



## FORMULATION AND EVALUATION TRANSDERMAL DELIVERY OF NAPROXEN MICROEMULSION GEL

G. Nagaraju<sup>1\*</sup>, V. Sirisha<sup>2</sup>, Kavati.Ramakrishna<sup>3</sup> and Hareesh Dara<sup>1</sup>

<sup>1\*</sup>Department of Pharmaceutical Chemistry, Dhanvanthari Institute of Pharmaceutical Sciences, Sujathanagar, Kothagudem.

<sup>1</sup>Department of Pharmaceutics, Sree College Of Pharmacy, Nayakulagudem, Kothagudem, Telangana.

<sup>2</sup>Department of Pharmaceutics, Dhanvanthari Institute of Pharmaceutical Sciences, Sujathanagar, Kothagudem.

<sup>3</sup>Department of Pharmaceutics, Pulipati Prasad college of pharmacy, Pulipati Prasad college of pharmaceutical Sciences, Khammam.

\*Corresponding Author Email: [gdp413@gmail.com](mailto:gdp413@gmail.com)

### ABSTRACT

*Naproxen is an NSAID used to treat inflammatory joint conditions including osteoarthritis. In this study, we set out to create a novel microemulsion formulation for transdermal administration of Naproxen. To choose excipients with excellent drug loading capacity, solubility of drug in different oils, surfactant, and co-surfactant was assessed in pre formulation tests. Capmul MCM C8 was chosen as the oil in the microemulsion's formulation, while labrasol and ethanol were chosen as the surfactant and co-surfactant, respectively. The concentrations of the oil phase, Smix, and distilled water used in the preparation of the Naproxen microemulsion were calculated using pseudo ternary phase diagrams. Three tests-a centrifugation tests, a heating and cooling cycle test, and a freeze thaw cycle test were used to determine the optimal formulation. The % transmittance, droplet size, and cloud point of the optimized formulations were also measured. Because of its high % transmittance, the MF2 formulation stands out as the best among the bunch. A minimum globule size of 35.2 nm was observed for MF-2. The zeta potential of MF2 was calculated to be +19.0mV. Compared to previous batches, the MF2 formulation demonstrated faster drug release during the in vitro diffusion test, with peak drug concentrations occurring between 4 and 8 hours after the test began. Microemulgel was created by adding a gelling agent to the microemulsion at a 1:1.2 ratio (microemulsion: gelling agent). When tested under a wide range of stability circumstances, the microemulgel (PN3) in question performed well. The microemulgel formulation (PN3) loaded with Naproxen was shown to cause no skin irritation in an in vitro test. Based on these findings, it seems that the microemulsion formulation of Naproxen might be an effective formulation for transdermal distribution.*

### KEY WORDS

Microemulsion, Microemulgel, Naproxen, Arthritis

### INTRODUCTION

New advancements in technology have made transdermal medicine delivery systems a viable choice for dosing patients. The clearance of the digestive system and the first pass of hepatic metabolism are two of the many advantages of transdermal medication delivery. Most failed attempts at oral medication

delivery (74%) may be attributed to several factors. The skin serves as a barrier against the outside world and can heal itself if it is ever compromised. There has been a rise in the use of transdermal medication administration in recent years. Medication administration through the transdermal route has gained popularity because of the ease it provides and

the drug's generally positive reputation for safety. Transdermal drug delivery is a practical choice since it is a tried-and-true, easy-to-implement, secure, and low-cost drug delivery method. A larger drug content in the dose form may be necessary if the medication is to be taken orally due to the many possible loss mechanisms. Medication has the potential to cause damage if administered incorrectly. It is possible for concentrations to be lower than the MEC when using conventional drug delivery techniques (MEC). Maintaining an adequate supply of MECs is critical in any sick situation. The needed low concentration is beyond the capabilities of conventional technologies. However, long-term MEC preservation may be possible with the advent of novel medication delivery strategies (transdermal, regulated, etc.). As their names imply, transdermal drug delivery systems strive to localize pharmaceutical administration and control the rate of distribution. Advantages of transdermal drug administration include the potential for regulated absorption of medications applied to healthy skin into circulation.

## MATERIALS AND METHODS

Naproxen drug was gifted by Gtosh Enterprises, Pune, India. Capmul MCM C8 from Abitec Corporation, USA, Castor oil, Oleic acid, Labrasol, Ethanol, Polyethylene Glycol 400, Tween 80, Carbopol 940 all are from Research lab, Mumbai.

### Solubility Study

Studying medication solubility is the primary goal of solubility testing, since it helps determine which solvent is best for developing dosage forms. Naproxen solubility was studied by dissolving 10 mg of Naproxen in water, ethanol, methanol, and acetonitrile, among other solvents.

### Solubility of Drug in Various Excipients: -

Naproxen was analyzed for their saturated solubility in a series of oils (Capmul MCM C8, Isopropyl myristate, Oleic acid, Castor oil, Labrafil M 2125 CS, Coconut Oil, Lemon Oil, Arachis Oil), surfactants (Span 20, Span 60, Span 80, Labrasol, Tween 20, Tween 60 & Tween 80), and co-solvents (PEG200, Overnight at room temperature, 10 ml stopper glass vials were filled to capacity with 5 g of oils, surfactants, and co-solvents, as well as excess quantities of Naproxen and Naproxen. After diluting methanol, the content of Naproxen in the supernatant was measured at a max of 331 nm using a UV spectrophotometer (Schimadzu), and the concentration of Naproxen was measured at 252 nm. An oil, surfactant, and co-solvent solution dissolved in methanol served as a control.

### Formulations and Development:

#### Selection of Surfactant and Co-Surfactants Ratio

Surfactant to co-surfactant ratios of 1:1, 2:1, or 3:1 was chosen as a starting point, with further refinement based on visual inspection and practical constraints in formulation. The combination of surfactant and co-surfactant was known as Smix. Swirl 250 ml of distilled water and add 2 ml of Smix at a 1:1, 2:1, and 3:1 ratio. The most transparent solution was chosen after considering a number of factors to determine the best formulation dilution. This tactic relies on trial-and-error methods and visual analysis.

#### Preparation of microemulsion of Naproxen:

Our previous work established the Microemulsion's composition, which includes Capmul MCM C8, Labrasol, ethanol, oil, surfactant, and co-surfactant, each of which contains Naproxen as part of the surfactant (1 gm). To create microemulsion formulations, the researchers used a previously disclosed approach. Naproxen (1 gm) was dissolved into the combination of oil, surfactant, and co-surfactant, and the mixture was stirred. A high-pressure homogenizer was used to break down the mixture until a clear solution was achieved.

Table 1: Optimized formulation of microemulsion for 100 ml.

| Batch No. | Naproxen | Capmul MCM C8 | Labrasol | Ethanol | Water |
|-----------|----------|---------------|----------|---------|-------|
| MF1       | 1        | 5             | 36       | 24      | 34    |
| MF2       | 1        | 10            | 32       | 21      | 36    |
| MF3       | 1        | 20            | 28       | 18      | 33    |
| MF4       | 1        | 25            | 24       | 15      | 35    |
| MF5       | 1        | 30            | 20       | 12      | 37    |
| MF6       | 1        | 35            | 16       | 9       | 39    |
| MF7       | 1        | 40            | 12       | 6       | 41    |
| MF8       | 1        | 45            | 8        | 3       | 43    |

|      |   |    |    |      |      |
|------|---|----|----|------|------|
| MF9  | 1 | 5  | 45 | 24   | 25   |
| MF10 | 1 | 10 | 41 | 21   | 27   |
| MF11 | 1 | 20 | 37 | 18   | 24   |
| MF12 | 1 | 25 | 23 | 15   | 36   |
| MF13 | 1 | 30 | 29 | 12   | 28   |
| MF14 | 1 | 35 | 25 | 9    | 30   |
| MF15 | 1 | 40 | 21 | 6    | 32   |
| MF16 | 1 | 45 | 17 | 3    | 34   |
| MF17 | 1 | 5  | 39 | 24.5 | 30.5 |
| MF18 | 1 | 10 | 35 | 21.5 | 32.5 |
| MF19 | 1 | 20 | 31 | 18.5 | 29.5 |
| MF20 | 1 | 25 | 27 | 15.5 | 31.5 |
| MF21 | 1 | 30 | 23 | 12.5 | 33.5 |
| MF22 | 1 | 35 | 19 | 9.5  | 35.5 |
| MF23 | 1 | 40 | 15 | 6.5  | 37.5 |
| MF24 | 1 | 45 | 11 | 3.5  | 39.5 |

#### Characterization of Microemulsion: -

##### Percentage transmittance: -

Microemulsions of Naproxen were diluted one hundred times with distilled water and examined visually for turbidity. The UV-VIS spectrophotometer was then used to determine its percent transmittance at 331nm using distilled water as a blank.

##### Cloud point measurement: -

Microemulsions that had been optimised were diluted with distilled water at a 1:250 ratio, then heated in a water bath. The point at which clouds suddenly become visible was identified as the cloud point using a UV-vis spectrophotometer to measure transmittance and ocular observation.

##### Droplet size determination

In a beaker, 10 milligrams of MF1-MF24 and CF1-CF24 microemulgel formulation was diluted with 50 milliliters of deionized water while being stirred with a glass rod. Analyses of particle size were performed on the resulting emulsion. Dynamic light scattering (DLS) using a zetasizer is used to quantify the size of the resulting droplets (Nano ZS, Malvern Instruments, UK). 25 degrees Celsius; red He-Ne laser; 4.0 milliwatts; 633 nanometers.

##### Zeta Potential Determination

Laser diffraction examination using a particle size analyser was used to ascertain the Zeta potential of the winning formulation (Malvern Zetasizer Nano Series ZS 90). The samples were diluted with distilled water at a ratio of 1:100 (v/v) and stirred for 1 minute. There were three sets of each experiment.

#### Preparation of Microemulgel of formulation

##### Selection of microemulsion and polymer Ratio:

Microemulsion and polymer ratios, including 1:0.5, 1:1, 1:1.2, and 1:1.5, were tested for free-flowing microemulgel before being narrowed down using the table below. Utilize a high-pressure homogenizer to completely dissolve a mixture of microemulsion and polymer at varying ratios of 1:0.5, 1:1, 1:1.2, and 1:1.5. This strategy relies on experimentation and close visual inspection.

##### Characterization of microemulgel:

##### Physical appearance:

Color, homogeneity, consistency, and pH were checked visually in the microemulgel formulations after they were created.

##### pH

Digital pH metre readings were taken from the microemulgels to establish their pH levels (Labindia Instruments, GMPH). After continuously monitoring the microemulgel composition, the electrode was dipped into it. Triplicate pH readings were taken for each batch.

##### Appearance of microemulgel

The formulas' aesthetic appeal was evaluated by holding them up to the light and taking a look at how they reflected it.

Where + average, ++ good, +++ excellent

##### Spreadability

The spread ability instrument was used to quantify this quality. The equipment consists of two slides: one is securely fastened in a wooden frame, while the other glides effortlessly over its surface. We stuffed two grammes of microemulgel (2 gm) in between the

apparatus's slides. After letting a 1 kilogramme weight sit on the slide for 5 minutes, the air was forced out from between the slides and a homogenous sheet of microemulgel formed. Carefully, we wiped the slides' borders to get rid of the extra gel. An 80-gm weight was pulled on the upper slide while the lower slide was securely fastened. Observe how long it takes centimetres (in seconds). Higher Spreadability is associated with shorter intervals.

Spreadability was then calculated using the following formula:

$$S = M \times L / T$$

Where, S = is the spreadability,

M = is the weight in the pan (tied to the upper slide),

L = is the length moved by the glass slide and

T = represents the time in seconds taken to separate the slide completely.

#### Extrudability

After the microemulgels were created, they were poured into the compressible tubes. The formula's extrudability has been tested.

Where + average, ++ good, +++ excellent

#### Rheological study:

Spindle speeds of 0.5, 1.0, 2.0, 2.5, 4.0, 5.0, 10.0, 50.0, and 100.0 revolutions per minute were used on a Brookfield Viscometer (Model RVT, Brookfield Engineering Laboratories, Inc., USA) to examine the flow behaviour of the gel compositions. At 25<sup>o</sup>C, the flow behaviour of the various formulations was evaluated by analysing the location.

#### Drug content determination: -

The 10 mg of Naproxen and Naproxen microemulgel was dissolved in 10 ml of dimethyl acetate in a separate 10 ml volumetric flask; the 0.1 ml of stock solution was then properly measured, transferred to a second 10 ml

volumetric flask, and filtered using Whatman filter paper. Naproxen and Naproxen concentrations in the aforementioned solutions were measured using a UV Spectrophotometer (Shimadzu UV 1800) set to max 331nm and 252nm, respectively. Standard calibration curves of Naproxen and Naproxen were used to calculate the exact concentrations of each drug in the formulation.

#### In vitro drug release study: -

The experiment employed a Franz diffusion cell that had an effective diffusion area of 7.1 cm<sup>2</sup>. Franz diffusion cell having donor compartment on the outside and receptor compartment on the inside, with the egg membrane between them. The release patterns of Naproxen and Naproxen were measured after being applied to the stratum corneum in the forms of ME (1%, w/w D), MBG (0.5%, w/w D), and 0.1 gm and 0.05 gm, respectively. In order to stimulate receptor activity, 25 ml of physiological saline solution was injected into the receptor chamber (pH 6.8 phosphate buffer). The receptor medium was magnetically agitated at 50 rpm and kept at 37<sup>o</sup> C. Taken at regular intervals, the samples were filtered through a cellulose membrane filter with a pore size of 0.45 m before being subjected to ultraviolet (UV) analysis. After each sample was taken, the buffer solution in the receptor chamber was immediately changed with new. Both the ME and MBG formulations' cumulative drug accumulation in the receptor chamber was shown vs time (t, h).

#### Stability of microemulgel

Clarity and phase separation observation, as well as UV assays of Naproxen and Naproxen, were used to determine the stability of a microemulgel containing the two drugs at 45 degrees Celsius for three months. For the same purpose of gauging physical stability, centrifuge tests were also performed. 15 minutes of centrifugation at 10,000 rpm were applied to the microemulgel samples.

**Table 2: Stability protocol**

| Stability study (conditions) |          |          |
|------------------------------|----------|----------|
| 45°C ± 2°C / 75 % RH ± 5% RH |          |          |
| 1 Month                      | 2 Months | 3 months |

#### 1.8.6. Skin Irritation study on rabbits:

##### Protocol Approval

Institutional Animal Ethics Committee (IAEC), Browns College of Pharmacy, Khammam No. IAEC/SGRS/2018/6 approved the in vivo study, which was India).

#### Animal Study

The irritancy potential of Microemulgel (CF2, PC3) loaded microemulgels was evaluated in rabbits by applying the chosen gels to their freshly shaved backs.

Here we detail how we choose the rabbits to use in this experiment.

We used a random number generator to split the rabbits into three groups of three. They had separate cages for each rabbit. Each test animal had the hair on the dorsal surface of its trunk neatly clipped off on both sides about 24 hours before the testing. Each hairless region on the test animals was divided into two portions (A and B) measuring around 6 square centimeters. The SLS solution (sodium lauryl sulphate) at 20% was chosen as the reference point.

#### The animals were treated as follows:

Group I- 20% w/v SLS solution (area A), Untreated (area B);

Group II- Microemulgel (CF2) (area A), untreated (area B);

Group III- Microemulgel (PC3) (area A), untreated (area B)

Each group had 500mg of the experimental formulation placed on the designated region A. Afterwards, a gauze patch secured with non-irritating tape was placed over the affected region (Transpore 3M surgical tape, 3M India Ltd, India). The B section served as the normative control for each set. The first round of tests was conducted with a single animal. Once the 24 hours of

exposure were up, any remaining formulation on the skin was gently washed off with distilled water so as not to compromise the skin's protective barrier. Dermal responses (erythema and edema) were observed and given a score between 0 and 4 at 1, 24, 48, and 72 hr.(s)

#### 1) For erythema and eschar formation:

- rating zero, no erythema.
- rating 1, very moderate erythema (barely perceptible).
- score 2, a properly described erythema.
- rating three, slight to extreme erythema.
- rating four.

#### (2) For edema formation:

rating 0: no edema.

rating 1: very slight edema (barely perceptible).

score 2: slight edema (edges of place well defined by means of specific elevating).

rating 3: slight edema (raised approximately 1 mm); and

score 4: severe edema (raised greater than 1 mm and extending past region of publicity).

At 1, 24, 48, and 72 hours, all the rabbits' erythema and edema scores were added together (s). The following formula was used to get the principal irritation index (PII) from the letter grades.

$$PII = \frac{\text{Sum of erythema grade at 1/24/48/72 hr(s)} + \text{Sum of edema grade at 1/24/48/72 hr(s)}}{\text{Number of animals}}$$

The irritation degree was categorized based on the PII values as negligible (PII = 0-0.4), slight (PII = 0.5-1.9), moderate (PII = 2-4.9) or severe (PII = 5-8) irritation.

## RESULTS AND DISCUSSION

### Compatibility Study:

The DSC curve of pure Naproxen with all excipients are given below in figure. As per DSC graph.

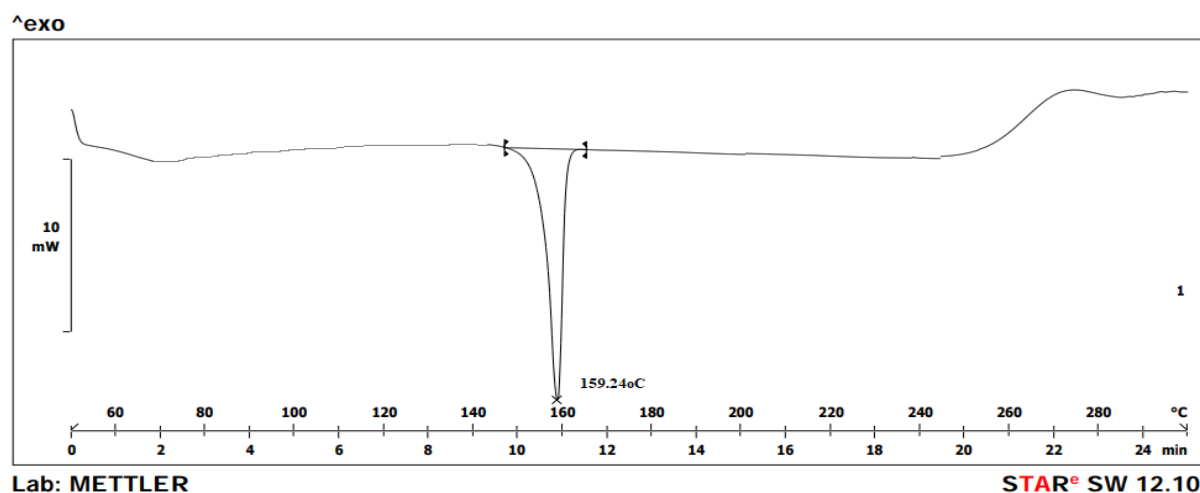
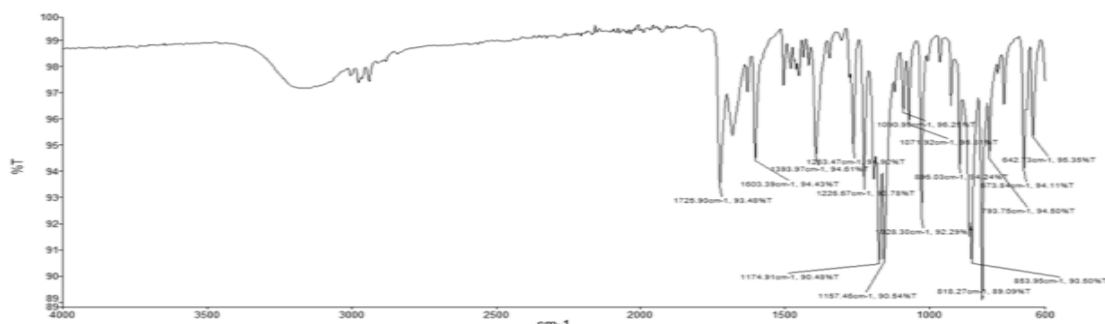


Figure 1: DSC thermogram of Naproxen +Excipients

### FTIR of drug



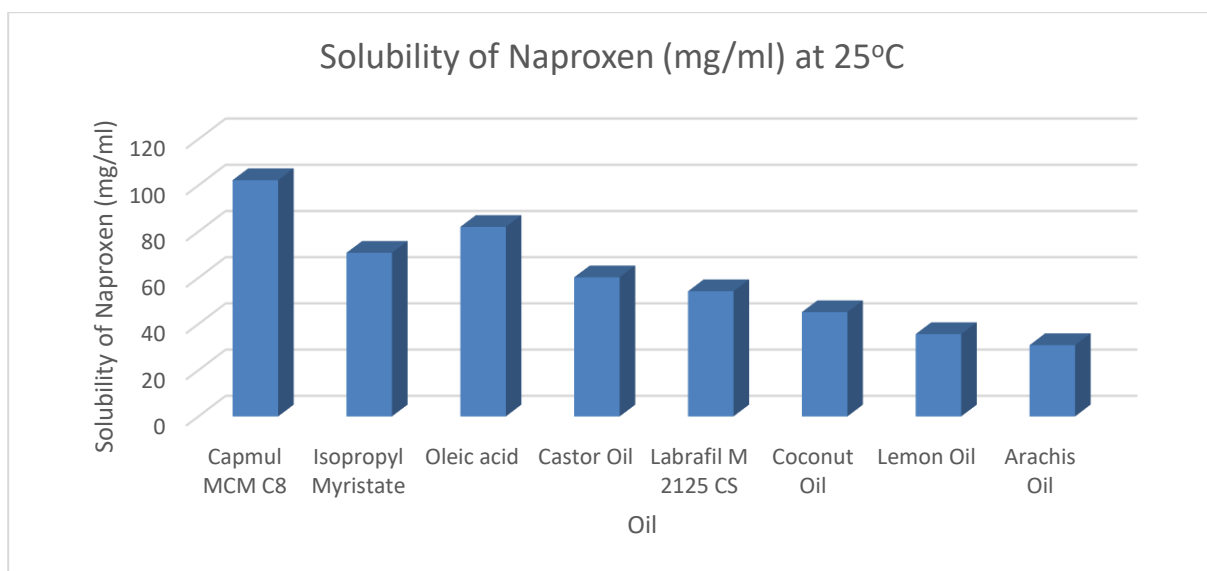
**Figure 2: IR spectra of Naproxen**

The FT-IR spectrometer was used to record the IR spectra of pure Naproxen, and the results were compared to the known frequencies of the drug's functional groups. In Table, we list the most prominent peaks and the functional classes to which they belong.

### The solubility of Naproxen in a variety of oils, surfactants, and co-surfactants.

**Table 3: Data for Solubility study of Naproxen in Various Oils**

| Sr. No | Oil                 | *Solubility of Naproxen (mg/ml) at 25°C |
|--------|---------------------|---|
| 1.     | Capmul MCM C8       | 102.24 ±2.23                            |
| 2.     | Isopropyl Myristate | 70.80 ±1.40                             |
| 3.     | Oleic acid          | 82.00 ±2.68                             |
| 4.     | Castor Oil          | 60.2 ±1.33                              |
| 5.     | Labrafil M 2125 CS  | 54.16 ±2.24                             |
| 6.     | Coconut Oil         | 45.12 ±1.01                             |
| 7.     | Lemon Oil           | 35.62 ±1.54                             |
| 8.     | Arachis Oil         | 30.85 ±0.96                             |



**Figure 3: Solubility of Naproxen in different oils**

### Compatibility study: -

Pre formulation compatibility studies of Naproxen and Naproxen with all excipients were carried out prior to preparation microemulsion. The daily observations of

compatibility study for 14 days were taken for colour changes, cake formation, liquefaction, and gas formation.

**Table 4: Excipients + Naproxen Compatibility Study**

| Sr.no | Physical Mixture         | Observations  |                |              |               |
|-------|--------------------------|---------------|----------------|--------------|---------------|
|       |                          | Colour Change | Cake Formation | Liquefaction | Gas formation |
| 1     | Naproxen + Moisture      | No            | No             | No           | No            |
| 2     | Naproxen + Capmul MCM C8 | No            | No             | No           | No            |
| 3     | Naproxen + Labrasol      | No            | No             | No           | No            |
| 4     | Naproxen + Ethanol       | No            | No             | No           | No            |
| 5     | Naproxen + Carbopol 940  | No            | No             | No           | No            |

**Characterization of microemulsion: -**

**Percentage transmittance: -**

100 µl of microemulsion dissolved in 250 ml of distilled water stir the solution up to 2 min and take the

absorbance of solution with the help of UV spectrophotometer.

**Table 5. Percentage transmittance of formulation of optimized formulation**

| Sr no. | Formula no. | % transmittance |
|--------|-------------|-----------------|
| 1      | MF2         | 95.41±0.95      |
| 2      | MF3         | 98.14±0.33      |
| 3      | MF4         | 65.14±0.45      |
| 4      | MF12        | 95.89±0.15      |
| 5      | MF13        | 72.10±0.23      |
| 6      | MF21        | 70.11±0.63      |

Formulation shows the percent transmittance above 96% except formula number MF4, MF13 and MF21 formulation that indicated that droplet size was nanometer range and transparent microemulsion was formed.

**In vitro drug release study of Microemulsion**

Out of the six microemulsion formulations tested for drug release in vitro, the best result came from Formulation MF2 (96.12%).

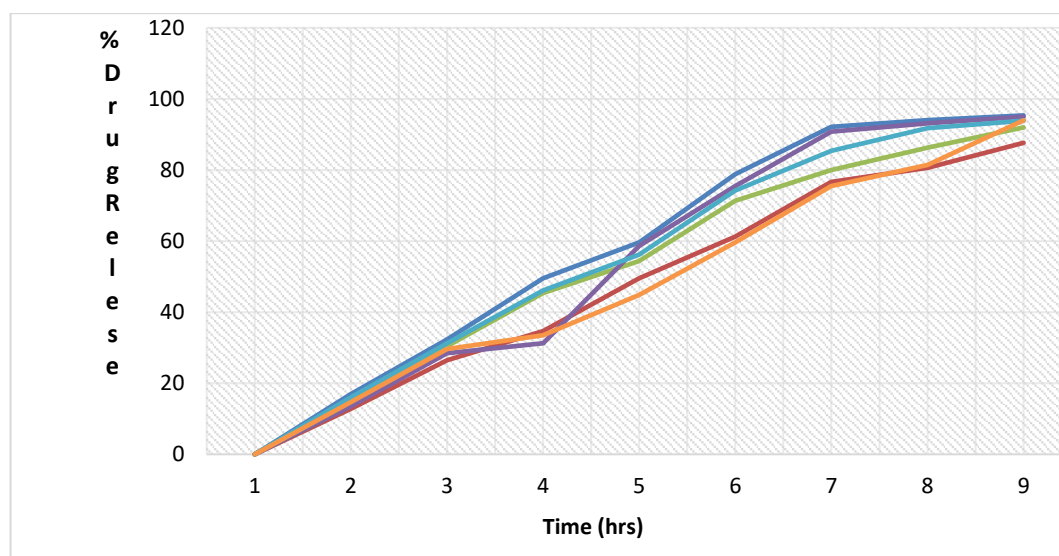

**Figure 4: Drug Release Profile of Optimized microemulsion formulation**

Figure 4 above compares the medication release of six different preparations. In comparison to batches MF3, MF4, MF12, MF13, and MF21, MF2 had a better in-

process drug release. At 8 hours, medication release is greatest with the MF2 formulation.



Based on these results, the MF2 formulation batch was chosen as the final formulation batch for further investigation due to its superior thermodynamic stability, percentage transmittance, drug content, and cloud point, and potential for more drug release in an in vitro diffusion test.

#### In vitro drug release study of Microemulgel

In vitro analysis of medication release from six distinct microemulgel formulations showed that Formulation P3 had the highest drug release (97.15 percent).

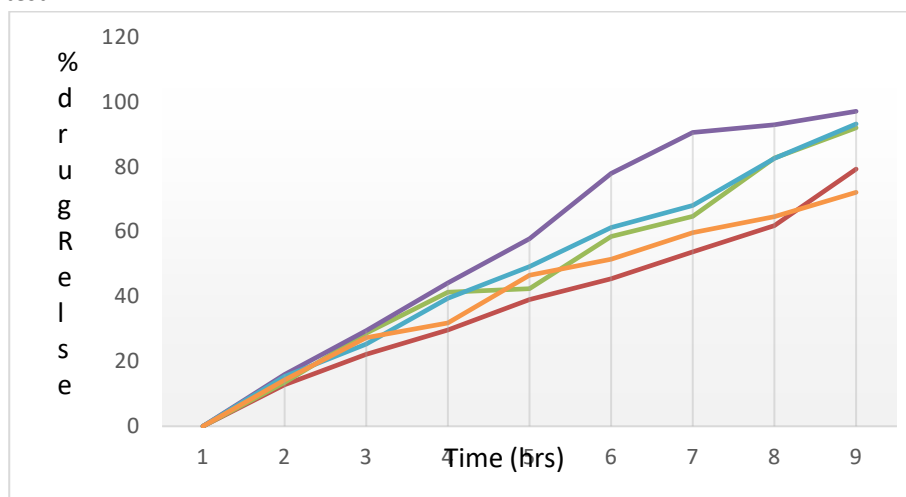


Fig 5. Drug Release Profile of Optimized microemulgel formulation

The above figure depicts a study comparing the rates of drug release from five different lots of preparation. Preparation batch P3 had the highest drug release compared to P1, P2, P4, and P5 formulations. At 8 hours, the B3 formulation exhibits more drug release.

Batch P3 was chosen as the final formulation batch due to its superior in vitro diffusion test drug release compared to the other batches studied.

#### Characterization of microemulgel: -

##### Physical appearance:

##### pH

After immersing the glass electrode into the microemulgel, the pH was measured digitally. A table containing the measured values is provided. The pH level shows whether or not the microemulgel may be used topically.

##### Viscosity

We used a Brookfield viscometer set to spindle no. 5 and 50 rpm to measure the viscosity of each microemulgel formulation at 25 °C. The table displays the microemulgel's viscosity from the first to the fifth performance category.

##### Appearance

All five batches (PN1 through PN5) seemed to be the same yellowish viscous translucent preparation that was uniform and shiny.

##### Spreadability

Table 44 displays the results of a measurement of spreadability from PC1 to PC5. It can be seen that the spreadability of a solution decrease as the concentration of carbopol 940 rises.

##### Extrudability

After the gels were made, they were placed in dismantlable tubes. This formulation's extrudability has been tested, and the findings are listed in Table 44.

Table 6: Physical appearance of microemulgel

| Batch code | pH        | Viscosity (cps) | Appearance | Spreadability | Extrudability |
|------------|-----------|-----------------|------------|---------------|---------------|
| PN1        | 7.2±0.86  | 10245±1.56      | +          | 34.12±0.65    | +             |
| PN2        | 7.10±0.26 | 10845±0.36      | +          | 35.21±0.44    | +             |
| PN3        | 7.3±1.02  | 11321±0.44      | ++         | 35.10±0.14    | ++            |
| PN4        | 6.9±0.23  | 11254±0.54      | +          | 34.22±0.26    | +             |
| PN5        | 7.4±0.89  | 12547±0.26      | +          | 33.21±0.91    | +             |



### Drug content material dedication: -

The drug content material of Naproxen in all the components become located to be inside the range 98-ninety-nine% in microemulgel which suggest entire solubilization of drug in formula.

**Table 7: Drug content Determination**

| Formulation | Drug content (%) |
|-------------|------------------|
| PN1         | 95.21±0.23       |
| PN2         | 94.74±1.05       |
| PN3         | 98.15±0.66       |
| PN4         | 96.12±0.89       |
| PN5         | 95.41±0.14       |

From the above study it can be concluded that PN3 formulation shows the higher drug content it means that is degradation of drug and complete solubilization of drug

### Stability Study

**Batch No.:** PN3 was put on stability as below mentioned condition.

**Condition:** Batch PN3 at 45°C±2°C / 75% RH ± 5 % RH

**Packaging:** Aluminum collapsible tube

**Description:** Transparent light yellow colored microemulgel.

**Table 8: First, Second- & Third-month Stability Data of Tablet at 45°C ± 2°C / 75% RH ± 5 % RH.**

| Parameters  | Initial             | 1 Months            | 3 Months            |
|---|---------------------|---------------------|---------------------|
| <b>Drug content (%)</b>   | PN3<br>98.78±0.23   | PN3<br>98.11±0.45   | PN3<br>97.30±0.22   |
| <b>Diffusion (%)</b>  | 0Hr 0               | 0                   | 0                   |
| <b>Medium: 25ml of pH 6.8 phosphate buffer, egg's membrane, 50 rpm.</b> | 1hr 13.45±0.26      | 14.10±1.05          | 13.54±0.23          |
|   | 2 hr 29.13±0.47     | 27.14±0.23          | 28.47±0.29          |
|   | 3 hr 41.12±0.59     | 40.22±0.65          | 42.12±0.44          |
|   | 4 hr 53.21±0.62     | 54.64±0.24          | 53.10±0.15          |
|   | 5 hr 71.11±0.14     | 70.14±1.02          | 70.45±0.26          |
|   | 6 hr 85.41±0.66     | 86.52±0.95          | 84.17±0.14          |
| <b>Clarity</b>  | Clear               | Clear               | Clear               |
| <b>Phase separation</b>   | No phase separation | No phase separation | No phase separation |
| <b>Centrifugation test</b>  | Stable              | Stable              | Stable              |

Microemulgel were evaluated for physical appearance, diffusion study, clarity, Phase separation, centrifugation test. There is no change in description of microemulgel after 3-month stability study. There was no variation observed in Clarity, phase separation and centrifugation test.

### Skin Irritation study on rabbits:

The protocol explained in methodology part employed for skin irritation study. Saline solution producing skin irritation responses compared with the irritation occurred after the application given below. Each group

containing 3 rabbits in it. Skin irritation was calculated on the bases of criteria 0 to 7 given in methodology part and obtained results represent in Table.

The animals were treated as follows:

**Group I-** 20% w/v SLS solution (area A), Untreated (area B).

**Group II-** Microemulgel (CF2) (area A), untreated (area B).

**Group III-** Microemulgel (PC3) (area A), untreated (area B).

**Table 9: Skin Irritation Study of Group (Group with SLS solution)**

| Sr. No. | Skin Irritation Symptom | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | D12 | D13 | D14 |
|---------|-------------------------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|
| 1       | 0                       | -  | -  | -  | -  | -  | -  | -  | -  | p  | p   | p   | p   | p   | p   |
| 2       | 1                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | p   | -   | p   | p   | p   |
| 3       | 2                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | p   | p   | p   |
| 4       | 3                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | p   | p   |
| 5       | 4                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | p   |
| 6       | 5                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 7       | 6                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 8       | 7                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |

**Table 10: Skin Irritation Study of Group (Microemulgel (CF2))**

| Sr. No. | Skin Irritation Symptom | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | D12 | D13 | D14 |
|---------|-------------------------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|
| 1       | 0                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | p   | p   | p   | p   |
| 2       | 1                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | p   | p   | p   |
| 3       | 2                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | p   | p   | p   |
| 4       | 3                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | p   |
| 5       | 4                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 6       | 5                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 7       | 6                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 8       | 7                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |

**Table 11: Skin Irritation Study of Group (Microemulgel (PC3))**

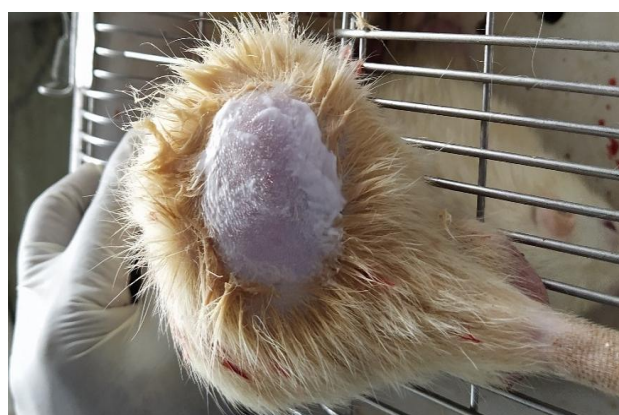
| Sr. No. | Skin Irritation Symptom | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | D12 | D13 | D14 |
|---------|-------------------------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|
| 1       | 0                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | p   | p   | p   |
| 2       | 1                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | p   | p   |
| 3       | 2                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | p   | p   |
| 4       | 3                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | p   | p   |
| 5       | 4                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 6       | 5                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 7       | 6                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 8       | 7                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |



A



**B**



**C**



**D**





**Figure 6: (A) Handling of rabbit for application of microemulgel**

**(B) Skin Irritation Study photos after application of formulation 14 days. (Formulation CF2);**

**(C) Skin Irritation Study photos after spreading formulation over skin 14 days. (Formulation CF2);**

**(D) Skin Irritation Study photos after application of**

**a) Group I- 20% w/v SLS solution; b) Group II- Microemulgel (CF2); c) Group III- Microemulgel (PC3) (area A) After 14 days.**

Results revealed that as saline solution is a skin irritant it was produced irritation with minimal erythema after 10 days and definite erythema, readily visible edema was produced after 12 days. Compared with this both the placebo and optimized batch did not show any type of irritation up to 10 days after that there was little erythema found with light redness at the site of application. These results of in-vivo skin irritation study suggested that microemulgel does not show any type of major irritation on rat skin for up to 14 days.

## SUMMARY AND CONCLUSION

Non-steroidal anti-inflammatory drugs (NSAIDs) taken orally are very efficient, their clinical use is typically restricted due to side effects include gastrointestinal mucosal irritation and ulceration. Microemulsion and microemulsion gel were created for transdermal administration in the current investigation to reduce these adverse effects and improve clinical efficacy. Microemulsions' low viscosity might be a hindrance in certain situations, notably those involving the pharmaceutical business. Efforts were undertaken to improve microemulsion's viscosity to counteract this shortcoming. The transdermal application of microemulsion gel was shown to be superior to that of microemulsion as a medium for drug delivery. A microemulsion for transdermal administration of Naproxen.

In order to be absorbed through the skin, medication must first be dissolved in a vehicle, making solubility one of the primary goals of a new pharmaceutical formulation. Therefore, to identify appropriate and

optimal components of microemulsions, the solubility of the selected medicine was tested in a number of oils, surfactants, and co-surfactants. Microemulsion formulations comprising Naproxen and Naproxen were developed using labrasol as the surfactant, ethanol as the co-surfactant, and Capmul MCM C8 as the oil phase, all based on the findings of solubility experiments.

Microemulsion formulation components were chosen for their documented biocompatibility, biodegradability, safety, and efficacy in topical/transdermal applications. Studies of drug-excipient compatibility are conducted to determine the nature and extent of any potential physical or chemical interactions between the two, and to forecast how these interactions will affect drug (Naproxen and Naproxen) and excipients were compatible with one another. Analysis by FTIR and DSC indicates that the drug and excipient mixture is stable. Several physicochemical characteristics of the chosen formulations were investigated. All microemulsions tested had a transparent, clear appearance with no visible particles. All the microemulsion formulations had high percentage transmittance when tested using a UV-Vis spectrophotometer. A study of cloud point measurements shows that all formulations create a stable microemulsion even at physiological temperature. Among the six formulations tested for in-vitro skin penetration, formulation MF2 exhibited the greatest drug release (96.12%) while formulation CF2 showed the highest drug release (97.85%). As a result of the analysis, a batch of MF2 & CF2 formulation was chosen as an optimized formulation due to its



superiority for increased drug release in an in vitro diffusion assay. Droplet size was measured to be 35.2 nm for the MF2Naproxen-loaded microemulsion and 103.2 nm for the CF2 Naproxen-loaded microemulsion. Microemulsions with small droplet size tend to be more stable than those with a larger droplet size because bigger droplets are more likely to aggregate or coalesce. The MF2 Naproxen-loaded microemulsion was found to have a zeta potential of +19.0 mV. Several physicochemical properties of the microemulsion gel were determined after it had been made. According to the results of a skin irritation investigation, the microemulsion gel formulations of Naproxen did not irritate the skin or result in erythema. Microemulsion and microemulsion gel formulations containing Naproxen were shown to be stable under all ICH-recommended stability parameters. The produced formulations' spreadability was sufficient, pointing to their convenience in use. An analysis of spreadability revealed that as formulation viscosity increased, spreadability decreased. In a nutshell, it can be concluded that the developed microemulsion gel might be a potential drug delivery vehicle for the transdermal delivery of Naproxen. Taken together these outcomes reveal that the microemulsion is probably a promising approach for the transdermal shipping of Naproxen. Though, giant work still wishes to be performed to clarify the mechanisms of drug delivery into the skin.

## REFERENCES

1. Abrar, B., Anis, S., Tanu, B., & Singh, S. (2012). Formulation and in-vitro evaluation of NSAID's gel. *Int J Curr Pharm Res*, 4(3), 56-58.
2. Aundhia, C., Patel, J., Patel, S., Sen, A. K., & Seth, A. (2019). Formulation and Evaluation of Microemulsion Loaded Gel of Naproxen for Topical Delivery. *International Journal of Pharmaceutical Research*, 11(2), 1924-1932.
3. Burki, I. K., Khan, M. K., Khan, B. A., Uzair, B., Braga, V. A., & Jamil, Q. A. (2020). Formulation development, characterization, and evaluation of a novel dexibuprofen-capsaicin skin emulgel with improved in vivo anti-inflammatory and analgesic effects. *AAPS PharmSciTech*, 21(6), 1-14.
4. Chandra, A., Sharma, P. K., & Irchiya, R. (2009). Microemulsion-based hydrogel formulation for transdermal delivery of dexamethasone. *Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm*, 3(1), 30-36.
5. Chen, H., Chang, X., Du, D., Li, J., Xu, H., & Yang, X. (2006). Microemulsion-based hydrogel formulation of ibuprofen for topical delivery. *International Journal of Pharmaceutics*, 315(1-2), 52-58.
6. Cirri, M., Bragagni, M., Mennini, N., & Mura, P. (2012). Development of a new delivery system consisting of in "drug-in cyclodextrin-in nanostructured lipid carriers" for ketoprofen topical delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, 80(1), 46-53.
7. Froelich, A., Osmalek, T., Snela, A., Kunstman, P., Jadach, B., Olejniczak, M., Roszak, G., & Biafas, W. (2017). Novel microemulsion-based gels for topical delivery of indomethacin: Formulation, physicochemical properties and in vitro drug release studies. *Journal of colloid and interface science*, 507, 323-336.
8. Ghosh, P. K., & Murthy, R. S. R. (2006). Microemulsions: a potential drug delivery system. *Current drug delivery*, 3(2), 167-180.
9. Goindi, S., Narula, M., & Kalra, A. (2016). Microemulsion-based topical hydrogels of tenoxicam for treatment of arthritis. *Aaps Pharmscitech*, 17(3), 597-606.
10. Guleri, K. T., & Preet, K. L. (2013). Formulation and evaluation of topical gel of aceclofenac. *Journal of Drug Delivery & Therapeutics*, 3(6), 51-53.
11. Hu, L., Hu, Q., & Yang, J. (2014). Enhancement of transdermal delivery of ibuprofen using microemulsion vehicles. *Iranian journal of basic medical sciences*, 17(10), 760.
12. Kalpana Madikattu et al, (2016), Microemulsion based Transdermal Gels of Isradipine to Enhance Bioavailability: In vitro and In vivo Evaluation, *Asian Journal of Pharmaceutics*, (Suppl), 9 (5), S23-S30.
13. Karade, P., Shah, R., Chougule, D., & Bhise, S. (2012). Formulation and evaluation of Naproxen gel. *Journal of drug delivery and therapeutics*, 2(3), 132-135.
14. Kogan, A., & Garti, N. (2006). Microemulsions as transdermal drug delivery vehicles. *Advances in colloid and interface science*, 123, 369-385.
15. Kumar, B., Jain, S. K., Prajapati, S. K., Mahor, A., & Kumar, A. (2010). Development and characterization of transdermal microemulsion gel for an antiviral drug. *International Journal of Pharmaceutical Sciences and Research*, 1(6), 57-74.
16. Kumar, M. S. (2014). Development of Naproxen Transfersomal gel for the Treatment of Rheumatoid Arthritis. *Indian Journal of Pharmaceutical and Biological Research*, 2(2), 7-13.
17. Kweon, J. H., Chi, S. C., & Park, E. S. (2004). Transdermal delivery of diclofenac using microemulsions. *Archives of pharmacological research*, 27(3), 351-356.
18. Lee, J., Lee, Y., Kim, J., Yoon, M., Choi, Y.W., (2005). Formulation of microemulsion Systems for Transdermal Delivery of Aceclofenac. *Arch Pharm Res*. 28(9), 1097 - 1102.
19. Mitra, S. (2013). Arthritis: classification, nature & cause—a review. *Am J Biopharmacol Biochem Life Sci*, 2(3), 1-25.

20. Naeem, M., Iqbal, T., Nawaz, Z., & Hussain, S. (2021). Preparation, optimization and evaluation of transdermal therapeutic system of Naproxen to treat inflammation for treatment of rheumatoid arthritis. *Anais da Academia Brasileira de Ciências*, 93.
21. Nitalikar, M. M., & Sakarkar, D. M. (2013). Formulation and evaluation of topical gel of Meloxicam with  $\beta$ -Cyclodextrin complex. *Research Journal of Pharmacy and Technology*, 6(7), 790-793.
22. Okur, N. U., Yavasoglu, A., & Karasulu, H. Y. (2014). Preparation and evaluation of microemulsion formulations of Naproxen for dermal delivery. *Chemical and pharmaceutical bulletin*, 62(2), 135-143.
23. Park, E. S., Cui, Y., Yun, B. J., Ko, I. J., & Chi, S. C. (2005). Transdermal delivery of piroxicam using microemulsions. *Archives of pharmacol research*, 28(2), 243-248.
24. Patel, J., Patel, B., Banwait, H., Parmar, K., & Patel, M. (2011). Formulation and evaluation of topical aceclofenac gel using different gelling agents. *Int J Drug Dev Res*, 3(1), 156-64.
25. Ramchandani, U., & Sangameswaran, B. (2013). Formulation and evaluation of topical gel of ketoprofen using different polymers. *International Journal of Pharmaceutical & Biological Archive*, 4(2), 323-326.
26. Rannou, F., Pelletier, J. P., & Martel-Pelletier, J. (2016). Efficacy and safety of topical NSAIDs in the management of osteoarthritis: evidence from real-life setting trials and surveys. In *Seminars in arthritis and rheumatism*, 45(4), S18-S21.
27. Ricci, M., Puglia, C., Bonina, F., Di Giovanni, C., Giovagnoli, S., & Rossi, C. (2005). Evaluation of indomethacin percutaneous absorption from nanostructured lipid carriers (NLC): in vitro and in vivo studies. *Journal of pharmaceutical sciences*, 94(5), 1149-1159.
28. Salimi, A., Jafarinezhad, S., & Kalantari, A. (2018). Transdermal delivery of ketorolac tromethamine using microemulsion vehicles. *Jundishapur J Nat Pharm Prod*, 13(4), 1-8.
29. Shah, N. V., Ghelani, T. K., Saini, V., Joshi, U. T., Seth, A. K., Chauhan, S. P., Aundhia C. J. & Maheshwari, R. A. (2011). Development and characterization of microemulsion based system of aceclofenac. *Indo Am J Pharm Res*, 2(1), 110-124.
30. Sheikh Shafiq. et al, (2007), Development and bioavailability assessment of ramipril nanoemulsion formulation. *Eur. J. Pharm. and Biopharm.* 66, 227–243.
31. Sheikh, A. A. A., Ali, S. S., Siddiqui, A. R., Zahir, Z., & Ahmad, A. (2011). Formulation development and characterization of aceclofenac gel containing linseed oil and ginger oleoresin. *International Journal of PharmTech Research*, 3(3), 1448-53.
32. Shewaiter, M. A., Hammady, T. M., El-Gindy, A., Hammadi, S. H., & Gad, S. (2021). Formulation and characterization of leflunomide/diclofenac sodium microemulsion base-gel for the transdermal treatment of inflammatory joint diseases. *Journal of Drug Delivery Science and Technology*, 61, 102-110.

Received:08.05.18, Accepted: 05.06.18, Published:01.07.2018

**\*Corresponding Author:**

**G. Nagaraju\***

Email: [gdp413@gmail.com](mailto:gdp413@gmail.com)