keep in an isothermal shaker at 37±1ºc for 72 hrs. The equilibrated samples were centrifuged (3000 rpm for 15 min) and the supernatant was filtered through 0.45 m membrane filter and diluted with ethanol. Drug content was quantified by using UV-VIS spectrophotometer (JASCO) at

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233 nm [4].

***Screening of components for nanoemulsion:*** Compatibility studies were carried out to investigate interactions between the drug and the polymers. Interaction studies were carried out by infrared spectroscopy and DSC [5]. On the basis of solubility studies, the oil was selected that possesses the best solubilization capacity for Etoricoxib. Screening of surfactant and co-surfactant was done on the basis of percent transmittance. Emulsification ability of surfactants to selected oil and their HLB values [6].

***Construction of phase diagrams:*** Pseudoternary phase diagrams were constructed using titration technique. Oleic acid was used as the oil phase. Surfactant co-surfactant mixture was composed of tween 80 as surfactant and propelyne glycol as co-surfactant. Three weight ratios (1:0, 1:1, and 2:1) of tween 80 to propelyne glycol were optimized to determine the optimum ratio which can result in maximum nanoemulsion existence area. The ratios of oleic acid to surfactant co-surfactant mixture were varied as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. These mixtures were titrated with water, drop wise using micro syringe until the onset of turbidity or phase separation the mixtures were stirred vigorously for a sufficient length of time for homogenization, and the end point was visually monitored against a dark background. This experiment was performed in triplicate to check reproducibility. From the end point, compositions of the titrated samples were calculated and plotted on the pseudoternary phase diagrams were constructed by using chemix softwere [7].

***Formulation of nanoemulsion:*** Various nanoemulsion formulation of Etoricoxib and Methyl salicylate was prepared by the low energy emulsification method (aqueous titration method). Different Nanoemulsion formulations were prepared by dissolving Etoricoxib and Methyl salicylate in a mixture of the oily phase (containing oil + surfactant). Aqueous phase prepared separately (containing Water + co-surfactant). Then prepared oil phase was drop wise added into a water phase with continues stirring at 500 rpm. [8] Then keep it stirring for 30min. The composition of the various batches prepared is given in (Table no: 1).

**Table No. 1: Composition of Etoricoxib and Methyl salicylate nanoemulsions used for optimization**

| Formulation code | Etoricoxib (%w/w) | Methyl Salicylate (%w/w) | Oleic acid (%v/v) | Smix (1:1) (%v/v) | Water (%v/v) |
|---|---|---|---|---|---|
| **NE1** | 1 | 2 | 7 | 66 | 27 |
| **NE2** | 1 | 2 | 8 | 62 | 30 |
| **NE3** | 1 | 2 | 9 | 64 | 27 |
| **NE4** | 1 | 2 | 10 | 68 | 12 |
| **NE5** | 1 | 2 | 11 | 60 | 19 |

**Characterization of the prepared nanoemulsion:**

***Drug content determination:*** The amount of drug present in the prepared nanoemulsion was analyzed by using U. V.spectrophotometer. Accurately weighed 1 gm quantity of prepared nanoemulsion diluted with 7.4 phosphate buffer. Further 1 ml of this filtrate was diluted to 10 ml in a volumetric flask. The absorbance of this solution was measured at 208 nm by using UV spectrophotometer [9].

***Polydispersity index (PDI), zeta potential and droplet size analysis:*** PDI, zeta potential and droplet size distribution of nanoemulsion are determined using Zetasizer. Samples were diluted 200 times with purified water. Diluted samples were directly placed into the module and measurements were made in triplicate after 2-min stirring. Droplet size was calculated from the volume size distribution [10].

***Viscosity determination:*** The viscosity of nanoemulsion formulations was determined by using Brookfield viscometer LV using spindle number 61 at 100 rpm [11].

***Transmission electron microscopy:*** The morphology of optimized nanoemulgel formulation was obtained by TEM. nanoemulsion was diluted 100 times and a drop was applied to the grid and a drop of phosphotungstic acid (PTA) was applied to the grid placing drops of the selected sample onto a glass slide and then estimated.

***In-vitro skin permeation studies:*** *In-vitro* skin permeation study was performed by using Franz diffusion cell for prediction of drug transport across the skin with an effective diffusional area of 28.27 $cm^2$. 100mg of Nanoemulsion formulation were taken from each formulation (NE1-NE5) and placed into each donor compartment. The receiver fluid was stirred with a magnetic bead at an agitation speed of approximately 100 rpm and temperature of 32 ± 1° C was maintained during the experiment. Samples of 2 ml were withdrawn at predetermined time interval up to 7 hr. Samples were analyzed for drug content using UV spectrophotometer at 208 nm. Optimized formulation was selected to incorporate with a gelling agent for further study [12].

**Evaluations of gel:**

***Spreadability test:*** Two glass slides of standard dimensions (2cm×5cm) were selected. 100gm weight was placed upon the upper slide and the gel between the two slides is pressed uniformly up to 1 minute to form a thin layer. The weight was removed and the excess of gel adhering to the slide was scrapped off. The experiment was repeated and mean time taken for three such determinations was calculated [13].

$$S = \frac{m.l}{t}$$

Where, m= mass, l= length of slide, t = time.

***Swelling index determination:*** 1g of carbopol 934, hydroxyl propyl methyl cellulose (HPMC) and gelatin were weighed separately and added to 25 ml measuring cylinder. Distilled water was added up to the required volume. All the gelling agents were allowed to swell for 3 hrs. The initial and final volumes occupied by the gelling agents were performed thrice for each gel base and reported [14].

$$SW = Wt - Wo$$

Where, St= Final volume of gel, Wo= Initial volume of a gel formulation of nanoemulgel: Prepared Nanoemulsion was incorporated into 1.5% carbopol 934 to formulate nanoemulgel.

***Preparation of nanoemulsion-based emulgel:*** 1 gm of Carbopol 934 which was selected as a gelling agent in a sufficient quantity of distilled water. After complete dispersion, the carbopol 934 was kept in the dark for 24 hrs to swell completely. Triethanolamine was added into swollen carbopol 934 to adjust the pH value of gel matrix. Nanoemulsion formulation (NE1) which showed highest *in-vitro* release were taken and incorporated with gel matrix and nanoemulsion-based emulgel were prepared after stirring by Remi stirrer for 30 minutes at 300rpm [14].

**Evaluation of nanoemulgel:**

***pH determination:*** Nanoemulgel is a topical formulation hence PH of the formulation should be suitable to the pH of the skin. It should not cause any skin irritation. pH was determined at room temperature by using digital pH meter.

***Drug content determination:*** The amount of drug present in the prepared gel was analyzed using u.v.spectrophotometer. Accurately weighed 1gm of the prepared gel was diluted with 10 ml of ethanol and further diluted up to 100 ml with phosphate buffer pH 7.4. Further 2 ml of this filtrate was diluted to 10 ml in a volumetric flask with phosphate

buffer. The absorbance of this solution was measured at 208 nm by using U. V spectrophotometer.

***Viscosity determination:*** The viscosity of formulation nano emulgel (NG) was determined by using Brookfield Viscometer with spindle number 64 at 10 rpm.

***In-vitro skin permeation studies as compared to marketed formulation:*** *In-vitro* skin permeation study was performed by using Franz diffusion cell for prediction of drug transport across the skin and to compare with a marketed formulation for observing effective permeation of nanoemulgel.

***Stability study:*** In the case with freeze/thaw cycles, Test tubes filled with the nanoemulgel were sealed and stored for 8 h in a freezer at 4° C and 40°C and then for 8 h at room temperature (25°C). The nanoemulgel was observed for any change. This cycle was repeated for 90 days [15].

## RESULT AND DISCUSSION

***Screening of excipients:*** Excipients are selected on the basis of Solubility of drug and higher emulsification ability. Tween 80 was selected as a surfactant due to its HLB value of 15 and propylene glycol was selected as co-surfactant due to its HLB value of 4.5. Mixing of high and low HLB value surfactants leads to formulate stable nanoemulsion formulations. Transient negative interfacial tension and fluid interfacial film are rarely achieved by the use of single surfactant hence the addition of co-surfactant is necessary. Therefore the co-surfactant selected was propylene glycol.

The oil phase is selected on the basis of solubility study. Olive oil, oleic acid, isopropyl myristate, castor oil are selected for solubility study. Etoricoxib shows higher solubility in oleic acid than other oils. Drug-drug and drug excipients compatibility were studied by FTIR and DSC. Drugs and excipients do not show any interaction.

***Determination of solubility of etoricoxib:*** To develop a nanoemulsion system for transdermal delivery, it should possess good solubility in the components of system Etoricoxib is having very low solubility hence solubility was studied in different oils. Among all oils, etoricoxib shows maximum solubility in oleic acid i.e. 23.79 mg/ml. (Table no: 2)

**Table No. 2: Solubilty of Etoricoxib in different oils**

| Sr. No. | Oils | Solubility (mg/ml) |
|---|---|---|
| 1 | Olive oil | 3.1235±0.25 |
| 2 | Oleic acid | 23.796±0.40 |
| 3 | Isopropyl myristate | 19.461±0.35 |
| 4 | Castor oil | 5.6891±0.29 |

***Values are expressed in mean ± SD, where n = 3.***

***Constructions of phase diagrams:*** Pseudoternary phase diagrams were separately constructed for each surfactant to cosurfactant ratio so that O/W nanoemulsion regions could be identified and nanoemulsion formulations could be optimized. In this study surfactant and co-surfactant used in various ratio i.e. Smix 1:1, 1:2 and 2:1. Smix ratio 1:1 shows the maximum area of emulsification as compared to others. Hence Smix ratio 1:1 selected for formulating nanoemulgel.

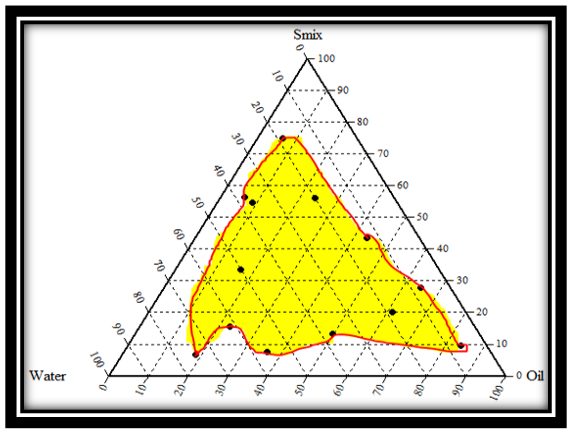


**Fig. 1: Psuedoternaryphase diagram of Smix ratio 1:1**

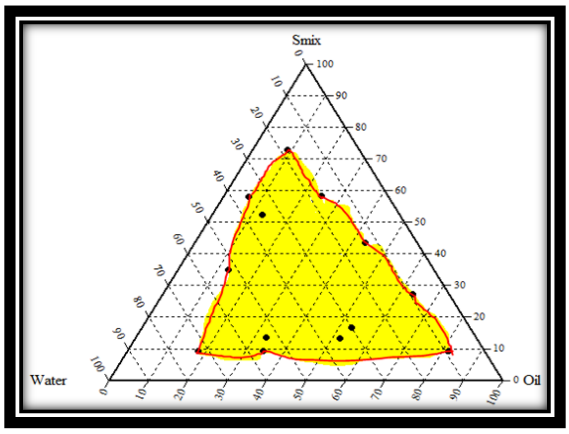


**Fig. 2: Psuedoternaryphase diagram of Smix ratio 1:2**

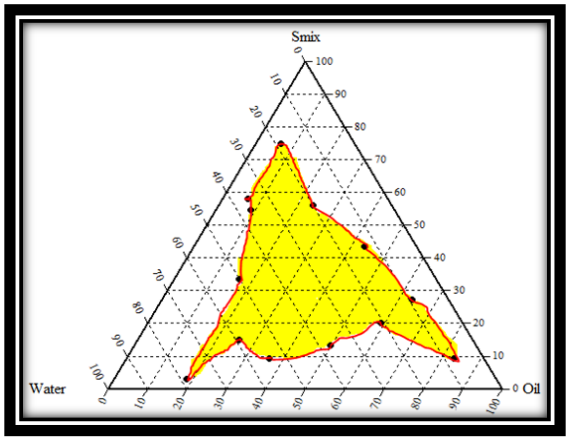


**Fig. 3: psuedoternaryphase diagram of Smix ratio 2:1**

***Drug content determination:*** Drug content and pH determination of nanoemulgel. The drug content of nanoemulgel formulation (Table no: 3) was in the range of. 99.05±0.340 % to 92.7±0.355 %. From the result, it was concluded that drug was uniformly distributed in the formulation and loss of drug was very low while formulating to the gel.

***Polydispersity index (PDI), zeta potential and droplet size analysis of the prepared nanoemulsion:*** Uniformity of droplet size within the formulation determined by using zeta seizer. Higher the polydispersity, lower the uniformity of the droplet size in the formulation. Although the polydispersity values of all the formulations were range from 0.346±0.347 to 0.472±0.361. It indicating uniformity of droplet size within each formulation, the polydispersity of formulation NE1 was lowest (0.346±0.347).

A droplet of various nanoemulsion formulations was found in a range of 220±0.486 nm to 932±0.394nm. NE1 formulation shows lowest droplet size i.e. 220±0.486 nm.

The viscosity of nanoemulsion was found to be low (89.0±0.686 to 98.3±0.525cps) and was not suitable for topical use which justified the incorporation of nanoemulsion into gel matrix, resulting into nanoemulgel having a high value of viscosities.

From above results (Table no: 4) it was found that NE1 is the best formulation among all formulations.

***Transmission electron microscopy:*** The result of TEM indicate that the optimized formulation (NE1) shows nanosized particle spherical in shape and smooth surface globules, this indicates good stability of optimized nanoemulgel (NE1) as shown in (fig no: 5).

***In-vitro skin permeation studies:*** The ex vivo permeation profiles of nanoemulgel through excised rat skin are shown in the graph (Fig. 4). Studies were carried out to confirm and to compare the permeation potential of the nanoemulgel formulations (NE–NE5). The cumulative amount of drug permeated, flux, were calculated for each formulation of nanoemulgel. Nanoemulsion formulations show transdermal flux from 23.15±0.843 µg/cm²/hr to 81.08±0.479 µg/cm²/hr.

Statistical evaluation of the flux throughout the 7 h of the study showed that among all the formulations, nanoemulsions NE1 exhibited maximum permeation at the end of 7 h and shows highest transdermal flux (81.08±0.479 µg/cm²/hr).

***Comparitive study of nanoemulgel and marketed gel:*** The PH value of nanoemulgel was found to be 6.14± 0.631, suitable for use of formulation for skin. Drug content of nanoemulgel formulation was 93.03±0.723%. The result showed that the the drug was uniformly distributed through the formulation & drug loss was minimum while formulating nanoemulgel.

The performance of topical formulation is monitored by its rheological behavior. Viscocity of nanoemulgel were found to be 36800± 0.460cps.

*In-vitro* skin permeation studies were carried out to compare & confirm permeation potential of nanoemulgel. Nanoemulgel shows highest permeation flux (71.32 ±0.733µg/cm²/hr) as compare to marketed gel(39.07 ± 0.52µg/cm²/hr). Nanoemulgel shows two more times permeation than marketed gel.

***Stability study:*** The stability studies were carried out at room temp, cool temperature, and 40ºc. Result obtained from stability study indicates that formulation is stable. From stability study (table no: 6) it can confirm that nanoemulgel formulation does not show any physical changes like phase separation, breaking or cracking. Hence it was found that nanoemulgel is a stable formulation.

**Table No. 3: Drug content determination**

| Sr. No. | Formulation code | Drug conent (%) |
|---|---|---|
| 1 | NE1 | 98.4±0.246 |
| 2 | NE2 | 97.5±0.303 |
| 3 | NE3 | 99.05±0.340 |
| 4 | NE4 | 98.03±0.472 |
| 5 | NE5 | 92.7±0.355 |

***Values are expressed in mean ± SD, where n = 3.***

**Table No. 4: Polydispersibility index (PDI), Zeta potential and Droplet size analysis. Characterization of the prepared Nanoemulsion**

| Sr. No. | Formulation code | Droplet size | Polydispersibility index | Zeta potential (mv) | Viscosity (cp) | Flux (µg/cm²/hr) |
|---|---|---|---|---|---|---|
| 1 | NE1 | 220±0.48 | 0.346±0.34 | -24.5±0.491 | 90.6±0.471 | 81.08±0.479 |
| 2 | NE2 | 815±0.41 | 0.444±0.48 | -10.39±0.347 | 94.1±0.625 | 31.60±0.478 |
| 3 | NE3 | 488.5±0.38 | 0.350±0.39 | -8.92±0.469 | 94.1±0.625 | 61.89±0.647 |
| 4 | NE4 | 588±0.50 | 0.350±0.45 | -13.71±0.635 | 98.3±0.525 | 49.98±0.974 |
| 5 | NE5 | 932±0.39 | 0.472±0.36 | - 21.6±0.291 | 89.0±0.686 | 23.15±0.843 |
| 6 | Nanoemulgel | - | - | - | 36800±0.46 | 71.32 ±0.73 |
| 7 | Marketed | - | - | - | 42600±0.79 | 39.07 ± 0.52 |

***Values are expressed in mean ± SD, where n = 3***

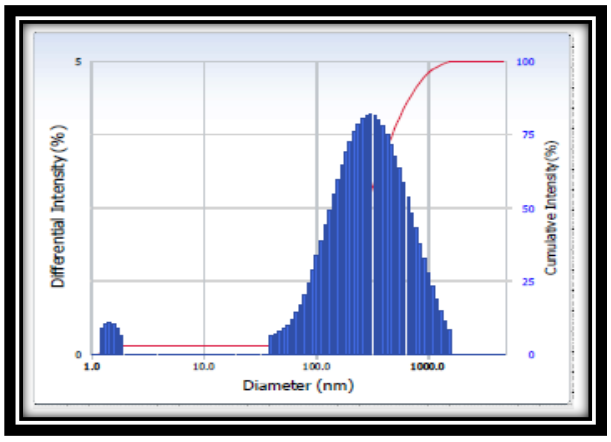


**Fig. 4: Droplet size analysis of NE1 formulation**

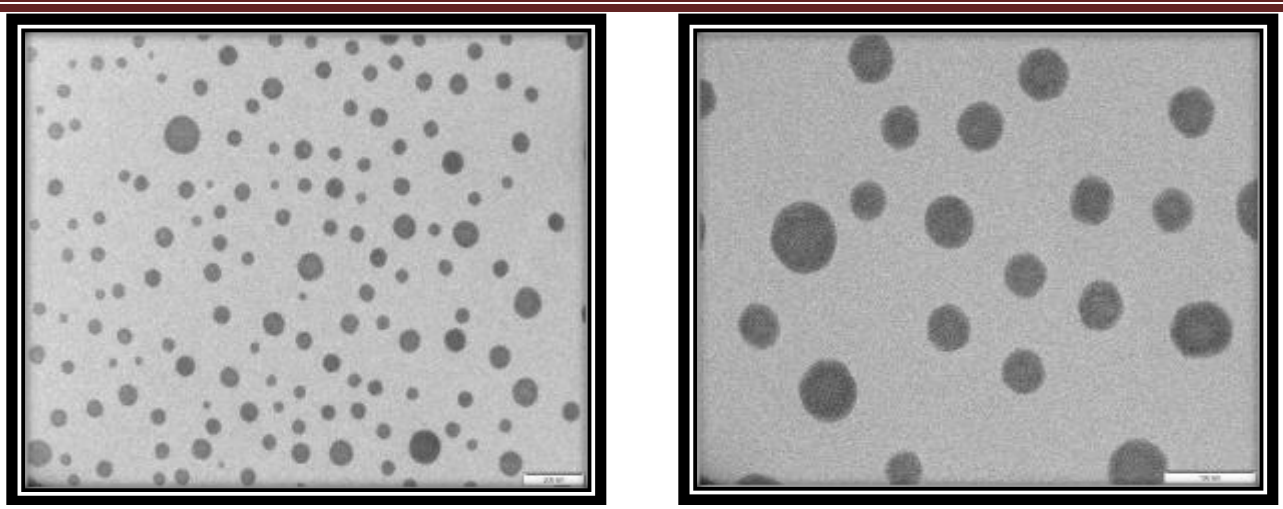

**Fig. 5: TEM images of NE1 formulation**

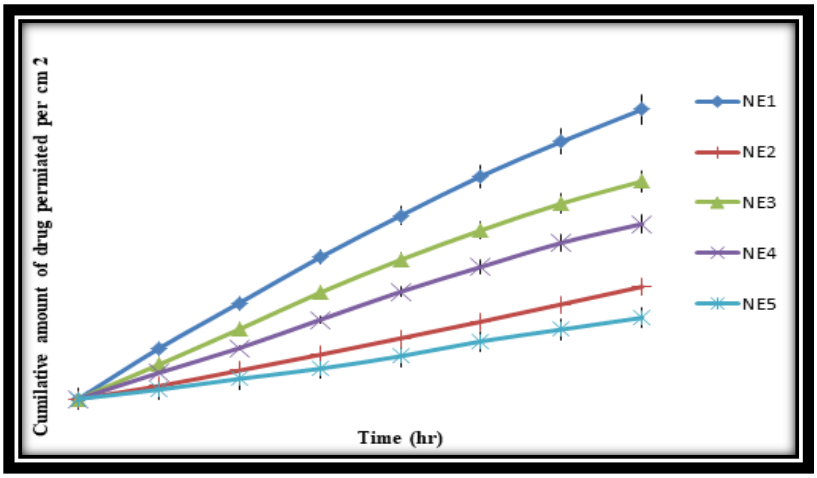


**Fig. 6: *In vitro* skin permeation study of nanoemulsion formulations**

**Table No. 5: pH, viscosity, swelling index, wt. extruded from tube and drug content of nanoemulgel and conventional gel formulations**

| Formulation code | pH | Swelling index (%) | Wt. extruded from tube (gm/cm²) | Drug content (%) | Spreadability (g.cm/sec) |
|---|---|---|---|---|---|
| **Nanoemulge** | 6.1±0.6 | 10±1.85 | 0.67± 0.58 | 93.03 ±0.72 | 4.8 ± 0.79 |
| **Marketed Gel** | 6.3±0.2 | 11±1.56 | 0.59± 0.55 | 89.15± 0.89 | 6.01 ± 0.92 |

***Values are expressed in mean ± SD, where n = 3.***

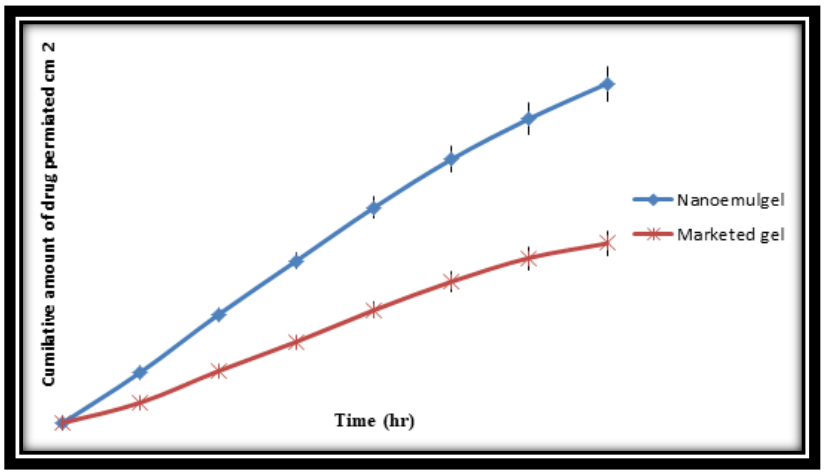


**Fig. 7*: in-vitro* skin permeation studies as compared to marketed**

**Table No. 6: Stability study of nanoemulgel formulation**

| FormulationCode | Time | Temperature | Breaking/ cracking | Phase seperation | pH | Drug content |
|---|---|---|---|---|---|---|
| NG | After 30 days | 4°c | _ | _ | 6.39±0.145 | 92.41±0.254 |
| | | 25°c | _ | _ | 6.54±0.254 | 91.64±0.244 |
| | | 40°c | _ | _ | 6.12±0.136 | 92.36±0.965 |
| | After 60 days | 4°c | _ | _ | 6.42±0.552 | 93.13±0.217 |
| | | 25°c | _ | _ | 6.47±0.132 | 92.39±0.248 |
| | | 40°c | _ | _ | 6.59±0.145 | 91.17±0.524 |
| | After 90 days | 4°c | _ | _ | 6.12±0.364 | 92.03±0.247 |
| | | 25°c | _ | _ | 6.78±10.524 | 93.18±0.741 |
| | | 40°c | _ | _ | 6.57±0.174 | 92.84±0.952 |

***Values are expressed in mean ± SD, where n = 3.***

## CONCLUSION

In present work, nanoemulsion of etoricoxib and methyl salicylate was formulated by low energy method and characterized for vesicle size, polydispersity index, zeta potential and % entrapment efficiency. It was observed that the vesicles of composite nanoemulsion formulations (NE1–NE5) varied in the size range of 220±0.486 to 932±0.394. Polydispersity index indicates a homogeneous population of nanoemulsion vesicle in the formulation, it was found to be 0.346±0.347 for NE1 formulation. NE1 formulation showed highest transdermal flux (81.08±0.479µg/cm$^2$/hr) across excised rat skin. The best nanoemulsion formulation i.e NE1 was formulated into nanoemulgel (NG) and transdermal flux was calculated and compared with conventional gel. It was observed that nanoemulgel formulation (71.32 ± 0.733µg/cm$^2$/hr) show a two-fold increase in transdermal flux as compared to marketed gel (39.07 ± 0.52µg/cm$^2$/hr). From the results, it can be concluded that nanoemulgel formulation is potential and effective transdermal drug delivery system for etoricoxib and methyl salicylate. Thus, can be concluded that nanoemulgel is a safe, effective and promising formulation for treatment of inflammatory conditions.

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