

A Novel Approach of Leflunomide Nanoemulgel for Topical Drug Delivery System

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ABSTRACT

Objectives: This research's primary goals are Leflunomide (LFD) nanoemulgel formulation and characterization for topical administration. **Materials and Methods:** A pseudo ternary phase diagram was created utilizing castor oil, Tween 20 as the surfactant, PEG 300 as a co-surfactant, and ethanol as the cosolvent. Spontaneous emulsification was used to create LFD-nanoemulgel, which is now commercially available. Gel matrix Carbopol 934 was employed to generate nanoemulgel in the prepared nanoemulsion. Studies on the LFD-globule nanoemulgel's size, physical appearance, viscosity, spreadability, TEM, FTIR drug content, release kinetics, and stability contributed to its characterization and assessment. Optimum nanoemulgel formulation contained 6% castor oil, 36% Tween 80 and PEG 300 as Smix (surfactant and co-surfactant mixture), 46% water, and 12% w/w carbopol 934. **Results:** The produced nanoemulgel was translucent and had a zeta potential of 26.12 mV and a particle size of 113.55 ± 1.73 nm. The improved formulation has a drug release rate

of $98.13\% \pm 1.20\%$. They were determined to be ideal for pH, viscosity, and spreadability. According to the stability analysis, the generated nanoemulgel was shown to be stable at temperatures ranging from $25 \pm 45^\circ\text{C}$, according to the stability analysis results. **Conclusion:** An effective formulation for topical medication delivery using LFD-loaded nanoemulgel has been developed. It may be an alternative drug therapy to the topical application of drugs to treat arthritis.

Keywords: LFD, Nanoemulgel, Topical delivery, Castor oil.

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INTRODUCTION

In terms of global illness burden, skin disorders account for 1.79 percent. Symptoms of skin illnesses include rashes, itching, and other skin abnormalities. Certain skin disorders may run in families while external sources bring others on. Systemic delivery of skin maladies is restricted by toxicity and patient dissatisfaction. In order to avoid gastrointestinal adverse effects of nonsteroidal anti-inflammatory medicines (NSAIDs), the skin was and still is used to apply APIs (preparations of API) on the skin surface.

The transdermal delivery of medicines to the skin has improved topical therapy for skin disorders by using new lipid-based carriers. Topical dosage forms such as ointments and creams are used to treat skin disease to avoid systemic side effects since they have a lower risk as lipid-based carriers have lately become critical techniques to improve medication penetration, safety, and efficacy in topical formulations. A practical and simple-to-prepare medicinal dosage form, nanoemulgel can deliver medication efficiently while causing minor adverse effects.¹

In recent years, leflunomide (LFD) has become one of the most effective, disease-modifying anti-rheumatic drugs.² Urcil, cytosine, and thymine nucleotides are required for rapid lymphocyte proliferation driven by antigen. Prodrug LFD undergoes isoxazole ring cleavage to become Teriflunomide's active drug.³ Although LFD has a positive effect on the body, oral administration can lead to gastrointestinal issues that are not ideal. A direct application to the diseased skin, such as arthritis, psoriatic lesions, or melanoma, will avoid oral or parenteral drug administration.⁴ Due to a lack of first-pass metabolism, the dosage can be reduced. Even though direct application to the sick skin maximizes local benefits

without any related systemic effect, a topical formulation of LFD is still uncommon. Solubility and permeability may be to blame for this and its other negative physical qualities. Although LFD's low molecular weight makes it ideal for topical use, its limited water solubility renders it unsuitable. A lack of lipophilicity prevents LFD from penetrating the skin.³

In order to improve the efficacy and utility of topical therapy, new approaches are required. Drug delivery methods using optically transparent nanoemulsions with globule sizes of 100 nm and 500 nm have piqued researchers' curiosity, as shrinking down to the nanoscale allows for greater skin penetration.⁵ In order to create a nanoemulgel, the viscosity of the nanoemulsion is raised with the inclusion of a gelling agent that facilitates transcutaneous delivery.⁶ Adhesiveness and film formation promote medication penetration due to occlusive and moisturizing qualities provided by nanosize. Formulation and characterization of LFD nanoemulgels for topical infections were the focus of this study's protocol.

MATERIALS AND METHODS

Chemicals, Reagents and Solvents

In addition to ethyl oleate, isopropyl palmitate and olive oil, the following solvents were acquired from Sigma Aldrich, USA. Leflunomide, Castor oil, ethanol, PEG300, Cremophor RH 40 and Labrafac CC were purchased from Sigma Aldrich, USA. Ethanol, polyethylene glycol 300, propylene glycol, Span 20, Tween 80, and Tween supplies were of analytical quality and used as received. For the duration of the investigation, only water

that had been double-distilled and passed through a 0.22 μm membrane filter was used.

Preparation of LFD Nanoemulsion

With the shake flask method, the solubility of LFD in various oil/modified oil mixtures was determined, including Captex 170, Acrysol K150, Capmul MCM, Captex 335, ethyl oleate, Castor oil, Capmul PG 12, isopropyl palmitate, Labrafil M1944CS, Labrafac CC, and olive oil. Based on the solubility experiments, Castor oil, Tween 80, PEG 300, and ethanol were selected as the oils, surfactants, co-surfactants, and cosolvents. The initial non-aqueous phase of the LFD nanoemulsion was made by dissolving 0.55g of LFD in 1mL of Transcutol HP using an ultrasonic bath and then combining it with castor oil in a 40°C water bath. At 38°C for 20 min, the ethanol was evaporated from the mixture, which was then placed in an appropriate-sized round bottom flask. To begin with, Tween 80 was dissolved in water and then used to pre-prepare 10 g of the aqueous phase. With continuous stirring on the magnetic stirrer, water was slowly added to the non-aqueous phase, then homogenized at 8000 RPM/min for 6 min. Three cycles of high-pressure homogenization at 350 bar were performed on this primary emulsion to produce the final O/W LFD nanoemulsion (Figure 1A).

Construction of Pseudo-ternary Phase Diagram

ProSim software V 1.0 was used to build a pseudo-ternary diagram to examine the nanoemulsion area at ambient temperatures of up to 25°C. Nanoemulsion was produced by combining water with the surfactant and cosurfactant mixture (Smix) and the oil phase in a suitable proportion. The weight ratios of Tween 80 and PEG300 (Smix) were used to create a pseudo-ternary diagram. As a result, a nanoemulsion was created by combining Smix and oil in various ratios such as 1:9, 2:9, 3:8, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. Our goal was to create water in oil nanoemulsion because LFD is a hydrophobic medication. This Figure shows all the various locations where nanoemulsions could form. The co-surfactant (Smix) surfactants are shown in the following tables: Titration values for oil and water, shown in pseudo-ternary charts.

Preparation of LFD Nanoemulgel

Carbopol 934 (0.05, 0.1, and 0.2g) was soaked in water to generate a 10g carbopol gel matrix before the LFD nanoemulgel was prepared by dissolving it in water. After that, 1 g of LFD nanoemulsion (LFD 0.05 g) was added to the gel matrix while stirring slowly and continuously. A sodium hydroxide aqueous solution was added to the mixture to produce the final LFD nanoemulgel (Figure 1B).

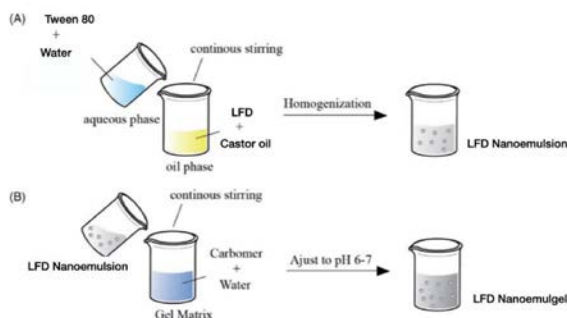


Figure 1: Schematic representation of the preparation of LFD nanoemulsion (A) and LFD nanoemulgel (B).

Optimization of LFD Nanoemulgel

Individual compositions should be researched to determine how they affect the LFD formulation (such as viscosity of nanoemulgel and Ke of nanoemulsion). These three components were tested in this study: Castor oil, Tween 80, PEG 300, and ethanol, all of which were found to have a significant impact on the results.

UV visible Spectrophotometer

In a volumetric flask, 100 ml of pH(6.8) phosphate buffer was dissolved in a weighed amount of leflunomide and filtered. Pipette out 1 ml of the sample and dilute it to 100 ml of phosphate buffer. A UV visible spectrophotometer was used to estimate the λ_{max} of LFD.

Fourier transform infrared (FT-IR) analysis

The FT-IR spectrophotometer was used to determine the drug-excipient compatibility of the pure drug and the physical mixture (8400S, Shimadzu Kyoto, Japan). A KBr press (Technosearch Instrument, Mumbai, India) was used to press the pure methotrexate and the physical combination into pellets or thin films of KBr in the range of 4000-400 cm^{-1} and to record FT-IR spectra in the range of 4000-400 cm^{-1} .

Characterization of LFD Loaded Nanoemulgel

Droplet size analysis and zeta potential

We diluted the optimized LFD nanoemulsion (1:1000, v/v) using a zeta sizer and evaluated the droplet size and zeta potential. The zeta potential and zeta potential of the LFD emulsion were measured in the same manner.

Viscosity and Conductivity of Nanoemulsion

The Brookfield viscometer and conductivity meter were used to measure the viscosity and conductivity of LFD. A 30 ml sample was obtained in a beaker and left to equilibrate for 5 min before dial readings were taken at 0.5, 1, 2.5, and 5 rpm using a spindle. At each speed, the viscometer was used to record the dial reading. The conductivity of the nanoemulsion was determined using a conductivity metre at room temperature. There were three copies of every decision taken.

pH Determination

The formulation's pH was measured at room temperature using a digital pH metre (Roletx, India). The pH of the LFD was critical because of its topical application, which necessitated that it be nonirritating.

Morphology Investigation

A scanning electron microscope was used to examine the three-dimensional internal structures of the optimized LFD nanoemulgel, optimized blank nanoemulgel, and 1% carbopol hydrogel (SEM; Su8020, Hitachi, Tokyo, Japan). The samples were prepared for SEM analysis by fast freezing in liquid nitrogen and freeze-drying for 48 hr.

Transmission Electron Microscopy (TEM)

LFD nanoemulgel was studied using a Hitachi (H-7500) TEM at room temperature for microstructure. Drying on a microscopic carbon-coated grid and viewing under a microscope after staining at an appropriate magnification were the methods used to obtain the photo-micrographs of LFD.

Differential Scanning Calorimeter (DSC)

DSC is used to identify changes in samples' thermal properties while heated. At the temperature range of scanning, a well-defined heat capacity is required for this approach. This approach can study phase transitions in emulsions, such as the melting of crystalline areas (the

solid fat proportions and ice crystals proportion). Fat crystallization has been linked to the stability of emulsions, which is also influenced by the surfactant utilized. DSC was used to measure the surfactant crystallization temperature. Differential scanning calorimetry (DSC) was used to characterize the aqueous suspensions of NE and dried NE, respectively (New Castle, DE, USA). All measurements were carried out using a nitrogen purge of 50 mL/min-1. From 80°C to 160°C, the temperature variation was wide. For the DSC of excipients and the DSC of LFD nanoemulgel in water that gradually released water when heated above 40°C, samples (approximately 10 mg) were carefully weighed and sealed in 40 L aluminium pans with a hermetic lid.

In vitro permeation study

Several different formulations of LFD were tested for permeability via an *in vitro* permeation investigation. A Franz diffusion cell system with an effective diffusion surface area of 2.27 cm² was used in this application. Diffusion cells were set up with the epidermis facing the donor compartment and the dermis facing the receptor compartment. A 6.5 mL reservoir of receptor buffer was placed in the receptor compartment (normal saline containing 30 percent methanol). The donor compartment was then filled with LFD nanoemulsion and LFD nanoemulgel, which contained the same amount of LFD. The diffusion chamber's temperature was then maintained at 37°C ± 0.5°C in a thermostatic water bath. At predefined intervals (1, 2, 4, 6, 8, 10, 12 and 24 h), samples from receptor chambers were obtained by replacing the same volume of fresh aerated receptor buffer. The LFD concentration was measured using HPLC after the samples were passed through a membrane filter (0.22 µm).

Skin Irritation Test

Tests were undertaken to determine the LFD nanoemulgel's skin irritant safety level. The backs of 15 healthy male rats (weighing between 180 and 220 g) were shaved and observed for 24 hr to see if any skin damage occurred. Rats' shaved back areas were split into two sections, one undamaged and the other damaged, after 24 hr of observation. A scalpel was used to generate abrasions on the skin to develop the wounded area. We then randomly assigned each rat to either saline or blank nanoemulgel or LFD nanoemulgel group, and the results were tallied. A 2cm × 2cm square was treated with the preparations on both sides. We maintained the same *ad libitum* access for all animals in a 25°C temperature and 55% humidity chamber. An evaluation of the animals' symptoms was conducted at 1, 24, 48, 72, and 96 hr and the severity of the symptoms was assessed.

Stability Studies

Stability testing of the LFD nanoemulgel was conducted for six months at room temperature to mimic patient use. Studies on the formulation's physical stability after six months of storage included tests such as a centrifugation cycle with an accelerated speed of 3000 revolutions per minute for 15 min, as well as chemical stability tests such as drug content, particle size, and zeta potential determinations (see below for more information on these tests).

Statistical Analysis

Data were expressed as mean ± SEM (*n*=3) using MS excel.

RESULTS

Selection of Excipients

The partitioning of drugs from lipid into the aqueous phase by interacting with surfactant and co-surfactant regulates and affects drug release from emulsion-based delivery systems. Because of this, it is critical to use the correct lipids and surfactants for stabilization. The choice of excipients

is also influenced by the formulation's ability to hold a large amount of a poorly soluble medication. The lipophilic medication should be solubilized to the greatest extent possible by the excipients that reduce the amount of drug product needed to give a therapeutic dose of the drug in an emulsified form that is optimal.⁸

The oil in the nanoemulsion must have a high solubilization capacity for the medicine, which is a crucial component. Castor oil had the highest solubility of LFD among oils and modified oils, at 91.39 mg/mL (Table 1). Since LFD has just 53.92 Å of polar surface area, it is more easily soluble in oil with a low/medium molar volume. Other factors include selecting an oil-water interface stabilizer surface active agent. When making an oil-water emulsion that remains stable, an HLB of at least ten is needed for the surfactant. Tween 20, Tween 80, Labrasol, Cremophor RH 40, and Cremophor EL were among the non-ionic surfactants we tested. These surfactants have HLBs greater than 12 and are all considered safe, biocompatible, and less toxic, and they form micelles at low concentrations. The miscibility of the surfactant with oil can be used to guide the selection process.

Instead of a supersaturated formulation, we chose a surfactant based on its ability to dissolve LFD, as we were not concerned about the problem of drug precipitation when diluting. This formulation will have no dilution because it is intended for topical use. Even if their HLB values are near, there was a significant difference in the solubility of LFD in a few chosen surfactants. When it came to solubility, Tween 80 was the best choice for LFD 160.28 mg/mL. Castor oil is better emulsified by Smix (Tween 80 and PEG 300). Improved emulsifying ability, reduced interfacial tension, increased interfacial fluidity and improved emulsion stability at low surfactant concentration can be achieved by using a cosolvent/

Table 1: Solubility of leflunomide in oils, surfactants, co-surfactants and cosolvents.

Phase type	Excipient	Solubility (mg/mL)
Oils	Captex 170	55.30 ± 1.30
	Acrysol K150	48.29 ± 2.03
	Capmul MCM	62.49 ± 2.48
	Captex 335	71.39 ± 2.23
	Ethyl oleate	81.10 ± 1.39
	Castor oil	91.39 ± 3.30
	Capmul PG 12	72.11 ± 2.13
	Isopropyl palmitate	60.39 ± 2.93
	Labrafil M1944CS	70.22 ± 2.01
	Labrafac CC	80.20 ± 1.39
Surfactants	Span 20	83.20 ± 1.33
	Cremophor RH 40	94.39 ± 1.93
	Cremophor EL	100.28 ± 4.12
	Labrasol	56.30 ± 2.44
	Tween 20	89.39 ± 2.01
	Tween 80	159.30 ± 1.39
Co-surfactants	Glycerin	59.12 ± 0.94
	PEG 300	89.11 ± 1.45
Cosolvents	Polyethylene glycol 300	135.93 ± 7.49
	Ethanol	247.20 ± 11.34
	Propylene glycol	139.64 ± 9.37
	Trancutol P	120.33 ± 10.54

Data are expressed mean ± SD (*n* = 3)

co-surfactant combination. Ethanol was chosen because of its high solubility of LFD at 247.20 mg/mL, making it the cosolvent of choice. Lipophilic medicines are better absorbed via the skin when ethanol is used.

Pseudo-ternary Phase Diagram Study

Nanoemulsion area and surfactant/cosurfactant ratio were determined using ternary phase diagrams, which were used to find the most stable LFD formulation. Oil, surfactant/cosurfactant, and water are shown in each corner of the phase diagram; the darker area implies a more vital nano emulsifying ability. Figure 2 indicates the maximum area in the pseudo-ternary phase diagram; hence, the Smix (1:2) ratio is selected for further drug release and stability experiments. The solubility analysis of Six in castor oil indicated that a minimum of 6% by weight of oily phase was required to meet the dose requirement, and with Smix maintained at 1:2, water at 46% by weight, and 12% gelling agent, nine batches of LFD nanoemulgel were made and characterized.

UV Spectroscopy

The absorption maxima of LFD were estimated at 276 nm in the phosphate buffer of pH 6.8.

The FT-IR Spectrum of Pure LFD

Figure 3 shows the FT-IR spectra of LFD. 3437.25 (O-H stretching, alcohol) was found to be the functional group in LFD, along with 2869.76 (C-H stretching), 1736.46 (C=O stretching), 1645.91 (C=N stretching), 1455.88 (O-H bending), 1349.16 (O-H bending), 1296.47 (C-N stretching), 1248.46 (C-O stretching), 1092.6 (C-O stretching), 841.39 (C-H bending). A small amount of shifting in the physical mixture's IR spectrum revealed these peaks. So there was no chemical interaction between drug and excipients in either the pure drug or the physical mixture, as evidenced by their respective correlation with all identifiable IR spectra peaks.

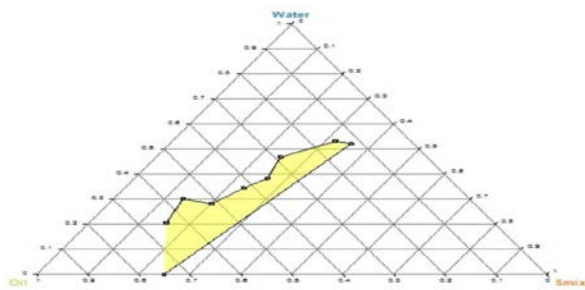


Figure 2: Pseudo-ternary phase diagram depicting nanoemulgel region.

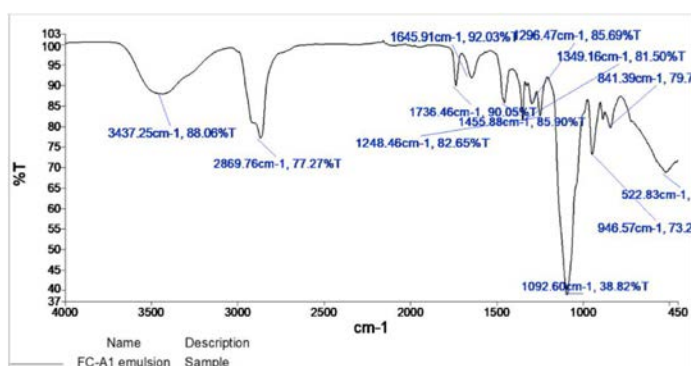


Figure 3: FT-IR spectrum for LFD-nanoemulgel.

Table 2: Composition of LFD nanoemulgel based on the ternary phase diagram.

Batch	Oil (% wt/wt)	Smix (%wt/wt)	Water (%wt/wt)	Gelling agent (%wt/wt)	Globule size (nm)	PDI	Zeta potential (mV)	% T
LFD1	6	24	58	12	214.16 ± 2.32	0.310 ± 0.08	26.32 ± 1.34	97.33
LFD2	6	26	56	12	183.11 ± 2.94	0.231 ± 0.002	31.43 ± 1.09	97.81
LFD3	6	28	54	12	175.11 ± 2.23	0.245 ± 0.005	30.94 ± 1.99	98.09
LFD4	6	30	52	12	169.74 ± 2.03	0.226 ± 0.007	30.55 ± 1.83	98.48
LFD5	6	32	50	12	150.34 ± 1.45	0.181 ± 0.008	29.38 ± 1.43	99.43
LFD6	6	34	48	12	146.27 ± 2.47	0.183 ± 0.003	28.11 ± 1.94	99.84
LFD7	6	36	46	12	113.55 ± 1.73	0.251 ± 0.009	26.12 ± 1.94	99.88
LFD8	6	38	44	12	135.36 ± 1.44	0.261 ± 0.002	27.12 ± 1.22	99.01
LFD9	6	40	42	12	147.74 ± 1.08	0.256 ± 0.004	28.09 ± 1.11	99.27

Data are expressed mean ± SD ($n = 3$)

Characterization of LFD Formulation

Droplet size and zeta potential

PDI 0.251 and an average droplet size of 113.55 1.73 nm were found in the optimized LFD nanoemulgel (Table 2). This nanoemulgel had an average zeta potential of -26.12 ± 1.94 mV, which implies that it was stable.

Conductivity, Viscosity, pH and Refractive Index

The conductivity, viscosity, and refractive index of LFD7 were 0.171 mS, 379.11 cP, and 1.501 A, respectively. The high viscosity of CSN ensured that it was delivered effectively through the skin. The conductivity values of 0.171 mS suggested that the LFD nanoemulgel is of the oil-in-water type, indicating that it transmitted electrical current. The pH of CSN was found to be between 6.5 to 6.8, which is close to the typical pH range for topical application. In terms of formulation, this could help reduce the irritation caused by LFD nanoemulgel while applied to the skin.

Morphology Analysis through SEM

LFD nanoemulgel's physical form is depicted in Figure 4. Because of the nanoemulsion, the LFD nanoemulgel was white semisolid, as depicted in the image. The viscosity and homogeneity of the mixture were excellent. One percent carbopol hydrogel appears to have tiny mesh pores, but the LFD nanoemulgel has interconnected pores with a random size distribution in the SEM images obtained. This porous construction allows for more significant drug loading, better drug distribution, and faster release time.

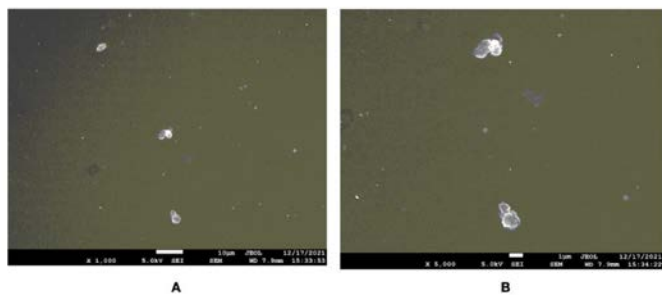


Figure 4: SEM images of the LFD nanoemulgel in the different scales of 10 μm (A) and 1 μm. (B) Abbreviations: LFD, Leflunomide; SEM, Scanning electron microscopy.

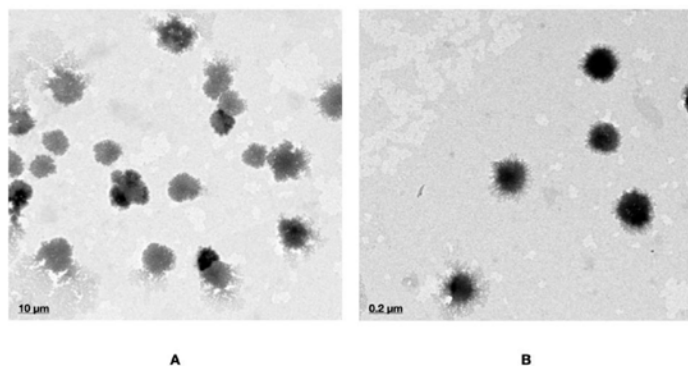


Figure 5: TEM images of the LFD nanoemulgel in the different scale of 10 μm (A) and 0.2 μm (B) Abbreviations: LFD, Leflunomide; TEM, transmission electron microscopy.

TEM Images

LFD nanoemulgel was found to have a spherical shape and a limited size distribution, as revealed by transmission electron microscopy (TEM). The samples were tested for homogeneity and birefringence using visual inspection in a cross polarizer to determine their composition. When viewed through a cross polarizer, nanoemulgel looked dark in colour. The measurements revealed that the formulations were colloidal dispersions with optical isotropy of 0.5. Figure 5 depicts the TEM imaging of LFD on two different scales.

DSC of LFD

Figure 6 shows DSC images for LDF nanoemulgel. The only thing that could be observed during heating nanoemulgel from room temperature to 160°C, the only thing that could be observed was water evaporation from the atmosphere. Having dried in the DSC pan, cooling induced crystallization, demonstrated by an exotherm that began at 30°C and persisted until the sample was dehydrated. After that, heating caused melting at 40°C. Similar exothermic and endothermic temperatures were generated throughout the cooling and heating operations. We exposed several different nanoemulgel components to DSC scanning to discover which materials were responsible for such thermal events on a single component and physical mixtures of components. DSC for LFD nanoemulgel is depicted in Figure 6 for (A) castor oil, (B) Smix, (C) Smix with oil, and (D) LFD nanoemulgel.

In vitro Drug Release

When it came to drug release, results showed that time had an effect. Table 3 shows the LFD release schedule. LFD 24-hr medication release

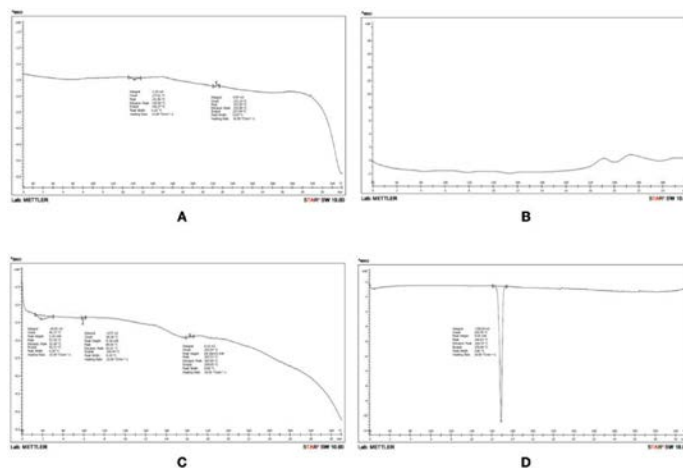


Figure 6: DSC for different ingredients of LFD formulation. A = Castor oil, B = Smix, C = Smix with oil, D = Leflunomide (LFD)

Table 3: In vitro drug release of CSN.

Time (h)	Absorbance	Dilution factor	Concentration (μg/ml)	% Drug release
1	0.214	20	48.5	30.12 ± 0.85
2	0.547	20	117.7	48.23 ± 1.12
4	0.989	20	211.49	63.11 ± 1.77
6	0.994	30	340.54	88.23 ± 1.23
8	1.115	30	376.52	92.22 ± 1.19
10	1.116	30	371.38	93.12 ± 1.32
12	1.115	30	372.34	95.33 ± 1.84
24	1.111	30	372.40	98.13 ± 1.20

was 98.13 percent. To a greater extent, smaller particle size allows for greater skin penetration. Tween 80, a surfactant, also helped increase the amount of medication released from the formulation.

Skin Irritation Test

It was determined that the LFD nanoemulgel had low skin toxicity and minimal skin irritation after additional testing.

Stability Studies of LFD Nanoemulgel

In instability studies, the LFD nanoemulgel exhibited no precipitation of drug, creaming, phase separation and flocculation on visual observation and was stable after centrifugation (3000 rpm for 15 min) at ambient temperature. The stability testing results revealed negligible changes in the formulation parameters after six months of storage, thus substantiating the stability of nanoemulgel for six months. The negligible changes in globule size, PDI, zeta potential and transmittance were 118.32 nm, 0.261, -27.23 mV and 99.71%, respectively.

The formulation was determined to be stable following centrifugation (3000 rpm for 15 min) at ambient temperature and to show no precipitation of drug, creaming, phase separation, or flocculation instability testing. For six months of storage, the stability of the formulation was confirmed by the results of stability testing, which showed no significant changes

in nanoemulgel parameters. There was no noticeable change in globule size, PDI, Zeta potential, or transmittance, all of which were unchanged.

DISCUSSION

Hepatotoxicity and liver dysfunction are possible side effects of long-term drug exposure (LFD).⁹⁻¹⁰ This study prepared a nanoemulgel of LFD to test its suitability for topical application on the skin. Preventing side effects of oral or parenteral drug administration by topical application increases local soft-tissue and joint concentration while decreasing systemic distribution.¹¹ We created a lipid nanoemulgel-based carrier system for LFD that is thermodynamically stable and easy to manufacture. Lipophilic drugs can now be converted into water-soluble compounds using a cutting-edge nanoemulgel, opening up new possibilities for topical drug delivery through the skin matrix. In addition, smaller drug particles allow for more profound and more extended penetration, indicating that nanoemulgel is appropriate for topical use.¹²

The partitioning of drugs from lipid into the aqueous phase by interacting with surfactant and co-surfactant regulates and affects drug release from emulsion-based delivery systems. Therefore, the selection of the proper lipid and stabilizers is critical. Excipient choice is also determined by the maximum amount of poorly soluble drugs loaded into a formulation. The lipophilic drug should be solubilized to the maximum extent possible by the excipients that reduce the amount of drug product needed to deliver an optimal therapeutic dose of the emulsified gel form of the drug. By preventing coagulation, zeta potential plays a vital role in emulsion stabilization. It is less critical because the gel was designed to be dissolved immediately. The semisolid gel is more practical from a practical standpoint than liquid formulation.

According to some research, transcutaneous drug delivery formulations may benefit from additional micellar structure provided by polymeric gel additives. The size of the LFD nanoemulgel globule ranged from 113.55 nm to 214.16 nm. Acceptable thermodynamic stability and narrow size distribution were found by performing the physicochemical characterization on the sample. The nanoemulgel's mechanical characteristics were suitable for easy and convenient application to the skin surface. At room temperature, the nanoemulgel had a viscosity of 0.171 mS. The gel is shear-thinning if its viscosity decreases. The product may be easily removed from the container and applied to the skin because of this feature.

LFD nanoemulgel is a safe and promising delivery method for topical injections. The nanoemulgel's release of the medication was likewise determined to be optimal. There is a report that nanoemulgel has a 1.45-fold higher permeation rate than the traditional formulation because of its larger surface area for transfer.¹³ The skin's structure was unaffected by the LFD nanoemulgel treatment. LFD nanoemulgel-treated skin was also free of haemorrhage, necrosis, and ulceration. Since there was no apparent inflammation in the rats' intact skin when the various LFD formulations were applied, these formulations were not irritating to the rats' intact skin.

CONCLUSION

An entirely new LFD nanoemulgel drug carrier was developed and characterized in this study. Liquid medications cannot hold this

nanoemulgel in place as long as this nanoemulgel does because of its superior bioadhesive property. Nanoemulgel's hydrogel matrix and O/W emulsion make it unique as a topical medicine delivery method. Hydrophilic drugs could be put into a hydrogel matrix and kept in place by the non-aqueous surface for lengthy periods. This LFD nanoemulgel is safe and promising for the treatment of Arthritis topically. Topical skin infections may benefit from the created formulation as a treatment option.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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