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Formulation and Evaluation of Microemulsion Gel for Transdermal Delivery of Naproxen

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ABSTRACT
Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) that is used to treat inflammatory joint disorders such as osteoarthritis. In this study, we set out to develop a novel microemulsion formulation for Naproxen transdermal delivery. To choose excipients with high drug loading capacity, the solubility of the drug in various oils, surfactants, and co-surfactants was tested in preformulation tests. The oil in the microemulsions formulation was Capmul MCM C8, whereas the surfactant and co-surfactant were labrasol and ethanol, respectively. Using pseudo ternary phase diagrams, the concentrations of the oil phase, Smix, and distilled water employed in the manufacture of the Naproxen microemulsion were estimated. A gelling agent was added to the microemulsion at a 1:1.2 ratio to form microemulgel (microemulsion: gelling agent). The microemulgel (PN3) in issue functioned effectively when tested under a variety of strength conditions. In vitro studies revealed that the microemulgel formulation (PN3) containing Naproxen caused no skin irritation. Based on these data, it appears that a Naproxen microemulsion formulation could be a successful formulation for transdermal delivery.

KEYWORDS: Microemulsion, Microemulgel, Naproxen, Arthritis

I. INTRODUCTION

Drug delivery system (DDS) is a generic term for a series of physicochemical technologies that can control delivery and release of pharmacologically active substances into cells, tissues and organs, such that these active substances could exert optimal effects. In other words, DDS covers the routes of administration and drug formulations that efficiently deliver the drug to maximize therapeutic efficacy while minimizing any side effect. [1] Depending on the delivery route, there are many types of administration modalities, such as oral administration, transdermal administration, lung inhalation, mucosal administration, and intravenous injection. Among them, the transdermal drug delivery system (TDDS) represents an attractive approach.Transdermal drug delivery system is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation. TDD has many advantages over other conventional routes of drug delivery. It can provide a non-invasive alternative to parenteral routes, thus circumventing issues such as needle phobia. A large surface area of skin and ease of access allows many placement options on the skin for transdermal absorption. Furthermore, the pharmacokinetic profiles of drugs are more uniform with fewer peaks, thus minimizing the risk of toxic side effects. It can improve patient compliance due to the reduction of dosing frequencies and is also suitable for patients who are unconscious or vomiting, or those who rely on self-administration. TDD avoids pre-systemic metabolism, thus improving bioavailability. [2]

TDDS has significantly influenced the delivery of various therapeutic agents, especially in pain management, hormonal therapy, and treatment of diseases of the cardiovascular and central nervous systems. TDDS does not involve passage through the gastrointestinal tract; therefore, there is no loss due to first-pass metabolism, and drugs can be delivered without interference from pH, enzymes, and intestinal bacteria. In addition, TDDS can be used to control drug release according to usage restrictions, thereby contributing to the high persistence of this method.[2,3] Most importantly, because TDDS is a noninvasive administration method and involves minimal pain and burden on the patient, drugs can be safely and conveniently

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administered to children or the elderly. [4] 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 a number of 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 as a result of the ease it provides and the drug's generally positive reputation for safety.

Naproxen is FDA-approved for treating acute gout, ankylosing spondylitis, bursitis, polyarticular juvenile idiopathic arthritis, osteoarthritis, tendonitis, rheumatoid arthritis, pain, and primary dysmenorrhea. It is the first-line treatment for acute gouty arthritis, osteoarthritis, musculoskeletal pain, inflammation, and dysmenorrhea. While naproxen and other NSAIDs are approved for the treatment of inflammatory arthropathies such as rheumatoid arthritis and ankylosing spondylitis, they do not alter the course of the disease, nor do they prevent joint and soft tissue destruction that are common sequelae of these diseases.Naproxen blocks arachidonate binding to competitively inhibit both cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, resulting in analgesic and anti-inflammatory effects. COX-1 and COX-2 are catalysts of arachidonic acid conversion to prostaglandin G (PGG), the first step of the synthesis of prostaglandins and thromboxanes involved in rapid physiological responses. COX-1 is constitutively expressed in most tissues, while COX-2 is only expressed in the brain, kidney, bones, reproductive organs, and select tumors such as colon and prostate cancers. COX-1 is responsible for prostaglandin synthesis in response to stimulation by circulating hormones and maintaining healthy renal function, gastric mucosal integrity, and hemostasis. COX-2 is inducible in many cells in response to specific mediators of inflammation (e.g., interleukin-1, tumor necrosis factor, lipopolysaccharide).

The goal of this study was to create an appropriate microemulsion gel system after screening oils, surfactants, and cosurfactants for transdermal delivery of tramadol naproxen in order to improve its dissolution and skin permeability while maintaining safety. [5,6]

II. MATERIALS AND METHODS

Materials

Naproxen was received as a gift sample from RPG Life Sciences Ltd., Mumbai. Capmul MCM was obtained from Abitech Corporation, U.S.A., Cremophore RH40, Tween 80 and Tween 20 was procured from BASF, Mumbai, and Propylene glycol was obtained from Pure Chem Lab, Pune. All other chemicals were of analytical grade.

Methods

Solubility Study

The solubility of Naproxen in various oils (Capmul MCM, Isopropyl myristate, Aniseed oil, Oleic acid, Castor oil, and Olive oil), surfactants (Cremophore RH 40, Tween 20, Tween 80, and Span 20) and co-surfactant (PEG400, Transcutol HP, and Polyethylene glycol) it was determined. In a vial, 2 ml of required solvent and excess quantity of the drug was added. The mixture was removed, filtrate and analyze by using UV spectrophotometer. All measurements were done in triplicates [7].

Preparation of microemulsion of Naproxen:

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

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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

All values are in ml

Optimization of Microemulsion: -

Thermodynamic Stability of microemulsion:

When the medicine precipitates in an excipient matrix, the performance of the microemulsion formulation might be severely impacted. In addition, inadequate formulation physical stability may lead to excipient phase separation, which affects both formulation and visual performance.

Thermodynamic Stability study of microemulsion (MF1-MF24) were performed as per procedure mentioned below

Heating cooling cycle:

Six cycles between refrigerator temperature i.e. 4 ^{0}C and 45 ^{0}C with storage at each temperature of not less than 48 h were studied. Those formulations, which were stable at these temperatures, were subjected to a centrifugation test.

Centrifugation:

Those formulations that complied with the heating cooling cycling test were centrifuged at 3500 rpm for 30 min. Those formulations which did not show any phase separation were taken for the freeze-thaw stress test.

Freeze-thaw cycle:

Three freeze-thaw cycles between -21 ^{0}C and +25 ^{0}C with storage at each temperature for not less than 48 h were done for the formulations. The result of the stability study of amlodipine and nifedipine loaded microemulsion was reported in Tables 22 and 42 respectively. Phase separation in the resulting formulations was then monitored. The optimal formulations are the ones that pass these three tests with the lowest concentration of Smix.

Characterization of Microemulsion: -

1. 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.

2. 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.

3. Droplet size determination

In a beaker, 10 milligrammes of MF1-MF24microemulgel formulation was diluted with 50 millilitres 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.

4. 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)

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and stirred for 1 minute. There were three sets of each experiment.

Preparation of Microemulgel of formulation

1. 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.

2. Method of Preparation of Trial Batches:

Firstly, microemulsions take in test tube on high pressure homogenizer. The carbopol 940 was then added with constant stirring, and the gel was kept at room temperature for 15 min to obtain a good microemulgel.

Preparation of trial batches:

1. Preparation of trial batches using different combination of microemulsion and polymer to selection of ratio.

On the basis of literature survey and laboratory work preliminary trials are design.

Table 2: Ratio of microemulsion and polymer

Trial Batch	Polymer	Ratio(O:P)
O1	Carbopol 940	1:0.5
O2	Carbopol 940	1:1
O3	Carbopol 940	1:1.2
O4	Carbopol 940	1:1.5
O5	Carbopol 940	1:2

On the basis of literature survey, preliminary trials and there results the following trials are design.

Characterization of microemulgel:

A) Physical appearance:

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

1. pH

Digital pH meter 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.

2. 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

3. Spreadability

The spreadability 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 the top slide to travel a distance of 5 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.

4. Extrudability

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

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

B) 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 251 °C, the flow behaviour of the various formulations was evaluated by analysing the location of the upward and downward curves in the rheogram.

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C) Drug content determination: -

The 10 mg of 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 concentrations in the aforementioned solutions were measured using a UV Spectrophotometer (Shimadzu UV 1800) set to lambda max 331nm. Standard calibration curves of Naproxen were used to calculate the exact concentrations of each drug in the formulation.

D)In **vitro drug release study: -**

The experiment employed a Franz diffusion cell that had an effective diffusion area of 7.1 cm^2. 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 was 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 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 1 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).

E) Stability of microemulgel

Clarity and phase separation observation, as well as UV assays of Naproxen were used to determine the stability of a microemulgel containing the drug 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.

Table3: Stability protocol

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

III. RESULT AND DISCUSSION

Drug Authentification:

Appearance, and color:

Naproxen sodium is an odorless crystalline powder, white to creamy in color.

Solubility:

It is soluble in methanol and water.

Melting point determination: -

The melting point of the drug matched with the values found in literature indicating the quality of sample.

Table 4: Melting point of Naproxen

Drug	**Melting point**	
	Practical	**Standard**
Naproxen	154°C	152°C-154°C

FTIR of drug:

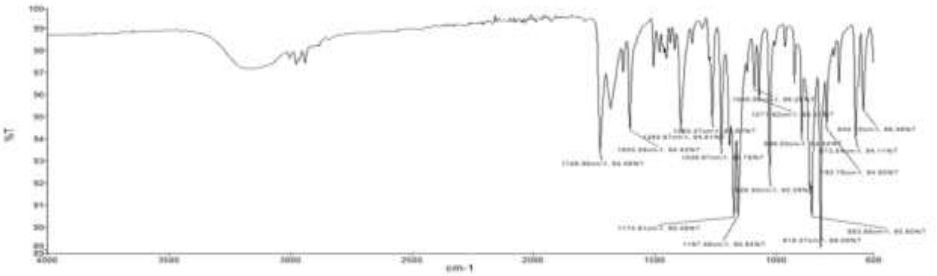

Figure 1. IR spectra of Naproxen

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IR Spectrum of Naproxen showed corresponding Wave Number (cm^{-1}) as per the group present in chemical structure; C=C-C stretch (3332.89); C= O (1603.31); Aryl-O stretch (1225.67) and Alkyl C-O stretch (1070.35).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.

UV spectrophotometric method for Naproxen
Determination of $\lambda_{max:}$-
Preparation of stock solution:

Calibration curve

In order to get a concentration of 100 g/ml, 10mg of Naproxen was added to 100 ml of methanol by weight. Ten millilitres were taken out of the solution and the rest was added to make up to a hundred millilitres. This final solution was used as a stock solution, and subsequent solutions with concentrations ranging from 5-30ug/ml were prepared by diluting the stock solution with methanol as needed. UV Spectrophotometer was used to examine the aforementioned solutions at a max wavelength of 331nm.

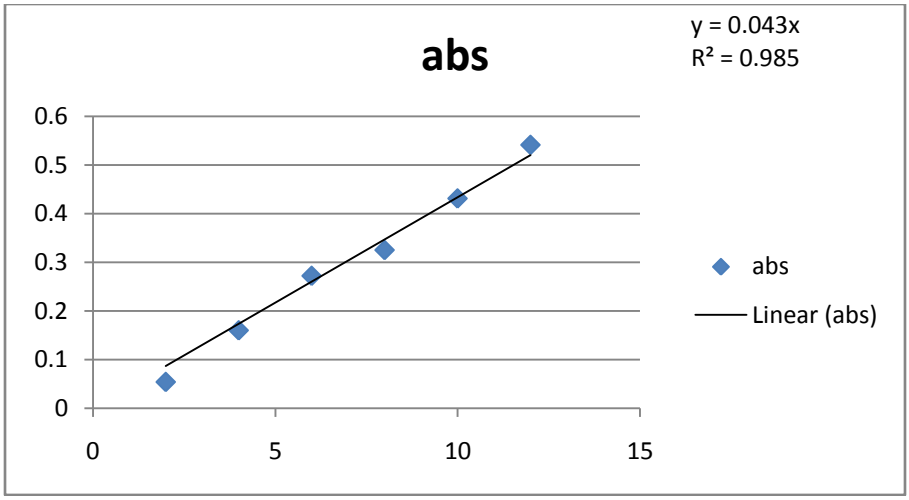

Figure 2. Calibration curve of Naproxen

Compatibility study: -

Preformulation compatibility studies of 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 5: 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

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Evaluation of Optimization of microemulsion:-

Centrifugation force is used to determine the separation behavior of the colloidal particles under the influence of gravitational field, as there was no separation observed the stability of developed microemulsion confirmed.

Table 6: Optimization of microemulsion - Naproxen

Ratio- 1:1

Formula no.	Oil:Smix	After centrifugation test	Heating cooling cycle	Freeze thaw cycle
MF 1	1:9	Stable	Stable	Stable
MF2	2:8	Stable	Stable	Stable
MF3	3:7	Stable	Stable	Stable
MF4	4:6	Stable	Stable	Stable

Ratio 2:1

Formula no.	Oil:Smix	After centrifugation test	Heating cooling cycle	Freeze thaw cycle
MF10	1:9	Stable	Stable	Stable
MF12	3:7	Stable	Stable	Stable
MF13	4:6	Stable	Stable	Stable

Ratio 3:1

Formula no.	Oil:Smix	After centrifugation test	Heating cooling cycle	Freeze thaw cycle
MF20	2:8	Stable	Stable	Stable
MF21	3:7	Stable	Stable	Stable

MF5-MF9, MF14-MF19, MF22-MF24 were found unstable after centrifugation process. No changes in the formulation MF1-MF4, MF10-MF13, MF20-MF21 are observed stable and subjected for further study. Formulation MF5, MF6, and MF14 in heating cooling cycle undergo creaming due to the proportion oil and MF1-MF4, MF10-MF13, MF20-MF21 are found stable and examined for freeze thaw cycle. Among this formulation increase toxicity due to which formulation MF1, MF10 and MF20 contain higher proportion of surfactant and co-surfactant. From the results of the Centrifugation Test, the Heating and Cooling Cycle, the Freeze Thaw Cycle, and the selection of the six formulations MF2, MF3, MF4, MF12, MF13, and MF21 from the various Smix (1:1, 2:1, 3:1) ratios, it was determined that the prepared microemulsion was stable.

Characterization of microemulsion: -

1) 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 7: 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

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From the above study it can be concluded that all 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.

2) Cloud point measurement

Formation of a stable nano-emulsion is due in large part to the cloud point in a Microemulsion made up of non-ionic surfactants. The cloudiness of the preparation caused by the dehydration of the polyethylene oxide moiety occurs at temperatures over the cloud point, leading to an irreversible phase separation and a negative impact on Naproxen absorption. Therefore,Microemulsion's cloud point should be above 37^{o}C so that phase separation doesn't occur on the skin.

Table 8: Cloud Point of Optimized Formulation

Formulation	**Cloud Point Temperature**
MF2	74
MF3	73
MF4	65
MF12	69
MF13	63
MF21	73

From the above study it can be concluded that all the formulation forms a stable microemulsion even at physiological temperature.

3) Droplet size measurement of microemulsion

Mean globule size of optimized formulation is given in Table 9. MF-2 was showing least globule size of 35.2nm shown in figure 3.

Table 9: Globule Size (nm) of liquid Formulation

Formulation	**Avg. Globule Size (nm)**
MF2	35.2nm

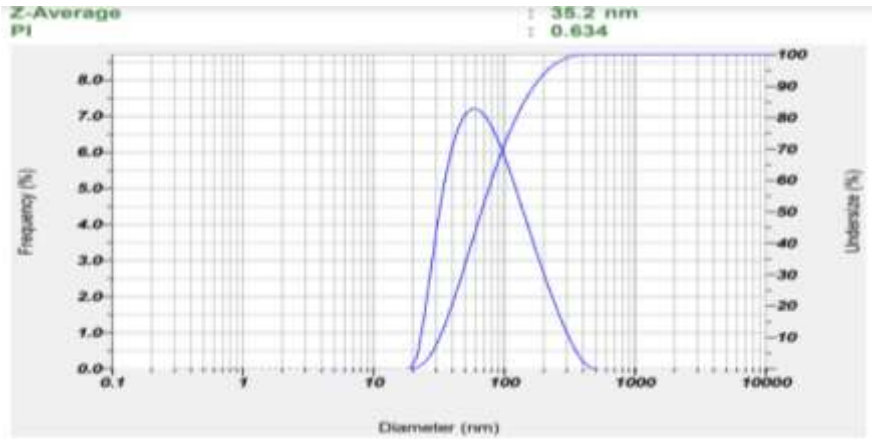

Figure 3: Graph of globule size determination

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4) Zeta potential (ZP) measurement of microemulsion

Zeta potential of MF2were found to be +19.0mV.

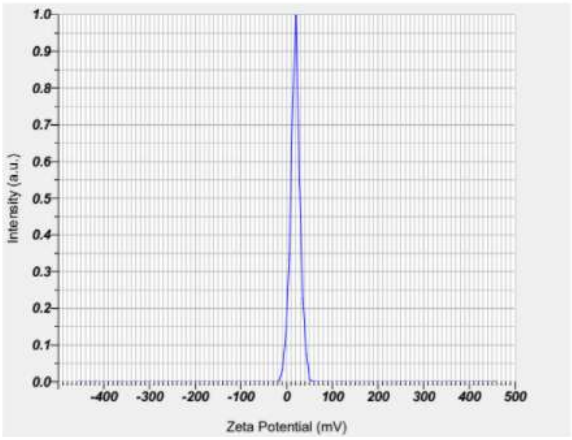

Figure 4: Zeta potential of Microemulsion

5) 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%).

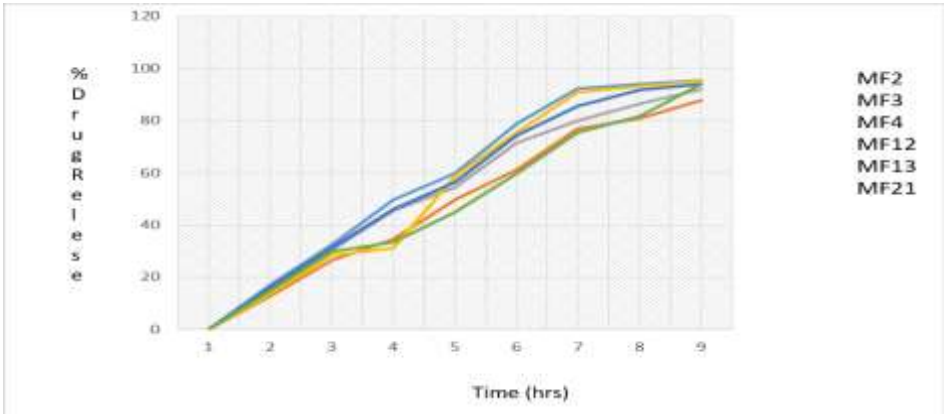

Figure 5: Drug Release Profile of Optimized microemulsion formulation

Figure 5 compares the medication release of six different lots of 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.

6) In vitro drug release study of Microemulgel

In vitro analysis of medication release from six distinct microemulgel formulations showed that Formulation PN3 had the highest drug release (97.15 %).

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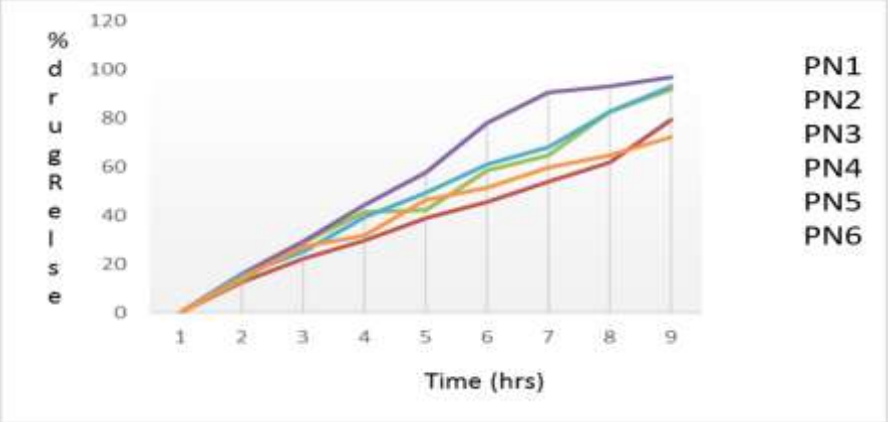

Figure 6: Drug Release Profile of Optimized microemulgel formulation

Figure 6 depicts a study comparing the rates of drug release from five different lots of preparation. Preparation batch PN3 had the highest drug release compared to PN1, PN2, PN4, and PN5 formulations. At 8 hours, the PN3 formulation exhibits more drug release. Batch PN3 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: -

1) Physical appearance:

a) 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.

b) 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.

c) Appearance

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

d) Spreadability

Table 10 displays the results of a measurement of spreadability from PN1 to PN5. It can be seen that the spreadability of a solution decreases as the concentration of carbopol 940 rises.

e) 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 10.

Table 10: 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	+

From the above study, it was concluded that the batch PN3 was selected as the promising formulation on the basis of pH, viscosity, appearance, spreadability, and extrudability.

f) Drug content determination: -

The drug content of Naproxen in all the formulation was found to be in the range 98-99% in microemulgel which indicate complete solubilization of drug in formulation.

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Table 11: 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

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

Parameters		Initial	1 Months	3 Months
Drug content (%)		PN3	PN3	PN3
		98.78±0.23	98.11±045	97.30±0.22
Diffusion (%) Medium: 25ml of pH 6.8 phosphate buffer, egg's membrane, 50 rpm.	0Hr	0	0	0
	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±014
Clarity		Clear	Clear	Clear
Phase separation		No phase separation	No phase separation	No phase separation
Centrifugation test		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.

IV. CONCLUSION

Preformulation studies were performed to determine the solubility of the drug in various oils, surfactants, and co-surfactants in order to select excipients with high drug loading capacity. Capmul MCM C8 was used as the oil in the microemulsions formulation, while labrasol and ethanol were used as the surfactant and co-surfactant, respectively. The concentrations of the oil phase, Smix, and distilled water used in the production of the Naproxen microemulsion were calculated using pseudo ternary phase diagrams. To make microemulgel, a gelling agent was added to the microemulsion at a 1:1.2 ratio (microemulsion: gelling agent). When tested under various strength settings, the microemulgel (PN3) in question performed well. In vitro investigations demonstrated that the Naproxen-containing microemulgel formulation (PN3) did not cause skin irritation. Based on these findings, it appears that a Naproxen microemulsion formulation could be a viable transdermal administration option.

CONFLICT OF INTERESTS
None declared by the authors.

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