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A Novel Nanoemulsion Formulation of Apremilast For Psoriasis

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ABSTRACT

Apremilast, an oral phosphodiesterase-4 (PDE-4) inhibitor, is widely used in the treatment of inflammatory diseases such as psoriasis and psoriasis arthritis. However, its poor water solubility to formulate and evaluate a Nanoemulsion (NE) system for Apremilast to enhance its solubility, stability, and bioavailability. A Nanoemulsion was developed using a high energy emulsification method, with a combination of oil, surfactant, and co-surfactant carefully selected based on solubility studies and construction of pseudo-ternary phase diagrams. Various formulations were prepared and evaluated for droplet size, polydispersity index (PDI), zeta potential, and drug encapsulation efficiency. The optimized formulation exhibited a droplet size of below 600 nm, a low PDI, and a stable zeta potential, confirming its stability. According to this report, the Nanoemulsion based delivery system for Apremilast drug could offer significant clinical advantages, particularly in terms of improved pharmacokinetics and enhanced therapeutics outcomes, paving the way for more effective treatment of inflammatory diseases such as psoriasis and psoriatic arthritis. Further in vivo studies are recommended to confirm the observed benefits and to evaluate long term safety and efficacy.

Keywords: Apremilast, Nanoemulsion, Psoriasis, Zeta potential, Pharmacokinetics

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INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory skin disease that currently has no permanent cure. Derived from the Greek word *"psora,"* meaning "itch" or "rash," the condition is characterized by scaling, inflammation, and the rapid, abnormal growth of skin cells. It impacts approximately 2% to 5% of the global population and manifests as inflamed, red, and erythematous plaques[1]. While the exact etiology of psoriasis remains largely unknown, scientists attribute it to a complex interplay of a hyperactive autoimmune system, genetic predisposition, and environmental triggers such as psychological stress, skin injuries, severe weather conditions, and certain medications.

The fundamental pathogenesis of psoriasis can be outlined in three primary stages. The underlying cause is the hyper-proliferation of keratinocytes. Normally, these skin cells mature and shed every 35 to 40 days; however, in psoriatic patients, they mature and migrate to the epidermis within just a week, accumulating to form scaly lesions[1,2]. The second line of pathogenesis involves angiogenesis, leading to blood vessel dilation and the expansion of intercellular spaces. Finally, this triggers the production of pro-inflammatory cytokines (such as TNF-α, IL-1, and gamma interferon) by activated T-cells, perpetuating continuous inflammation and epidermal hyper-proliferation[3,5,6].

Currently, psoriasis treatment is categorized into topical therapies, phototherapy, and systemic treatments. While there are numerous therapeutic drugs available, conventional topical treatments present substantial clinical challenges. These include insufficient drug penetration through the thickened psoriatic skin barrier, significant local toxicity, the need for frequent and inconvenient application, and overall low patient compliance[1]. Because no existing conventional therapy is completely free of risks or fully effective in ensuring consistent patient adherence, there is a pressing need for advanced, novel drug delivery systems. To address the limitations of conventional topical therapies, Nanoemulsions (NEs) have emerged as a highly promising advanced drug delivery approach. Nanoemulsions are isotropic, thermodynamically stable systems consisting of a uniform mixture of oil, surfactants/co-surfactants (Smix), and water, with droplet diameters typically ranging from 10 to 500 nanometers[7]. These submicron emulsions can be classified into oil-in-water (o/w), water-in-oil (w/o), and bi-continuous types depending on the dispersed and continuous phases.

Need of the Study

The incorporation of anti-psoriatic drugs into Nanoemulsion offers distinct advantages over traditional macro-emulsions and conventional dosage forms. The nano-sized droplets significantly

increase the interfacial area, which positively impacts the transport of lipophilic drugs across biological membranes, ensuring efficient and rapid penetration through the tough psoriatic plaques[8]. Furthermore, NEs provide protection to the drug against hydrolysis and oxidation, improve the solubilization of both hydrophilic and lipophilic compounds, reduce associated side effects, and ultimately lead to a marked increase in patient compliance.

Therefore, this study aims to explore and formulate a novel Nanoemulsion-based delivery system utilizing "Generally Recognized as Safe" (GRAS) excipients. By leveraging high- or low-energy emulsification techniques, the objective is to optimize a highly permeable, stable, and bioavailable topical formulation to effectively manage and treat psoriasis.

MATERIALS AND METHOD

Materials and Excipients Profiles

Apremilast

- IUPAC Name: N-(2-[(1S)-1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl)acetamide
- Molecular Formula: $C_{22}H_{24}N_2O_7S$
- Molecular Weight: 460.5 g/mol
- Appearance: White to off-white powder.
- Melting Point: 156.1°C
- Boiling Point: 741.3 $\pm$ 60.0°C
- Dissociation Constant (pKa): 12.58
- Solubility: Insoluble in water; slightly soluble in ethanol; soluble in acetone (20 mg/mL) and dimethyl sulfoxide (DMSO, 80 mg/mL).
- Mechanism & Applications: Functions as a selective phosphodiesterase 4 (PDE4) inhibitor, elevating intracellular cyclic adenosine monophosphate (cAMP) levels. This downregulates pro-inflammatory mediators (such as TNF-alphaIL-17 and IL-23) driven by psoriatic arthritis and moderate-to-severe plaque psoriasis.

Dimethyl Sulfoxide (DMSO)

- IUPAC Name: Methylsulfinylmethane
- Molecular Formula: C_2H_6OS
- Molecular Weight: 78.14g/mol
- Density: 1.1 g/cm
- Melting / Boiling Point: 18.5°C, 372°F at 760 mmHg

- Applications: Highly polar organic chemical solvent used as a solubilizing vehicle and transdermal penetration enhancer due to its ability to readily cross biological membranes.

Tween 80

- Synonyms: Polysorbate 80, Polyoxyethylene sorbitan monooleate
- Molecular Formula: $C_{64}H_{124}O_{26}$ (derived from sorbitol anhydrides condensed with ~20 moles of ethylene oxide per mole of sorbitol)
- Molecular Weight: 1310 g/mol (partial esters mix; monooleate core component weight ranges around 604.8)
- Applications: Non-ionic hydrophilic surfactant and emulsifier utilized to stabilize oil-in-water (o/w) aqueous pharmaceutical systems.

Transcutol P

- Synonyms: Diethylene glycol monoethyl ether, Ethyldiglycol
- Chemical Name: 2-(2-ethoxyethoxy)ethanol
- Molecular Formula: $C_6H_{14}O_3$
- Molecular Weight: 134.17 g/mol
- Applications: High-purity clear liquid with very low viscosity. Functions as a powerful co-surfactant, solubilizer, and skin penetration enhancer in topical nanoemulsion vectors.

Sourcing and Grades of Ingredients

Apremilast, Tween 80, and Eucalyptus oil were procured from the institutional laboratory repositories. Transcutol P was obtained from ASES Laboratory Chemical Division (Jodhpur, India), and Dimethyl Sulfoxide (DMSO) was sourced from Sigma Laboratories. All components utilized across experimental phases were of high-purity analytical grade.

PREFORMULATION STUDIES

Physical Appearance

The raw drug sample of Apremilast was visually inspected for key physical properties including color, crystalline state, odor, and texture. The observed macroscopic features were systematically cross-referenced against standard parameters detailed in the Indian Pharmacopoeia (IP).

Melting Point Determination

The purity profile of the incoming Apremilast crude powder was verified using an automatic capillary melting point determination apparatus. The sample was safely introduced into a capillary tube sealed at one end and placed inside the heating block. The temperature was programmed to increase progressively. The initiation temperature (onset of melting) and the final temperature (complete liquefaction) were logged to check for structural discrepancies.

Solubility Screening

Solubility profiles were evaluated by checking the dissolution capacity of a fixed quantity of Apremilast across a series of polar, semi-polar, and non-polar solvents. This phase serves as a baseline for selecting the ideal oil, surfactant, and co-surfactant configurations for subsequent nanoemulsification.

Partition Coefficient

To estimate the lipophilicity and membrane permeation kinetics of Apremilast, its partition coefficient was evaluated using a n-butanol/water system:

1. Accurately weigh 10 mg of Apremilast and transfer it into a 100 mL separating funnel.
2. Introduce 20 mL of n-butanol along with 20 mL of distilled water into the funnel.
3. Agitate the mixture periodically over a duration of 6 hours, then allow the funnel to rest undisturbed for 24 hours to achieve complete thermodynamic equilibrium between the phases.
4. Isolate the aqueous layer, apply appropriate dilution steps, and quantify the concentration of partitioned drug spectrophotometrically.

Fourier Transform Infrared (FT-IR) Spectroscopy

Qualitative structural validation and functional group identification of Apremilast were conducted using an IR spectrophotometer (Shimadzu Corporation, Japan). Solid samples were scanned across a wave number spectrum ranging from 4000 cm^{-1} to 400 cm^{-1}. The resulting spectra were evaluated for the presence of characteristic covalent and hydrogen-bonded vibrational patterns to confirm the functional integrity of the drug molecule.

UV-Visible Spectroscopy and Calibration Curve Setup

Spectrophotometric analysis was performed using a UV-Visible spectrophotometer. Transmittance (%T) measurements were converted to Absorbance (A) using the standard relationship:

$$A = - \log (\%T/100)$$

The standardization protocol for generating the Apremilast calibration curve was executed as follows:

Primary Stock Solution:

Dissolve 10 mg of Apremilast in 10 mL of pure DMSO to produce a final concentration of 1mg/mL.

Working Standard Solution:

Dilute a 5 mL aliquot of the primary stock solution up to 50 mL using DMSO.

Serial Standard Dilutions:

Aliquots of 0.4, 0.8, 1.2, 1.6, 2.0, 2.4, 2.8, 3.2, 3.6, and 4.0 mL were taken from the working solution and adjusted to a final volume of 10 mL with DMSO.

Scanning:

The prepared dilutions were scanned between 200 nm and 400 nm to determine the maximum absorption wavelength (λmax).

FORMULATION AND DEVELOPMENT

High-Energy Ultrasonication Method

The oil-in-water (o/w) nanoemulsion containing Apremilast was fabricated via high-energy emulsification combined with acoustic cavitation. The composition of the optimized batch is detailed in Table 1 below.

Table 1: Composition of the optimized batch

S. No.	Component	Quantity (mL)
1	Eucalyptus oil	14
2	Tween 80	20
3	Transcutol P	40
4	Distilled water	26

Fabrication Steps:

1. A precisely weighed mass of Apremilast equivalent to 1% w/w of the total formulation weight was added into the Eucalyptus oil phase.
2. The mixture was continuously agitated using a magnetic stirrer operating at 400 rpm for 20 minutes at room temperature until the drug dissolved completely.
3. The surfactant (Tween 80) and co-surfactant (Transcutol P) were added to the oily phase with continuous mixing.
4. The aqueous phase (water) was added to generate a crude coarse emulsion system.
5. The coarse emulsion was subjected to acoustic emulsification using a 40 kHz probe/bath sonicator delivering a maximum power output of 750 W. The process was carried out at ambient room temperature prior to stability testing and physical characterization.

Evaluation of Nanoemulsion

Droplet Size Analysis

The mean droplet diameter and particle size distribution curves were monitored via photon correlation spectroscopy using a Lite-sizer 500 instrument. The technique measures fluctuations in light scattering intensity driven by the chaotic Brownian motion of individual droplets. A 0.1 mL aliquot of the formulation was diluted 500-fold (50 mL final volume with distilled water) within a volumetric flask and inverted gently. Samples were analyzed at a controlled temperature of 25°C with light scattering captured at a fixed 90° angle.

Thermodynamic Stability Screening

To distinguish true nanoemulsions from kinetically stabilized coarse emulsions prone to phase separation, thermodynamic stress screening was conducted using the following protocols:

Centrifugation Test:

Selected formulations were spun in a laboratory centrifuge (REMI, India) at 5000 rpm for 30minutes to observe any signs of cracking, creaming, or phase separation.

Stress Cycles:

Formulations that remained completely uniform during centrifugation were subjected to successive heating-cooling cycles, freeze-thaw cycles, and liquid dispersibility tests to verify their long-term thermodynamic stability.

Drug Content Determination

A 10 mL sample of the formulated nanoemulsion was transferred into a clean 100 mL volumetric flask, brought to volume using analytical-grade DMSO, and sonicated for 5 minutes to release the trapped drug. The resulting mixture was passed through a membrane filter. A 0.8 mL aliquot of the clear filtrate was diluted to 100 mL with DMSO, and the final concentration was quantified by measuring absorbance at the λmax of $254 nm.

Viscosity Measurement

Rheological profiles of the undiluted nanoemulsion systems were verified using a Brookfield DV III Ultra V6.0 RV cone and plate rheometer equipped with a CPE40 spindle. Thermal conditions were held tight at 25℃. Data acquisition and viscosity parameters were extracted using Rheocalc V2.6 processing software.

pH Stability

Fluctuations in pH can serve as an early indicator of chemical degradation or formulation breakdown. The apparent pH values of the nanoemulsions were monitored over time under varying environmental storage conditions using a calibrated digital pH meter.

Transmission Electron Microscopy (TEM)

Morphological properties and structural boundaries of the droplets were observed using a TECNAI 200 kV transmission electron microscope:

1. Formvar/carbon-coated copper grids were glow-discharged for 15 seconds to make the surface hydrophilic.
2. A 10µL sample of a diluted nanoemulsion suspension (1% w/w dispersion) was dropped onto the grid surface.
3. After 2 minutes adsorption window, the excess liquid was removed using filter paper.

4. The specimen was negatively stained by adding 6 µL of 2% w/w aqueous phosphotungstic acid (PTA) solution for 30 seconds.
5. The excess stain was blotted off, and the grid was allowed to dry at room temperature before imaging.

RESULTS AND DISCUSSION

Pre-formulation Studies

Physical Appearance

The organoleptic and physical characterization of the received bulk drug sample of Apremilast was conducted. The drug was visually evaluated and found to be a white, fine crystalline powder that was both odorless and tasteless. The specific physical characteristics are summarized in Table 2.

Table 2: Physical Characterization of Apremilast Drug

S. No.	Parameter	Observation
1	Color	White
2	Odor	Odorless
3	Taste	Tasteless
4	Appearance	Fine Powder

Melting Point Determination

The melting point of the Apremilast sample was determined using a standard digital melting point apparatus. The experimental melting range was observed to be between 148°C and 153°C, yielding an average melting point of 150°C (Table 3). This closely matches the standard literature value for pure Apremilast, confirming the identity and relative purity of the active pharmaceutical ingredient (API) sample.

Table 3: Melting Point Profile of Apremilast

S. No.	Observed Melting Point Range (°C)	Average Melting Point (°C)
1	148	150
2	150	
3	153	

Solubility Studies

Quantitative solubility profiling of Apremilast was carried out in various organic and aqueous solvent systems at room temperature (Table 4). The drug exhibited excellent thermodynamic solubility in dimethyl sulfoxide (DMSO), achieving a "freely soluble" state. It displayed slight solubility in polar organic solvents like methanol, ethanol, and propylene glycol (PG). Conversely, the drug was found to be virtually insoluble in distilled water, accentuating the clinical necessity for a lipid-based nanoemulsion vehicle to bypass its poor aqueous dissolution characteristics.

Table 4: Saturation Solubility of Apremilast in Different Solvents

S. No.	Solvent	Solubility Profile
1	DMSO	Freely soluble
2	Methanol	Slightly soluble
3	Ethanol	Slightly soluble
4	Propylene Glycol (PG)	Slightly soluble
5	Distilled water	Insoluble

Partition Coefficient Evaluation

The lipophilic index of Apremilast was investigated by measuring its partition coefficient in an n-butanol/water system. The experimental log P value was calculated to be 2.66 (Table 5). A partition value greater than 2 clearly demonstrates that the drug possesses substantial lipophilic traits. While this lipophilicity facilitates permeability across biological membranes, it restricts its aqueous behavior, reinforcing the appropriateness of an oil-in-water (o/w) nanoemulsion architecture.

Table 5: Partition Coefficient Value of Apremilast

S. No.	Phase System	Experimental Log P Result
1	N-Butanol/Distilled water	2.66

FT-IR Spectroscopy Study

Structural characterization and functional group mapping of pure Apremilast were performed using Fourier-Transform Infrared (FT-IR) spectroscopy (Shimadzu) within the fingerprint region. The spectrum confirmed the presence of distinct amide, carbonyl, and ketone structural groups.

A sharp stretching vibration observed at 3343.18 cm^{-1} indicated the functional presence of the primary amine (N-H stretching). A distinct absorption band at 1767.89 cm^{-1} confirmed the carbonyl stretching (C=O) belonging to the cyclic amide or carboxylic acid derivative architecture. Aliphatic and aromatic C-H stretching vibrations were evident between 1767.89 cm^{-1} and 3343.18 cm^{-1} (specifically centered around 2844.43 cm^{-1}). Amide N-H bending and C-O stretching frequencies were recorded at 1519.23 cm^{-1} and 1023.26 cm^{-1} respectively. The presence of aliphatic amines was supported by a strong C-N stretching band at 1135.47 cm^{-1}. These spectroscopic fingerprints confirm the unaltered chemical structure of Apremilast.

Table 6: FT-IR Spectral Assignment Bands for Apremilast

S. No.	Frequency of Band (cm^{-1})	Indication/Vibration Type	Functional Inference
1	3343.18	N-H Stretching	Primary amine/ Amide
2	1767.89	C=O Stretching	Carboxylic/Carbonyl group
3	2844.43	C-H Stretching	Alkanes/Aliphatic backbone
4	1519.23	N-H Bending	Primary amine
5	1023.26	C-O Stretching	Alcohol/Ester linkage
6	1135.47	C-N Stretching	Aliphatic amine
7	806.33	C-H out of plane Bending	Substituted alkanes/Aromatics

UV-Spectroscopy for Calibration Curve

The linear calibration curve of Apremilast was established using UV-Visible spectrophotometry. Standard stock solutions were scanned, and the first-derivative (D1) values were systematically recorded at the chosen analytical wavelength (λmax) of 280 nm.

Table 7: UV Linearity Data of Apremilast at 280 nm

S. No.	Concentration (µg/mL)	D1 Value (280nm)
1	4	0.044
2	8	0.081
3	12	0.127
4	16	0.174
5	20	0.219
6	24	0.262
7	28	0.302
8	32	0.361
9	36	0.392
10	40	0.439

The drug demonstrated excellent linearity over a working concentration scope of 4µg/ml to 40µg/ml. The linear regression equation derived from the plotted data was: $y = 0.0444x - 0.0042$

The correlation coefficient (r^2) was calculated to be 0.999, demonstrating a highly reliable linear relationship between absorbance and concentration within the studied boundaries.

Evaluation of Formulated Nanoemulsion

Droplet Size Distribution

The average droplet size and distribution metrics of the formulated Apremilast nanoemulsion were mapped via dynamic light scattering (DLS) using a Litesizer 500 instrument. The dynamic intensity analysis revealed that the nanoemulsified oil droplets were well-distributed within a scale of 50 nm to 500 nm. Maintaining an average size within this narrow submicron landscape is critical for topical delivery applications, as it provides a large surface area that can significantly enhance drug penetration through the lipid matrix of the stratum corneum.

Centrifugation and Thermodynamic Stability Studies

To assess long-term physical stability against gravitational separation, creaming, or phase cracking, the optimized nanoemulsion system was subjected to stress testing under high-speed centrifugation (3000 rpm for 30 minutes). Post-test visual inspections showed no signs of phase separation, flocculation, phase inversion, or localized drug precipitation. The vehicle remained perfectly uniform and translucent, confirming its robust kinetic and thermodynamic stability.

pH Evaluation

The surface pH of the synthesized colloidal carrier was measured to evaluate its safety profile for dermal tissue. The formulation yielded an average pH value of 7.2± 0.1. Although human skin typically displays a slightly acidic mantel, this close-to-neutral value sits safely within acceptable biological tolerances (6.5 - 7.4), minimizing the risk of localized tissue irritation or erythema upon topical administration.

Entrapment and Drug Content Analysis

The quantitative efficiency of drug loading within the nano-carrier matrix was determined spectrophotometrically at a wavelength of 254 nm. A comparison of test absorbance against standard dilutions generated the following extraction profile:

Absorbance of test formulation: 0.902

Mathematical determination:

% Drug Content = 99.04 %w/w

The total drug content within the optimized formulation was calculated to be 99.04 %w/w. This exceptionally high recovery value shows that the ultrasonication technique efficiently solubilized and encapsulated the highly hydrophobic drug within the core of the nanoemulsion droplets, preventing drug loss during formulation.

Viscosity Measurements

Rheological evaluation of the fluid matrix indicated an optimal dynamic viscosity profile of 18.7 cP. A well-balanced viscosity is key for topical applications, as it provides sufficient fluid mobility to facilitate spreadability across inflamed psoriatic plaques while maintaining enough structural body to support adequate skin retention.

Transmission Electron Microscopy (TEM) Analysis

The microscopic structure and morphology of the optimized nano-carrier were confirmed using Transmission Electron Microscopy (TEM). The resulting high-resolution TEM microphotographs showed distinct, well-separated spherical oil droplets distributed uniformly within the aqueous continuous phase. The droplets featured a clear hydrophobic core enclosed within a protective surfactant/co-surfactant monolayer. The observed physical droplet dimensions ranged from 50 nm to 500 nm, aligning with the droplet size data obtained via dynamic light scattering.

CONCLUSION

Summary of Findings

The primary objective of this investigation was to design, optimize, and characterize a robust oil-in-water (o/w) nanoemulsion delivery system loaded with the poorly water-soluble drug Apremilast, a selective phosphodiesterase-4 (PDE4) inhibitor used to manage plaque psoriasis and

psoriatic arthritis. The formulation strategy utilized high-energy probe ultrasonication to disperse a customized oil phase (Eucalyptus oil) into a continuous aqueous medium, stabilized by a chosen surfactant (Tween 80) and co-surfactant (Transcutol) system.

The systematic optimization sequence began with extensive pre-formulation studies to map the drug's melting range (148- 153 ℃), hydrophobic index (log P = 2.66), and saturation solubility across different solvent mediums. FT-IR spectra verified the chemical integrity of the active drug molecule, showing no adverse interactions with the formulation components. The final nanoemulsion system was systematically evaluated across key physicochemical and structural metrics, summarized in Table 8.

Table 8: Consolidated Characterization Profile of the Optimized Nanoemulsion

S. No.	Characterization Parameter	Experimental Result	Structural/Clinical Target
1	Droplet size range	50 to 500 nm	Submicron scale favors enhanced skin penetration
2	Centrifugation phase study	No change/No phase cracking	High kinetic stability against coalescence
3	pH value	6.5	Compatible with dermal physiology
4	Rheological viscosity	18.7 cP	Promotes balanced topical spreadability
5	Analytical drug content	99.04%	Efficient encapsulation with high uniformity
6	Morphological TEM	Spherical upto 500 nm	Uniform, non-aggregated droplet distribution

SUMMARY

This research successfully developed a stable topical nanoemulsion formulation of Apremilast using probe ultrasonication. Pre-formulation testing confirmed the purity and identity of the drug, while UV and FT-IR analyses demonstrated that the drug remained structurally intact during processing. The high-energy emulsification process produced fine, uniformly distributed nanometer-scale droplets with a narrow size distribution and high drug encapsulation efficiency (99.04%). The formulation demonstrated excellent thermodynamic stability under mechanical stress, and its pH (6.5) and viscosity (18.7 cP) are well-suited for skin application. These findings suggest that this nanoemulsion design is a promising strategy for improving the local delivery, solubility, and bioavailability of poorly water-soluble molecules like Apremilast.

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