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Development and Evaluation of Leflunomide Nanoemulgel: A Novel Topical Delivery System for Treatment of Rheumatoid Arthritis

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ABSTRACT

Background:
Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by persistent synovial inflammation, joint pain, and progressive cartilage destruction. Leflunomide, a widely used disease-modifying antirheumatic drug (DMARD), effectively suppresses T-cell proliferation by inhibiting dihydroorotate dehydrogenase. However, its oral administration is limited by poor aqueous solubility, first-pass hepatic metabolism, and systemic side effects including hepatotoxicity and gastrointestinal discomfort. These limitations necessitate the development of an alternative drug delivery approach that enhances local efficacy while reducing systemic exposure.

Objective:
The present study was undertaken to formulate and evaluate a leflunomide-loaded nanoemulgel for topical application to improve local anti-inflammatory activity, enhance drug permeation through the skin, and reduce adverse systemic effects in the management of rheumatoid arthritis.

Methods:
A nanoemulsion of leflunomide was prepared using oleic acid as the oil phase, Tween 80 as the surfactant, and propylene glycol as the co-surfactant via the spontaneous emulsification technique. The optimized nanoemulsion was then incorporated into a Carbopol 940 hydrogel base, and phenoxyethanol was used as a preservative. The nanoemulgel was evaluated for various physicochemical properties, including droplet size, polydispersity index (PDI), zeta potential, pH, viscosity, spreadability, and drug content. *In-vitro* drug release studies were performed using Franz diffusion cells over a 24-hour period and compared to a conventional leflunomide gel.

Results:
The optimized nanoemulgel exhibited a mean droplet size below 200 nm, low PDI (< 0.3), and a stable zeta potential, indicating good formulation stability. The pH and viscosity were within acceptable limits for dermal application, and the formulation showed excellent spreadability and over 95% drug content uniformity. *In-vitro* release studies demonstrated 74% cumulative drug release over 24 hours from the nanoemulgel, significantly higher than the conventional gel, confirming improved release and potential for enhanced topical efficacy.

Conclusion:
The developed leflunomide-loaded nanoemulgel, comprising oleic acid, Tween 80, propylene glycol, and phenoxyethanol, showed promising physicochemical characteristics and superior drug release behavior. These findings support its potential as an effective and safe topical therapeutic system for the localized treatment of rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disorder characterized by persistent synovial inflammation, joint stiffness, pain, and irreversible cartilage damage. It affects approximately 0.5–1% of the global population, with a higher prevalence in women and the elderly, contributing to reduced mobility and quality of life if untreated.[1] The pathophysiology of RA involves immune dysregulation, pro-inflammatory cytokine release, and infiltration of immune cells into the synovial joints, leading to chronic inflammation and joint destruction. [2]
Leflunomide, a synthetic isoxazole derivative, is a widely used disease-modifying antirheumatic drug (DMARD) in RA therapy. It exerts its action by inhibiting dihydroorotate dehydrogenase, a key enzyme in the de novo synthesis of pyrimidines, thereby

suppressing T-cell proliferation and reducing inflammation. [3] Despite its therapeutic potential, oral administration of leflunomide is often associated with poor aqueous solubility, low bioavailability, and serious systemic side effects such as hepatotoxicity, gastrointestinal discomfort, and hypertension.[4,5] These challenges have prompted the search for alternative drug delivery systems that can enhance localized therapeutic action while minimizing systemic exposure.

Topical drug delivery is gaining significant attention in the treatment of inflammatory joint diseases, as it allows for direct drug targeting at the site of action, bypassing hepatic first-pass metabolism and reducing systemic toxicity.[6] However, the efficiency of topical delivery depends on the physicochemical characteristics of the drug and its ability to penetrate the stratum corneum, which poses a major barrier, particularly for poorly water-soluble drugs like Leflunomide.[7] To overcome these limitations, nanoemulgel systems have emerged as a promising strategy. Nanoemulgels combine the advantages of nanoemulsions—such as enhanced solubilization, small droplet size, and increased surface area for absorption—with the favorable rheological and application properties of hydrogels.[8] Nanoemulsions promote better skin penetration and drug permeation, while the gel matrix ensures sustained release and patient compliance.[9]

In this context, the present study focuses on the development and evaluation of a leflunomide-loaded nanoemulgel, incorporating biocompatible excipients such as oleic acid (oil phase), Tween 80 (surfactant), propylene glycol (co-surfactant), and phenoxyethanol (preservative). The aim is to enhance the topical delivery of leflunomide, maximize local anti-inflammatory effects, and minimize systemic side effects, offering a novel therapeutic approach for the management of rheumatoid arthritis.

Materials and Methods

Leflunomide (gift sample, Khandelwal Laboratories Pvt. Ltd., Mumbai, India) served as the model drug. Oleic acid (oil phase), Tween 80 (surfactant), propylene glycol (co-surfactant), Carbopol 940 (gelling polymer), triethanolamine (pH modulator) and phenoxyethanol (preservative) were analytical grade and procured from Institutional Laboratory Facilities. All chemicals and reagents were of analytical grade, and distilled water was used throughout the study. [10]

Pre-formulation studies

- **Organoleptic evaluation:** Leflunomide presented as a pale-yellow, odour-free crystalline solid.
- **Melting point:** The capillary method gave 166 – 168 °C, corroborating literature values.[11]

Spectroscopic characterisation

- **FTIR:** Spectra were captured from 4000–400 cm^{-1} (4 cm^{-1} resolution) using an ATR accessory after blending drug with KBr (1:100 w/w).[12]
- **UV:** A methanolic solution (10 µg mL^{-1}) was scanned from 200–400 nm; λ_max was 276 nm.[13]

Equilibrium solubility

Approximately 100 mg drug was placed in 10 mL of each solvent (distilled water, methanol, ethanol, PBS pH 7.4), shaken at 150 rpm (25 ± 1 °C) for 24 h, equilibrated statically for a further 24 h, filtered (0.45 µm), diluted and analysed at 276 nm.[14]

Drug-excipient compatibility

Physical mixtures of drug with each excipient (1:1 w/w) were examined by FTIR for peak shifts, loss or new band formation, indicating potential interaction. [12]

Calibration curve

A 100 µg mL^{-1} stock in PBS pH 6.8 was serially diluted to 10–50 µg mL^{-1}. Absorbance at 276 nm versus concentration produced a linear plot ($r^2 > 0.999$). [13]

Solubility screening for nanoemulsion components

Leflunomide (100 mg) was dispersed in 3 mL of each oil (castor, olive, ethyl oleate, oleic acid, sesame), surfactant (Tween 80/60/20) and co-surfactant (glycerin, propylene glycol, ethanol, PEG 400/200). Mixtures were vortexed, incubated (37 ± 1 °C, 72 h), centrifuged (5000 rpm, 15 min) and the supernatant diluted with methanol for UV quantification at 276 nm.[15]

Pseudo-ternary phase diagram construction

Surfactant:co-surfactant blends (Smix) were prepared in 1:1, 1:2 and 2:1 mass ratios and combined with oil in nine proportions (1:9 – 9:1). Each 1.5 mL blend containing 20 mg drug was titrated with distilled water (45–50 °C) up to 85 % total volume under vortexing. The clarity–turbidity transition was logged to delineate nanoemulsion zones; compositions remaining transparent across the dilution range were shortlisted. [16]

Preparation of leflunomide nanoemulsion

Drug was dissolved in oleic acid. The aqueous phase (Tween 80:propylene glycol 3:1 w/w) was added dropwise under mechanical stirring (1000 rpm, 15 min) to form a coarse emulsion, which was probe-sonicated (20 kHz, 400 W; 30 s on/10 s off; total 10 min) to yield droplets < 200 nm.[17]

Formulation of leflunomide nanoemulgel

Carbopol 940 P (1 % w/w) was dispersed in distilled water and allowed to hydrate overnight. After neutralisation with triethanolamine (pH 6.5–6.8), the nanoemulsion was incorporated into the gel base (nanoemulsion:gel 1:10) under gentle stirring. Phenoxyethanol (0.5 % w/w) was added, and the final gel inspected for homogeneity, pH and absence of air bubbles. [18]

Evaluation of Nanoemulgel

Droplet size and zeta potential

The optimised leflunomide (LFD) nanoemulsion was diluted 1:1000 (v/v) with de-ionised water and analysed by dynamic light scattering (Zetasizer Nano ZS, Malvern Instruments, UK) at 25 °C. Mean hydrodynamic diameter, polydispersity index (PDI) and zeta potential were recorded from three consecutive runs. [19]

Viscosity

Apparent viscosity of the nanoemulgel (25 ± 0.5 °C) was measured with a Brookfield DV-III Ultra rheometer fitted with spindle #64. Readings were taken at 10, 20 and 50 rpm, and the mean of triplicate measurements was reported. [20]

pH

Formulation pH was determined at ambient temperature using a calibrated digital pH meter. Each sample was measured in triplicate after equilibrium for 2 min. [21]

***In-vitro* permeation**

Permeability was assessed in Franz diffusion cells (effective area = 2.27 cm^2, receptor volume = 6.5 mL). Dermatomed porcine ear skin was mounted with the stratum corneum facing the donor chamber and the dermis facing the receptor. [22] Receptor medium comprised normal saline containing 30 % (v/v) methanol, maintained at 37 ± 0.5 °C and continuously stirred. Equal LFD doses of nanoemulsion and nanoemulgel were placed in the donor compartment. Aliquots (0.5 mL) were withdrawn at 1, 2, 4, 6, 8, 10, 12 and 24 h, immediately replaced with fresh aerated medium, filtered (0.22 µm) and quantified by HPLC at 260 nm. Cumulative amount permeated per unit area (µg cm^{-2}) was plotted against time. [23]

Stability testing

Samples were stored for six months at ambient conditions (25 ± 2 °C/60 ± 5 % RH) to simulate patient use.[24] Physical stability was examined monthly by centrifugation (3000 rpm, 15 min) for phase separation, followed by droplet size, PDI, zeta potential, viscosity and pH determinations as described above.

RESULTS AND DISCUSSION

Preformulation studies

- **Identification of drug**

Leflunomide is white crystalline powder.

- **Melting point**

The melting point of the drug aligned with the reported value, confirming that the received samples meet the expected specifications. Variations in the melting point can occur due to the presence of impurities. Leflunomide is reported to have a melting point of 165-166°C. Using the capillary method, the drug started to melt at 162°C and was completely melted at 165°C.

- **Spectrophotometric analysis**

FTIR Spectrophotometry

FTIR study was performed on Drug and different excipients for determination of functional groups that will describe the identity. Table 1 has the different sample used for FTIR and their results shown in Figure 1, 2, 3, 4 and 5 for Leflunomide, Oleic acid, Tween 80, Propylene glycol and Carbopol 940 respectively.

Table 1:

Standard	Sample	Element
Leflunomide		
3200-3400 cm^{-1}	3333cm^{-1}	NH stretching
2900-3000 cm^{-1}	2930 cm^{-1}	CH stretching
600-1400 cm^{-1}	1693 cm^{-1}	Isoxazole ring
1400-1600 cm^{-1}	1504cm^{-1}	C=C stretching
1500-1600 cm^{-1}	1540cm^{-1}	C=O
Oleic acid		
2900-3000 cm^{-1}	2923.4 cm^{-1}	CH stretching
1700-1800 cm^{-1}	1708.2 cm^{-1}	C=O stretching
1200-1300 cm^{-1}	1285.3 cm^{-1}	C-O stretching
Tween 80		
2900-3000 cm^{-1}	2953cm^{-1}	C-H stretching
1700-1800 cm^{-1}	1738.1cm^{-1}	C=O stretching
1200-1300 cm^{-1}	1220cm^{-1}	C-O stretching
Propylene Glycol		
3500-3600 cm^{-1}	3500 cm^{-1}	OH stretching
1200-1300 cm^{-1}	1208 cm^{-1}	C-O stretching
Carbopol 940		
2900-3000 cm^{-1}	2950. cm^{-1}	OH stretching
1700-1800 cm^{-1}	1750.2 cm^{-1}	C=O stretching
1200-1300 cm^{-1}	1661 .6cm^{-1}	COC
800-850 cm^{-1}	832.4cm^{-1}	CH bending

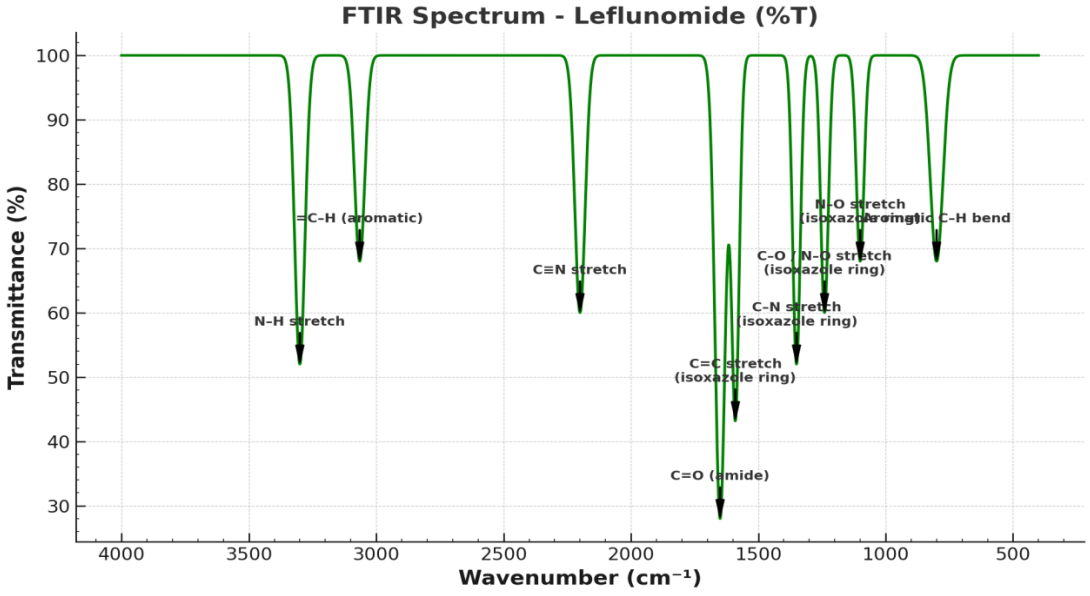

Figure 1: FTIR spectra of Leflunomide

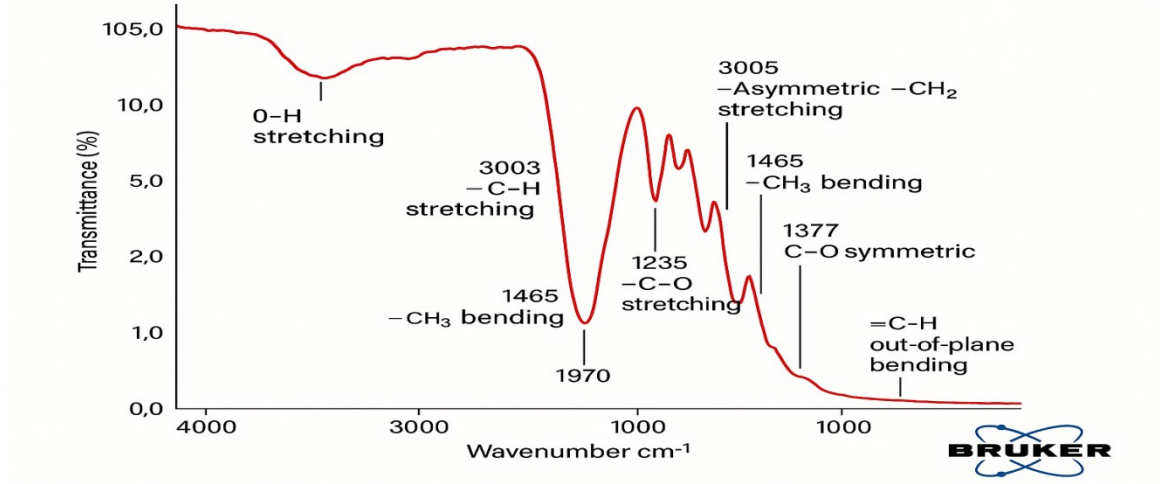

Figure 2: FTIR spectra of Oleic acid

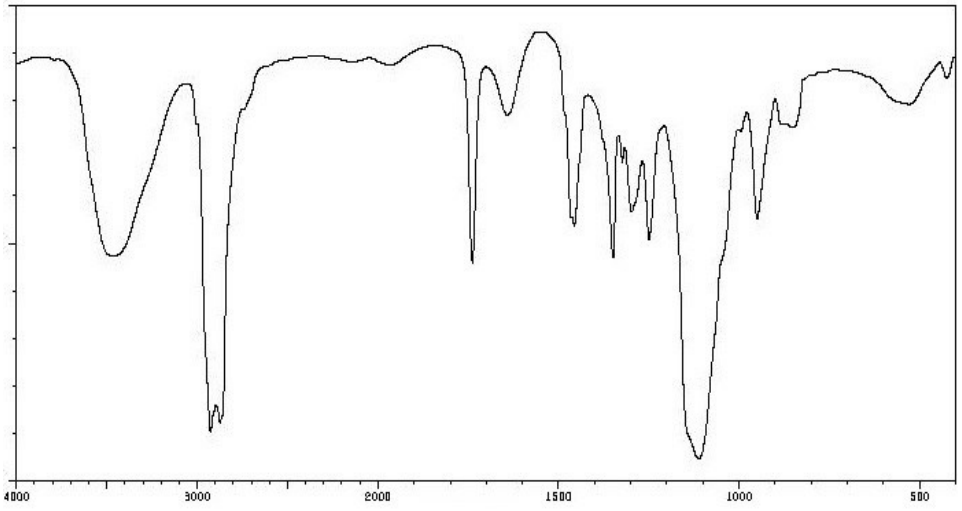

Figure 3: FTIR spectra of Tween 80

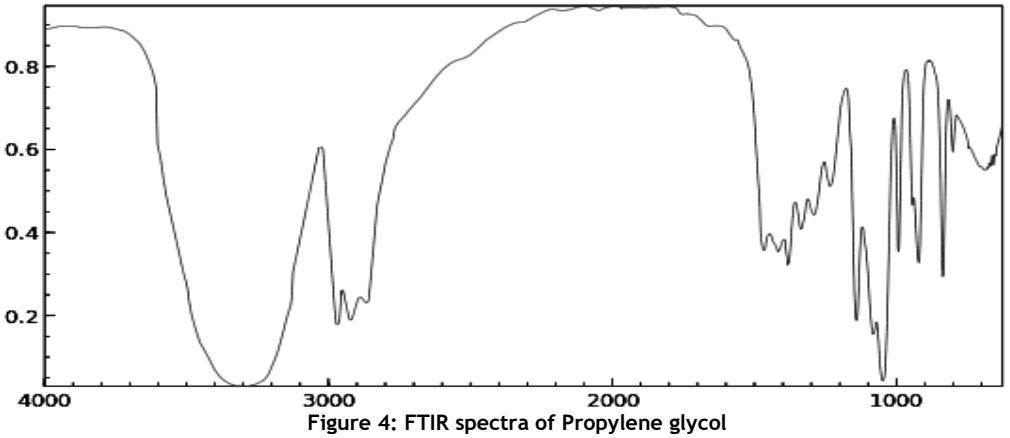

Figure 4: FTIR spectra of Propylene glycol

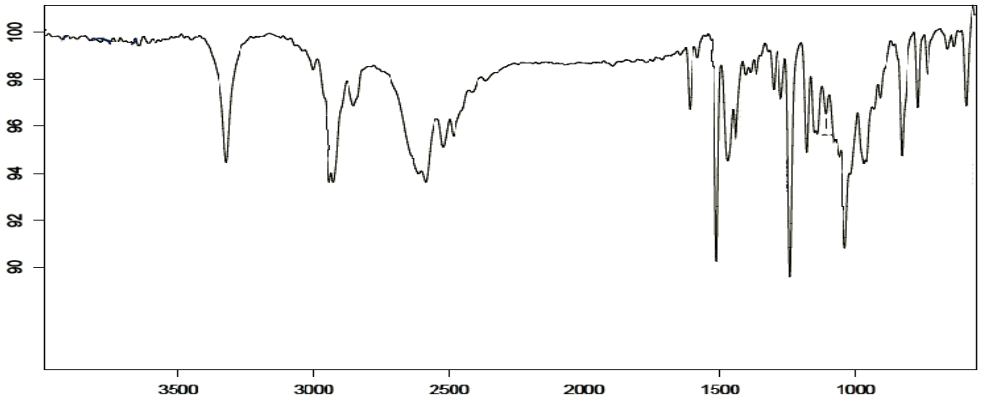

Figure 5: FTIR spectra of Carbopol 940

UV Spectrophotometry

UV spectrophotometer shows maximum absorption of Leflunomide at 276 nm shown in Fig 6.

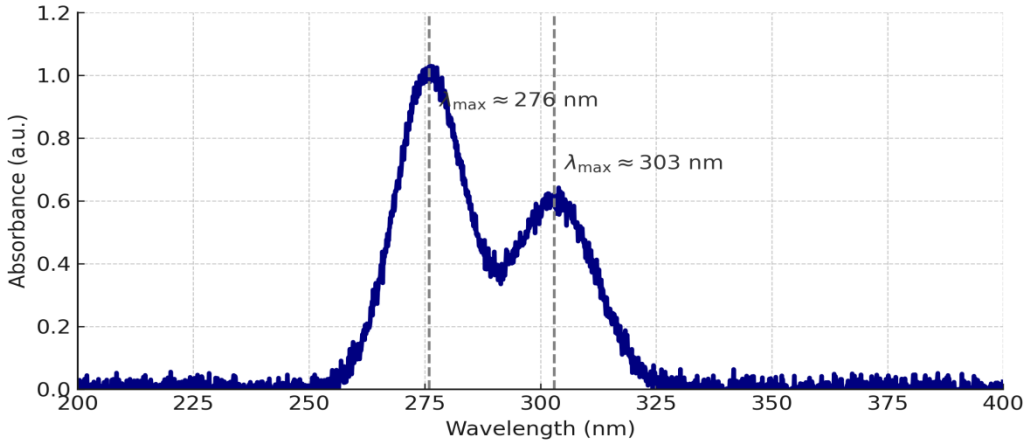

Figure 6: UV scan showing lambda max of Leflunomide.

- **Solubility studies**

Determination of solubility of Leflunomide was done using different solvents like Ethanol, DMSO, Dimethylformamide, Acetone, Ethyl acetate and water, results is shown in Table 2.

Table 2: Quantitative solubility of Leflunomide

Solvent	Solubility
Ethanol	246 mg/ml
DMSO	54 mg/ml
Dimethyl Formamide	25mg/ml
Acetone	48 mg/ml
Water	0.27 mg/ml

DSC Thermogram

Differential Scanning Calorimetry (DSC) has been employed to analyze the thermal properties and polymorphism of leflunomide, a medication used to treat rheumatoid arthritis. Figure 7 displays a sharp endothermic peak at approximately 167.5 °C, indicative of its melting point.

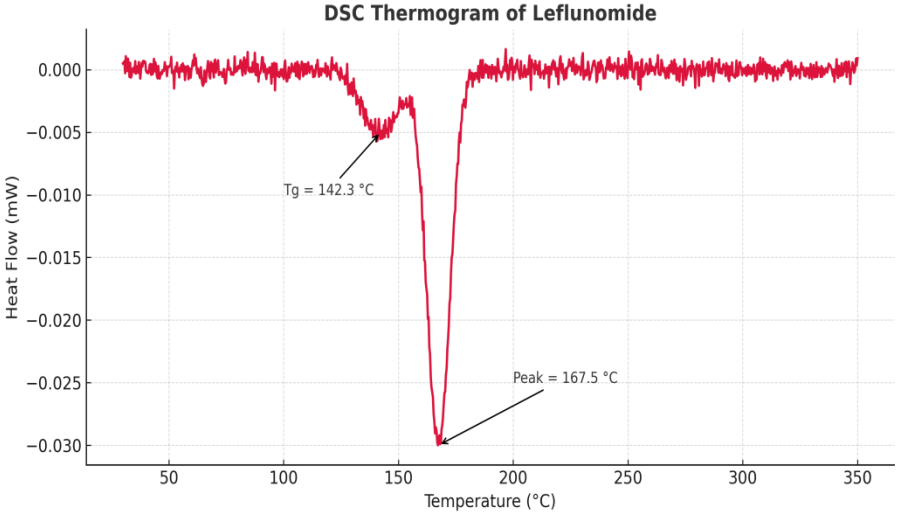

Figure 7: DSC thermogram of pure leflunomide

Drug- excipients compatibility studies

Compatibility studies were carried out using FTIR. Blend containing Drug, polymer and permeation enhancer was used for FTIR analysis. Results show that there is no interaction between drug and excipients.

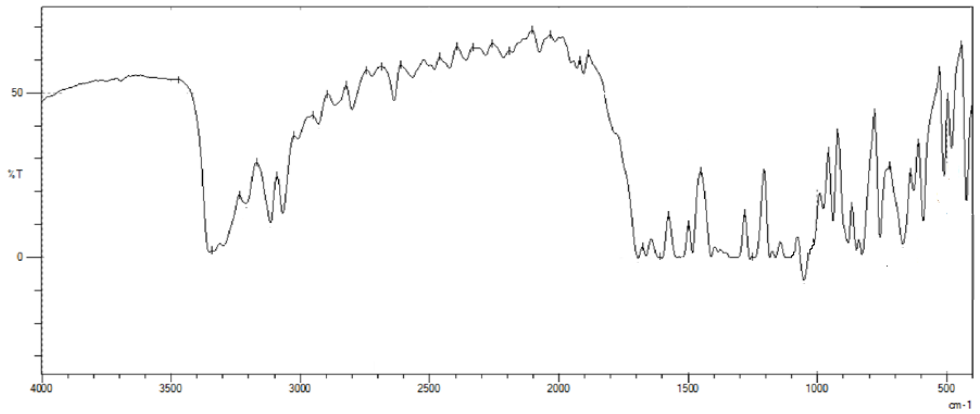

Figure 8: FTIR Spectra of Blend

Preparation of standard calibration curves

A calibration curve for Leflunomide was created using phosphate buffer 6.8 pH at λmax 276 nm. The correlation coefficient for the standard curve was 0.9955, close to 1, indicating a strong linear relationship between the concentration range of 2-10 µg/mL (Table 3 and Fig. 9). This suggests that the drug follows Beer-Lambert Law within this concentration range.

Table 3: Standard Calibration Curve of Leflunomide at 276 nm (mean ± SD, n=3)

Conc.	Absorbance±SD	Statistical result
2µg/ml	0.146±0.002	Y=0.075x-0.0104 R^2=0.9994
4µg/ml	0.285±0.001	
6µg/ml	0.436±0.002	
8µg/ml	0.585±0.001	
10µg/ml	0.746±0.002	

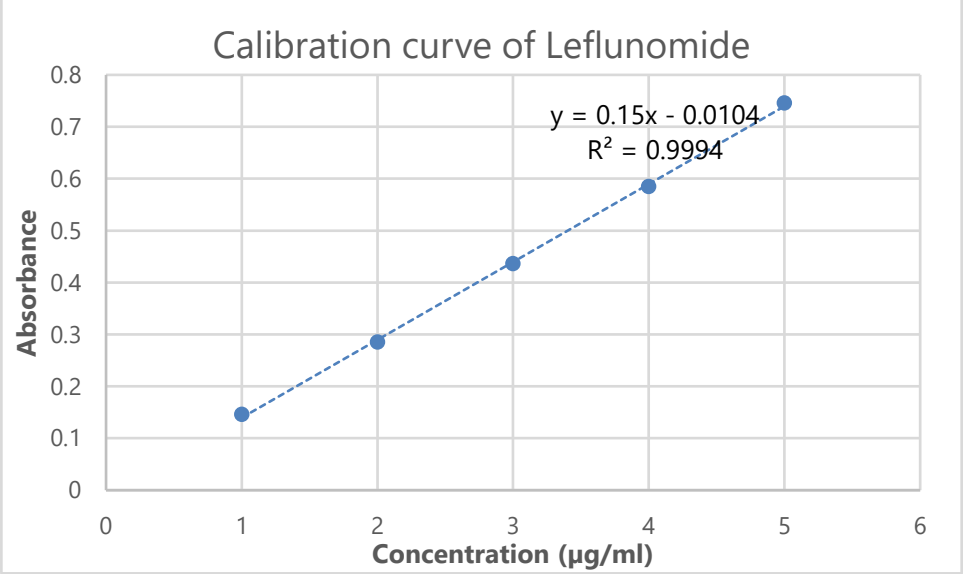

Fig. 9: Standard Calibration Curve of Leflunomide

Formulation Development

- **Determination of solubility in various solvents (oils, surfactants and co-surfactants)**

Table 4: Quantitative solubility of Drug in different oils, surfactants and co-surfactants

S.No	Oils	Solubility (mg/ml)
1	Castor oil	4.25
2	Olive oil	3.77
3	Ethly oleate	4.12

4	**Oleic acid**	**10.65**
5	Sesame oil	1.49
6	**Tween 80**	**68.29**
7	Tween 60	52.26
8	Tween 20	34.59
9	Glycerin	3.06
10	**Propylene glycol**	**110.46**
11	Ethanol	22.49
12	PEG 400	46.22
13	PEG 200	35.45

- **Selection of oils, surfactants and co-surfactants**

As reported in Table 4, maximum solubility of leflunomide in oils was found in oleic acid. Among surfactants and co-surfactants, the maximum solubility of leflunomide was found in tween 80 (surfactant) and propylene glycol (co-surfactant).

- **Formulation of Nanoemulsion**

Formulation of nanoemulsion using Oleic acid as oil phase and tween 80 and propylene glycol as surfactant and cosurfactant respectively

Construction of ternary phase

Surfactant (tween 80) and cosurfactant (propylene glycol) were mixed (Smix) in 3 different ratio with each other as reported in table 5.

Table 5: Ratio of surfactant and cosurfactant (Smix) used for construction of pseudo-ternary phase diagram

Sr. No	Code	Surfactant (Tween 80)	Co-surfactant (Propylene Glycol)
1	Smix-A	1	1
2	Smix-B	2	1
3	Smix-C	1	2

Oil phase (Oleic acid) was mixed with each ratio of Smix in 9 different ratios as shown in table 6.

Table 6: Ratio of oil phase and Smix used for construction of pseudo-ternary phase diagram

Sr. No	Code	Ratio (Oil phase: Smix)	Oil Phase Volume (ml)	Smix Volume (ml)
1	CN90	09:01	1.35	0.15
2	CN80	08:02	1.2	0.3
3	CN70	07:03	1.05	0.45
4	CN60	06:04	0.9	0.6
5	CN50	05:05	0.75	0.75
6	CN40	04:06	0.6	0.9
7	CN30	03:07	0.45	1.05
8	CN20	02:08	0.3	1.2
9	CN10	01:09	0.15	1.35

Overall, with 3 Smix ratios, total 27 formulations were made by slowly titrating with distilled water up to 85% (8.5 ml) of total volume. The volume of water at which system starts to get translucent or turbid was noted. Thus, for each Smix ratio total 9 formulations were made as given in table 7 to table 9 and on the basis of the observations, pseudoternary phase diagram was made for each combination of Smix ratio with oil phase using

Table 7: Observation table for Nanoemulsion formulations using Smix-A (1:1)

Sr. No	Code	Ratio (Oil phase: Smix)	Oil Phase Volume (ml)	Smix Volume (ml)	Volume of Distilled Water at which System Becomes Translucent or Turbid (ml)	Description After Addition of Distilled Water up to 85% of Total Volume (8.5ml)

1	CN90A	9:1	1.35	0.15	0.1	Turbid system with phase separation within 1 hour
2	CN80A	8:2	1.2	0.3	0.35	Turbid system with phase separation within 1 hour
3	CN70A	7:3	1.05	0.45	0.7	Turbid system with phase separation within 1 hour
4	CN60A	6:4	0.9	0.6	0.95	Turbid system with phase separation within 1 hour
5	CN50A	5:5	0.75	0.75	1.3	Turbid system with phase separation within 1 hour
6	CN40A	4:6	0.6	0.9	2.3	Translucent system
7	CN30A	3:7	0.45	1.05	3.3	Translucent system
8	CN20A	2:8	0.3	1.2	-	Remains transparent up to 8.5 ml of water addition
9	CN10A	1:9	0.15	1.35	-	Remains transparent up to 8.5 ml of water addition

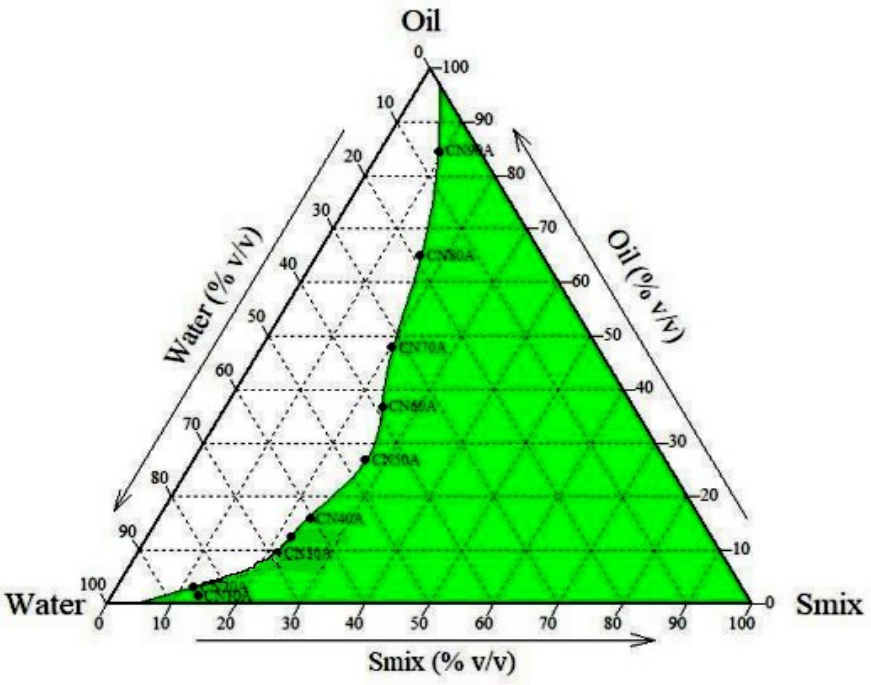

Figure 10: Pseudo-ternary phase diagram for Smix 1:1 combinations. Shaded area represents nanoemulsion region.

Table 8: Observation table for Nanoemulsion formulations using Smix-B (2:1)

Sr. No	Code	Ratio (Oil phase: Smix)	Oil Phase Volume (ml)	Smix Volume (ml)	Volume of Distilled Water at which System Becomes Translucent or Turbid (ml)	Description After Addition of Distilled Water up to 85% of Total Volume (8.5ml)
1	CN90B	9:1	1.35	0.15	0.15	Turbid system with phase separation within 1 hour
2	CN80B	8:2	1.2	0.3	0.4	Turbid system with phase separation within 1 hour
3	CN70B	7:3	1.05	0.45	0.9	Turbid system with phase separation within 1 hour
4	CN60B	6:4	0.9	0.6	1.1	Turbid system with phase separation within 1 hour

5	CN50B	5:5	0.75	0.75	1.3	Turbid system
6	CN40B	4:6	0.6	0.9	2.1	Translucent system
7	CN30B	3:7	0.45	1.05	3.5	Translucent system
8	CN20B	2:8	0.3	1.2	-	Remains transparent up to 8.5 ml of water addition
9	CN10B	1:9	0.15	1.35	-	Remains transparent up to 8.5 ml of water addition

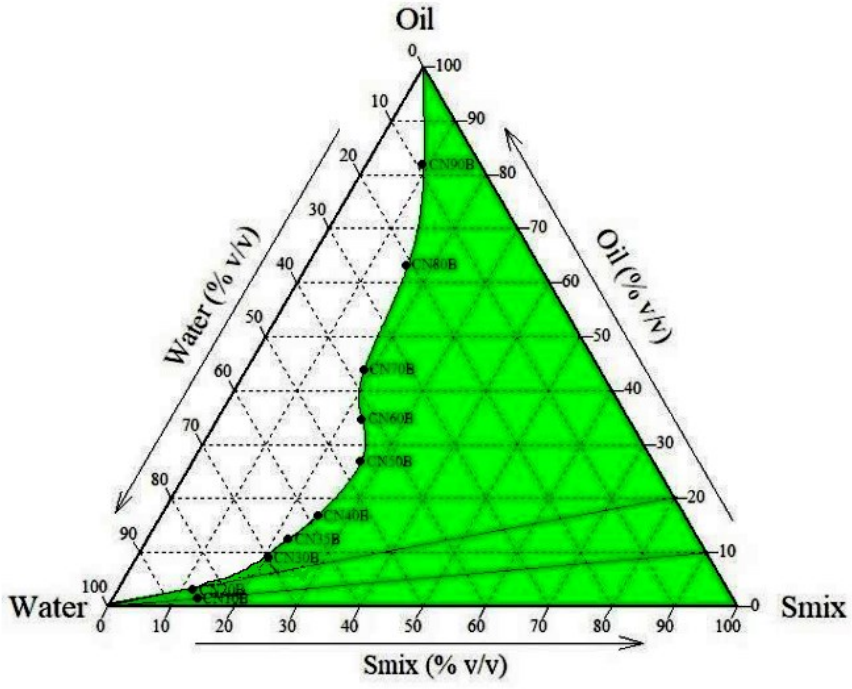

Figure 11: Pseudo-ternary phase diagram for Smix 2:1 combinations. Shaded area represents nanoemulsion region.

Table 9: Observation table for Nanoemulsion formulations using Smix-C (1:2)

Sr. No	Code	Ratio (Oil phase: Smix)	Oil Phase Volume (ml)	Smix Volume (ml)	Volume of Distilled Water at which System Becomes Translucent or Turbid (ml)	Description After Addition of Distilled Water up to 85% of Total Volume (8.5ml)
1	CN90C	9:1	1.35	0.15	0.1	Turbid system with phase separation within 1 hour
2	CN80C	8:2	1.2	0.3	0.3	Turbid system with phase separation within 1 hour
3	CN70C	7:3	1.05	0.45	0.6	Turbid system with phase separation within 1 hour
4	CN60C	6:4	0.9	0.6	0.7	Turbid system with phase separation within 1 hour
5	CN50C	5:5	0.75	0.75	1.15	Turbid system with phase separation within 1 hour
6	CN40C	4:6	0.6	0.9	1.9	Turbid system
7	CN30C	3:7	0.45	1.05	3.1	Translucent system
8	CN20C	2:8	0.3	1.2	3.5	Translucent system
9	CN10C	1:9	0.15	1.35	4.5	Translucent system

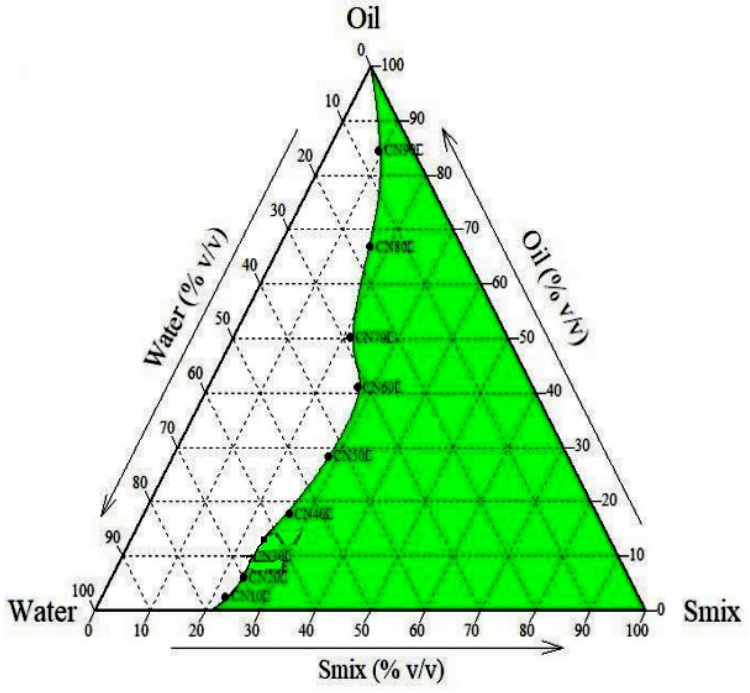

Figure 12: Pseudo-ternary phase diagram for Smix 2:1 combinations. Shaded area represents nanoemulsion region.

Selection of the formulations from phase diagram

The pseudo-ternary phase diagrams were constructed to identify the blend of excipients (ratio of oil phase and Smix) that give maximum nanoemulsion region in the diagram and maximum dilutable lines. Maximum nanoemulsion region will provide the flexibility in formulation composition. A fully dilutable line at a ratio of oil phase to Smix mixture will ensure the stability of nanoemulsion. On the basis of phase diagrams, Area of nanoemulsion region (shaded area) was calculated and fully dilutable lines were identified in each phase diagram as mentioned in table 10.

Table 10: Summary of pseudo-ternary phase diagrams

Sr. No.	Oil Phase	Smix Ratio (Tw 80: PG)	% Nanoemulsion Region	Fully Dilutable Lines at Oil Phase: Smix
1	Oleic acid	Smix A (1:1)	64.93	None
2	Oleic acid	Smix B (2:1)	67	2:8 (CN20B), 1:9 (CN10B)
5	Oleic acid	Smix C (1:2)	61.47	None

As shown in table 10, maximum nanoemulsion region was found at Smix-B (tween 80 and propylene glycol 2:1) as compared to other Smix ratio. It shows that higher surfactant amount in Smix, produces larger nanoemulsion regions. All nanoemulsion formulations using Smix-B are presented in figure 13.

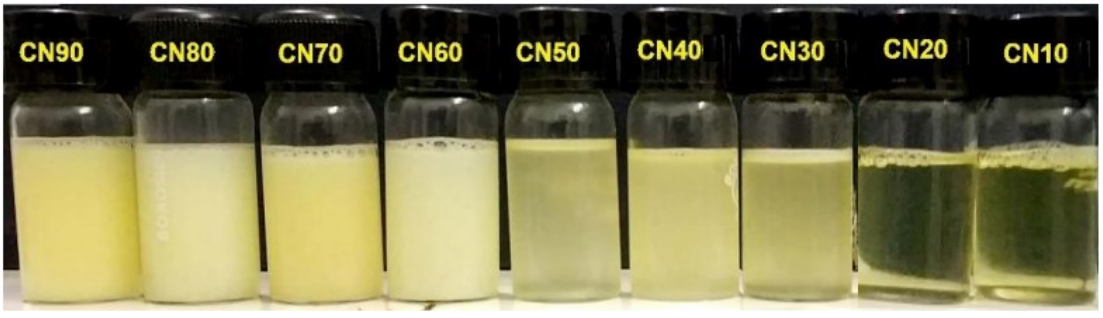

Figure 13 : Nanoemulsion formulations (CNB) using Smix-B

Preparation of Nanoemulgel Formulation:

Preparing gel formulation by dispersing 1% Carbopol 940P in distilled water and was stirred using magnetic stirrer for 30 mins then allowing it to hydrate and swell for 6 hours. The selected nanoemulsion (CN20B, CN10B) and gel formulation were mixed in the ratio 1:10. The pH of the resulting formulations was adjusted with triethanolamine.

Ingredient	F1 (CN20B containing nanoemulgel)	F2 (CN10B containing nanoemulgel)
Nanoemulsion	10 mL containing 20 mg of Leflunomide	10 mL containing 20 mg of Leflunomide
Carbopol 940 P	1%	1%
Water	q.s to 100 mL	q.s to 100 mL
Triethanolamine	0.5 g	0.5 g

Table 11: Evaluation Results of prepared nanoemulgel

Parameter	F1 (CN20B containing nanoemulgel)	F2 (CN10B containing nanoemulgel)
Droplet size	113.55 nm	135.36 nm
Zeta potential	26.12 mV	27.12 mV
Viscosity	37600 cP	37750 cP
pH	5.6	5.6

Table 12 : *In-vitro* permeation study

Time (h)	F1 (%)	F2 (%)
0	0	0
1	13	12
2	24	22
4	35	31
8	43	39
12	56	53
18	65	62
24	77	74

Table 13 : Stability testing

Parameter	F1 (CN20B containing nanoemulgel)	F2 (CN10B containing nanoemulgel)
Droplet size	118.55 nm	120.36 nm
Zeta potential	27.12 mV	26.12 mV
Viscosity	38000 cP	38200 cP
pH	5.6	5.6

In the stability studies, the LFD nanoemulgel showed no signs of drug precipitation, phase separation, or flocculation upon visual inspection and remained stable after centrifugation (3000 rpm for 15 minutes) at room temperature. The stability test results indicated minimal changes in the formulation's parameters after six months of storage, confirming the nanoemulgel's stability over that period. There were negligible alterations in the globule size (118.55 and 120.36 nm), zeta potential (27.12 and 26.12 mV), viscocity (38000 and 38200 cP) and pH (5.6 for both the formulation) The formulation was deemed stable after centrifugation (3000 rpm for 15 minutes) at ambient temperature, showing no signs of instability such as drug precipitation, phase separation, or flocculation. The six-month stability test further affirmed the formulation's stability, with no significant changes observed in its nanoemulgel characteristics.

CONCLUSION

Rheumatoid Arthritis is a chronic, systemic autoimmune disorder that primarily affects the joints, leading to inflammation, pain, stiffness, and eventual joint damage. Despite the availability of several treatment options, effective and targeted drug delivery remains a challenge. Novel drug delivery systems such as nano

emulgels offer promising advantages by enhancing the bioavailability, targeted delivery, and sustained release of anti-rheumatic drugs like leflunomide. The formulation and evaluation of a nano emulgel of leflunomide could significantly improve therapeutic outcomes in RA patients, offering better symptom management and reduced systemic side effects.

Drug and excipients were selected on the basis of literature review. Preformulation studies were done to identify the purity of drug and excipients. Melting point, FTIR, Lambda max determination and solubility studies on Leflunomide authenticate the drug. A drug and polymer compatibility study was evaluated using FTIR spectroscopy. Result of this study reveals that there was no interaction found between drug and polymer.

Formulation of nanoemulgel begins from ternary phase diagram, for which solubility of Leflunomide were determined in various solvents (oils, surfactants and co-surfactants). Oleic acid, Tween 80 and propylene glycol were selected as oils, surfactants and co-surfactants for preparation of nanoemulgel. In construction of ternary phase, Surfactant (tween 80) and cosurfactant (propylene glycol) were mixed (Smix) in 3 different ratio i.e. Smix-A 1:1, Smix-B 2:1 and Smix-C 1:2 with each other. Oil phase (Oleic acid) was mixed with each ratio of Smix in 9 different ratios starts from 9:1 to 1:9. Overall, with 3 Smix ratios, total 27 formulations were made by slowly titrating with distilled water up to 85% (8.5 ml) of total volume. The volume of water at which system starts to get translucent or turbid was noted. Thus, for each Smix ratio total 9 formulations were made as given in table 7 to table 9 and on the basis of the observations, pseudoternary phase diagram was made for each combination of Smix ratio with oil phase. Maximum nanoemulsion region was found at Smix-B (tween 80 and propylene glycol 2:1) as compared to other Smix ratio. It shows that higher surfactant amount in Smix, produces larger nanoemulsion regions.

Nanogel was prepared by 1% Carbopol 940P dispersing in distilled water and was stirred using magnetic stirrer for 30 mins then allowing it to hydrate and swell for 6 hours. Nano-emulgel of selected nanoemulsion formulations (CN20B, CN10B) were prepared by adding it with gel in the ratio 1:10. The pH of the resulting formulations was adjusted with triethanolamine.

Prepared nanoemulgel were undergone for evaluation using different parameters, results of evaluation were given below

Parameter	**F1(CN20B containing nanoemulgel)**	**F2(CN10B containing nanoemulgel)**
Droplet size	113.55 nm	135.36 nm
Zeta potential	26.12 mV	27.12 mV
Viscosity	37600 cP	37750 cP
pH	5.6	5.6

In *In-vitro* permeation studies, prepared nanoemulgels shows permeation of 77 and 74% of drug for the formulation F1 and F2 respectively. The LFD nanoemulgel remained stable with no signs of drug precipitation, phase separation, or flocculation after centrifugation (3000 rpm, 15 mins) and six months of storage. Minimal changes were observed in globule size (118.55–120.36 nm), zeta potential (27.12–26.12 mV), viscosity (38000–38200 cps), and pH (5.6), confirming its physical and chemical stability. Overall, the nano-emulgel of leflunomide was successfully formulated and demonstrated good stability, optimal physicochemical properties, and potential for improved topical delivery in the treatment of rheumatoid arthritis.

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