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DESIGN AND DEVELOPMENT OF APREMILAST MICROEMULSIONAS A POTENTIAL DOASGE FORM FOR THE EFFICIENT TREATMENT OF PSORIATIC NAIL DYSTROPHY THROUGH TRANSUNGUAL ROUTE

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Keywords:

Apremilast, Microemulsion, Psoriatic nail dystrophy, Transungual rout

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ABSTRACT: The aim of present study was to develop microemulsion formulation of apremilast for the topical treatment of nail psoriasis, a challenging condition due to the nail's dense structure limiting drug penetration. Apremilast, a PDE4 inhibitor, offers an effective systemic approach but faces bioavailability challenges and potential side effects when administered orally. To address these issues, apremilast-loaded microemulsion was formulated using oleic acid, Tween 80 and PEG 600, optimized through a Box-Behnken design. The resulting microemulsion exhibited desirable characteristics, including particle size, PDI, and zeta potential, indicative of stability and effective drug delivery. *In-vitro* studies revealed an 81.63% drug release over 24 hours, highlighting the formulation's sustained release capabilities. *Ex-vivo* transungual permeation tests using goat hoof membranes further supported enhanced drug permeation to the target site, outperforming the pure drug suspension. These findings suggest that apremilast-loaded microemulsion can provide a more targeted, efficient, and safer alternative for nail psoriasis therapy, improving patient compliance through topical application. This novel approach has potential implications for enhanced nail disease management and future topical drug delivery advancements.

INTRODUCTION: Nail psoriasis is a chronic inflammatory condition, an autoimmune disease, affects both fingernails, toenails and leads to various nail abnormalities like pitting, splinter haemorrhaging of the nail bed, crumbling, discoloration, thickening and separation of the nail from the nail bed. It affects children and adults, equally affecting both males and females. This condition is caused by an overactive immune response that triggers rapid skin cell turnover, affecting the nails growth and structure [1].

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Nail psoriasis (NP) has a prevalence that ranges from 10 to 82% among patients with psoriasis. In 5 to 10% of patients, nail psoriasis manifests in the absence of cutaneous symptoms. NP can be associated with pain, cosmetic concerns and impaired finger function that can significantly impact the patient's quality of life. Nail psoriasis is difficult to treat because the dense nail structure limits medication penetration and slow nail growth delays visible improvement [2].

Traditional therapies like topical steroids often struggle to reach the inflammation at the nail matrix and nail bed. Additionally, nail psoriasis involves complex immune pathways, requiring targeted therapy. Nail is one of the difficult site to treat psoriasis [3]. Apremilast is effective for nail psoriasis due to its systemic action and specific mechanism.

As a PDE4 inhibitor, it reduces inflammatory cytokines (e.g., TNF-α, IL-17, IL-23), directly addressing inflammation. Taken orally, it reaches the nail bed and matrix through the bloodstream, bypassing the nail plate barrier. Apremilast also has a favourable safety profile compared to other systemic options, supporting long-term use. Clinical studies show that it significantly reduces symptoms like pitting, onycholysis, and hyperkeratosis, with effects visible within a few months, making it a strong choice for patients needing sustained treatment [4]. Apremilast is a BCS class IV drug with low solubility and low permeability and it was found to have poor therapeutic efficiency in the case of nail psoriasis due to its insufficient delivery of apremilast into the nail apparatus. Oral administration of apremilast is also associated with severe side effects like diarrhoea, headache, upper respiratory tract infection and abdominal pain [5].

Microemulsions are ideal for delivering apremilast in nail psoriasis treatment due to their superior penetration abilities. The tiny droplets in microemulsions can effectively pass through the dense nail plate, reaching the nail bed and matrix where psoriasis inflammation begins. Additionally, microemulsions enhance the solubility and stability of apremilast, ensuring a higher concentration at the target site [6]. They also allow for sustained drug release, maintaining therapeutic levels for longer periods, which could improve treatment efficacy and reduce dosing frequency. Furthermore, microemulsions are gentle on sensitive nail tissues, making them suitable for long-term use. These benefits make microemulsions an excellent choice for delivering apremilast in nail psoriasis therapy [7]. Therefore, the development of a novel formulation of apremilast to improve its physical and biopharmaceutical properties is highly desirable. Hence, the present study is aimed to develop apremilast loaded microemulsion formulation for topical administration as a single dose application to sustain the release of the drug and improve patient compliance.

MATERIALS AND METHODS:

Materials: Apremilast was obtained as gift sample from Dr Reddy's laboratories Ltd, Hyderabad, India. Oleic acid was purchased from SD Fine Chemicals Ltd, India, Tween 80 was purchased from SD Fine Chemicals Ltd, India, PEG 600 was purchased from Loba Chemie Pvt Ltd, India. All other materials and solvents used were of analytical method.

Methods:

Screening of Oils, Surfactants and Co-Surfactants: To find out the suitable oil which can be used as the oil phase in microemulsion, the solubility of Apremilast in various oils (oleic acid, clove oil, olive oil) was measured. The solubility of Apremilast in various surfactants (Tween-80, Span 80, Tween 20) and cosurfactants (Glycerol, PEG 600, propylene glycol) was also determined. 5 mg of apremilast was added in 5 mL of the selected oil, surfactant, and co-surfactant in stoppered vials (capacity 25.0 mL) and then was stirred continuously at 25 ± 0.5ºC for 48 hrs. to achieve equilibrium. The equilibrated samples were then centrifuged at 3,000 rpm for 15 minutes. The supernatant was separated, filtered and after appropriate dilution, solubility was determined by UV Spectrophotometer at 230 nm [8].

Construction of Pseudo Ternary Phase Diagram: The existence of microemulsion regions was determined by using pseudo ternary phase diagram. Oleic acid as oil phase, Tween 80 as Surfactant and PEG 600 as cosurfactant were selected from the solubility studies. Pseudo ternary phase diagrams were constructed by titrating the blend of oil and surfactant: co-surfactant mixture (Smix) without drug by incremental amounts of water. Mixture of surfactant and cosurfactant were prepared in different weight ratios (1:1, 1:2, 2:1, 3:1). Each Smix was mixed with oil in different weight ratios (oil: Smix) 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1. Each mixture of oil and Smix was subjected to vortex mixing to form homogenous mixture before titration with water. During titration the aqueous phase was added in drop wise until turbidity is formed. The change in composition upon incremental addition of water with different oil to Smix ratios [9]. All mixtures that formed transparent microemulsion systems were marked and plotted on the triangle graph using Ternary Plot.com.

Preparation of Apremilast Microemulsion:

Method of Preparation of Microemulsion: Apremilast loaded microemulsion were prepared

by phase titration method technique. To know the effect of oil, Smix ratio and water concentration, various formulations (F1-F17) were prepared as shown in **Table 1**. Oleic acid and smix was mixed in a beaker at a temperature 75 ˚C and vortexed at 150 RPM. To this mixture 2% Apremilast was added and heated for 10 min, until the drug gets completely soluble in the mixture. The aqueous phase was added slowly to this oil phase and vortexed for a period of 2 min. The droplet size was further reduced by ultra-homogenization at 10000, 15000, 20000 RPM for 5, 10, 15 min and collected [10].

Optimization by Experimental Design: Design Expert software version 13 was used to optimize the batches F1-F17 as shown in **Table 1.** Data of all batches was uploaded in the software and then analysed subjecting to ANOVA. The advantage of this software is the reduction in the number of experiments required for formulating the batches thus saving time, energy and aids in checking only the minimum number of batches by which the relationship between various factors on their responses can be determined. The experiments were performed using Response surface analysis also known as Box-Behnken design (BBD) by using Design Expert software 13. A Response surface with statistical model incorporating interactive and polynomial terms were utilized to optimize and assess the responses. Experimental design was adopted to optimize the batches. A high-resolution Box-Behnken design (BBD) was employed to optimize the three critical factors. BBD is a popular quadratic response surface method, which is particularly useful when the levels of factors being studied are at near the extreme levels of those factors. BBD can also address the issue of runs with all extreme values and of star points required.

A 17-run BBD (including 5 center point runs) was constructed in the optimization trials using 3 critical factors at 3 levels to evaluate main effects, interaction effects as well as quadratic effects. Five center point trials were included to assess the reproducibility of method of preparation of microemulsion. Formulation variables such as concentration of oil (X1), Smix ratio (X2) and concentration of water (X3) were the main factors that affect the particle size (Y1) and PDI (Y2) of Microemulsion. Three different levels of variables are given in the table below. In this work two independent variables were studied in three levels: low, medium and high, which were represented by the transformed values of –1, 0 and +1, respectively. Values of these selected variables are shown in **Table 1.**

TABLE 1: FACTORS AND THEIR LEVELS USED IN BBD FOR OPTIMIZATION

Factors	Levels used		
	-1	0	+1
Independent factors			
A = Concentration of oil (% w/v)	40	50	60
B = Smix ratio	1:1	2:1	3:1
C=Concentration of water (% w/v)	10	15	20
Dependent factors		**Constraints**	
Y1 = particle size (nm)		Minimum	
Y2=PDI		Minimum	

TABLE 2: EXPERIMENTAL RUNS GENERATED BY BBD AND RESPONSES OBTAINED FROM OPTIMIZATION OF APREMILAST IN TERMS OF PARTICLE SIZE AND PDI

Runs	Critical factors			Response variables	
	Conc. of oil (%)	Smix ratio	Conc. of Water (%)	Particle size (nm)	PDI
1	50	2:1	15	94.23	0.654
2	50	3:1	10	117.45	0.587
3	50	1:1	10	136.38	0.762
4	50	2:1	15	110.67	0.629
5	60	1:1	15	115.6	0.812
6	50	3:1	20	137.28	0.539
7	50	2:1	15	113.67	0.699
8	40	3:1	15	142.48	0.796
9	40	1:1	15	98.34	0.659
10	50	1:1	20	151.94	0.621

11	60	2:1	10	120.7	0.935
12	40	2:1	20	131.38	0.750
13	50	2:1	15	95.37	0.692
14	60	1:1	20	84.25	0.454
15	60	3:1	15	99.72	0.723
16	50	2:1	15	102.83	0.632
17	40	2:1	10	95.23	0.654

The non-linear quadratic model for particle size generated by the response surface is of the following equation.

Particle size nm (Y1) = -249.287 + 13.45×A - 71.15×B +3.26×C +1.50×AB - 0.36×AC -0.21×BC - 0.08×A^2+19.27×B^2 + 0.52×C^2.

In equation (Y1) negative sign for co-efficient of B indicated that as the smix ratio increase particle size decreases. Negative sign for co-efficient of AC indicated that as the Concentration of oil and concentration of water increase particle size decreases. Negative sign for co-efficient of BC indicated that as the Smix ratio and concentration increase particle size decreases and positive sign for co-efficient of A indicated that as the concentration of oil increase particle size increases. Positive sign for co-efficient of C indicated that as the Concentration of water increase particle size increases. Positive sign for co-efficient of AB indicated that as the concentration of oil and Smix ratio increase particle size increases

PDI (*Y*2) = 0.263- 0.034563×A - 0.186625×B - 0.179820×C +0.005650×AB - 0.002885×AC -0.004650×BC + 0.000787×A2 + 0.007650×B2 - 0.001664×C2.

In equation (Y2) negative sign for co-efficient of A indicated that as the concentration of oil increase PDI decreases. Negative sign for co-efficient of B indicated that as the Smix ratio increase PDI decreases. Negative sign for co-efficient of C indicated that as the concentration of water increase PDI decreases. Negative sign for co-efficient of AC indicated that as the Concentration of oil and concentration of water increase PDI decreases. Negative sign for co-efficient of BC indicated that as the Smix ratio and concentration increase PDI decreases and Positive sign for co-efficient of AB indicated that as the concentration of oil and Smix ratio increase PDI increases.

Attenuated Total Reflectance-Fourier Transform Infrared (ATR-FTIR) Spectroscopy: Drug excipient compatibility studies were carried out using ATR to evaluate interaction, if any, between drug and excipients and to ensure the apremilast encapsulation into the microemulsion. The peaks in the FT-IR graphs were compared and change in transmittance in the graphs was observed.

Characterization of Microemulsion:

Measurement of Particle Size and PDI: The particle size and the distributions of the sizes of the microemulsion were measured using an Malvern Zeta sizer nano ZS-90.

Measurement of Zeta Potential: The zeta potential of the optimised batch was measured using zeta sizer Horiba scientific SZ-100. Applied voltage was set at 3.4v, The zeta potential was measured for microemulsion to know the surface charge of the particle and to provide know about the stability information.

Drug Content: Drug loaded microemulsion containing an equivalent of 15 mg of drug were dissolved in methanol and stirred at 600 rpm for 3 hours. The drug concentration in the supernatant was then measured to extract the entrapped drugs and analyzed after further dilutions using the validated UV spectrophotometric method at 230 nm.

***In-vitro* Drug Release Study:** Apremilast loaded Microemulsion *in-vitro* drug release study was performed using Franz diffusion cells using dialysis membrane - 150 (molecular weight cut off 12000-14000 HIMEDIA-LA401-5MT) which was mounted between both Donar and receiver compartment. Microemulsion equivalent to 15mg of drug was placed in donar compartment. The receptor compartment was filled with phosphate buffer pH 5.5 as the receptor medium. The donor and the receptor compartment were separated by activated dialysis membrane. The media in the receptor compartment was stirred on a magnetic stirrer at 50 RPM for 24 hrs, maintained at 37±0.50 C. 3 mL of sample was withdrawn from receiver solution at different time intervals, and the

diffusion cell was replenished to their marked volumes with fresh buffer solution. Obtained solution was diluted when needed and analyzed for the % of drug released by UV Spectrophotometer [11].

Transungual Permeation Study: Hooves from freshly slaughtered goat, free of connective and cartilaginous tissues, were taken from the local slaughterhouse and soaked in distilled water for 24 h. From the lower part of the hooves, a section of about 1 mm thickness was cut. The hoof membrane was placed carefully on the Franz diffusion cell of 84-mL capacity, and the surface area available for permeation was 3.2 cm^2. About 1 g of Microemulsion and aqueous drug suspension (containing the same equivalent amount of drug as contained in 1-g Microemulsion) were applied evenly on the surface of the membrane. The receptor compartment was filled with solvent (phosphate buffer pH 7.4) and the whole assembly was maintained at 37 ± 1°C with constant stirring (100 rpm) for 24 h. 3 mL of sample was withdrawn from receiver solution at different time intervals and the diffusion cell was replenished to their marked volumes with fresh buffer solution. Obtained solution was diluted when needed and analyzed for the % of drug released by UV Spectrophotometer [12].

RESULTS AND DISCUSSION:

Screening of Oils, Surfactant and Co-surfactant: Solubility of Apremilast in various oils, surfactant and co-surfactant was performed. Highest solubility was found in oleic acid (2.75 mg/ML) as compared to the oils and it was selected as oil phase. Tween 80 and PEG 600as surfactant and co-surfactant were selected on the basis of high solubility. In tween 80, solubility was found 6.06 mg/mL and in PEG 600 it was found 1.57 mg/ml. Solubility data of apremilast is given in **Table 3.**

TABLE 3: DATA OF SOLUBILITY STUDIES

Sl. no.	Components	Use in Microemulsion	Solubility (mg/mL)
1	Oleic acid	Oil	2.75
2	Clove oil	Oil	1.02
3	Olive oil	Oil	0.89
4	Tween 80	Surfactant	6.06
5	Span 80	Surfactant	1.22
6	Tween 20	Surfactant	4.45
7	Glycerol	Co-surfactant	0.467
8	PEG600	Co-surfactant	1.57
9	PG	Co-surfactant	0.854

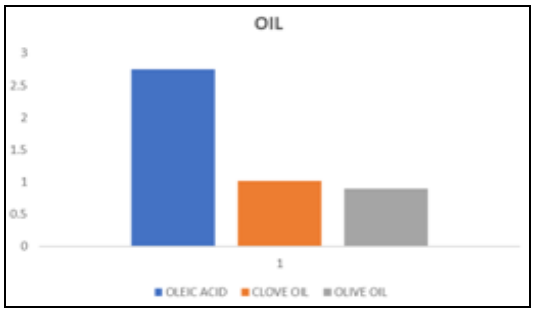

FIG. 1: SOLUBILITY STUDY OF APREMILAST IN VARIOUS OILS

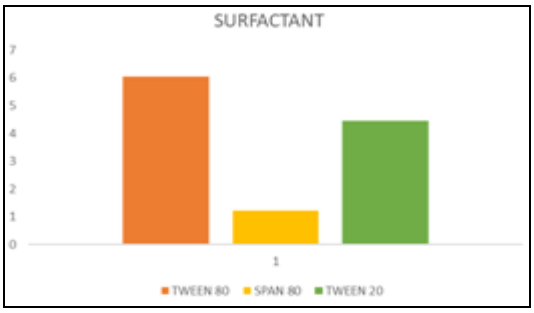

FIG. 2: SOLUBILITY STUDY OF APREMILAST IN VARIOUS SURFACTANT

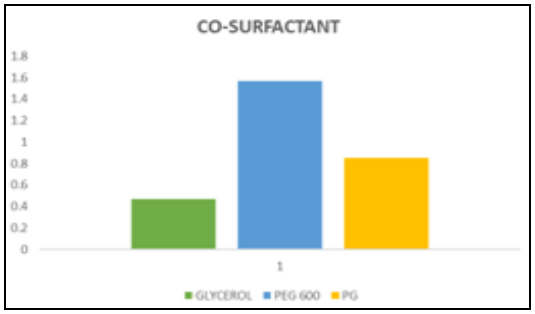

FIG. 3: SOLUBILITY STUDY OF APREMILAST IN VARIOUS CO-SURFACTANT

Construction of Pseudo Ternary Phase Diagram:

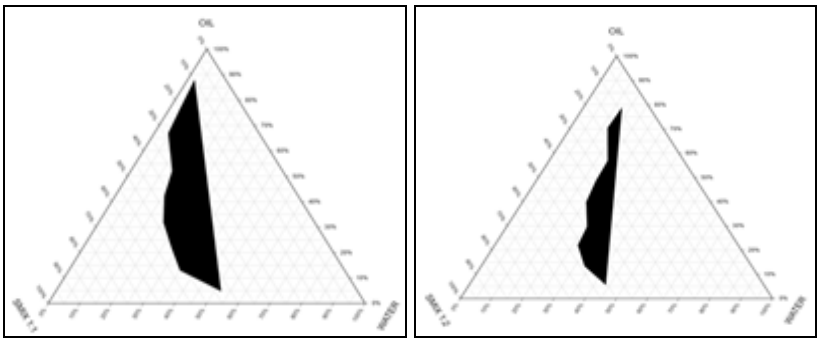

FIG. 4: SHOWS THE PSEUDO TERNARY DIAGRAM FOR SMIX RATIO (1:1) AND (1:2

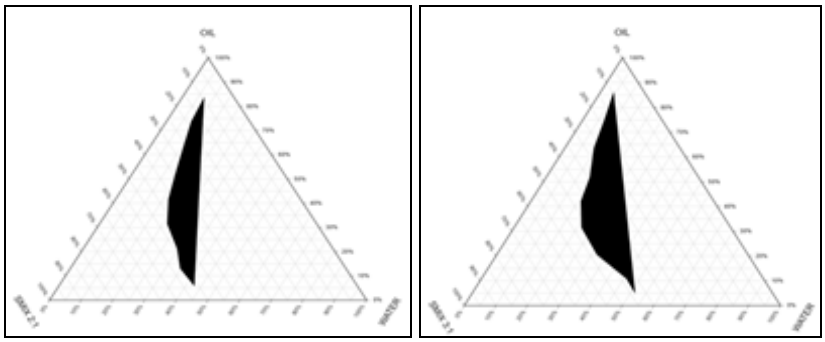

FIG. 5: SHOWS THE PSEUDO TERNARY DIAGRAM FOR SMIX RATIO (2:1) AND (3:1)

According to the visual representation and emulsification area of Smix ratios of microemulsion the Smix ratio of (1:1) has shown the biggest emulsifying region and was considered as most satisfactory and it was selected for the preparation optimized formulation.

ATR-FTIR Studies: FT-IR results are shown in the **Fig. 1** and **2.** The IR spectrum of apremilast shows the presence of main bands: N-H stretching of the amine group at 3362 cm^{-1}, C=O stretching of the ester group at 1702 cm^{-1}, C-H stretching of the aromatic ring at 2902 cm^{-1}, C=C stretching of the aromatic ring at 1567 cm^{-1}, and S=O stretching of the sulfonyl group at 1165 cm^{-1}, as illustrated in **Fig. 3.**

The IR spectrum of Physical Mixture 1 exhibits characteristic bands corresponding to O-H stretching of the alcohol group at 3374 cm^{-1}, C-H stretching of the aliphatic group at 2921 and 2853 cm^{-1}, N-H stretching of the amine group at 3410 cm^{-1}, C=O stretching of the ester group at 1739 cm^{-1}, C-O stretching of the ester group at 1267 cm^{-1}, and C-H bending of the aromatic ring at 772 cm^{-1}, as shown in **Fig. 4.**

It was been observed that there were no major shifts in the spectral values of drug, indicating no chemical interaction Each excipient charcterstictics peaks are present without significant shifts indicating no strong interactions or no chemical incompatibilities between apremilast and excipients. These minor shifts fall within expected limits and are likely due physical interactions rather than chemical incompatibilities

The apremilast N-H stretching was found at 3362 cm^{-1} and in the ATR report of physical mixture the drug peak was found in 3419 cm^{-1}indicating there is no physical or chemical interaction between drug and excipients.

The presence of all functional groups such as hydroxyl, ester amine, aliphatic groups in respective theoretical ranges for each compound in the physical mixtures, confirms that apremilast does not react with this excipient Hence, it can be concluded that there is compatibility between drug and excipients used.

Drug maintains its identity without undergoing any interaction with the excipients and the ATR spectra support the compatibility of apremilast with excipients used, making them suitable for formulation together without risk of significant interactions.

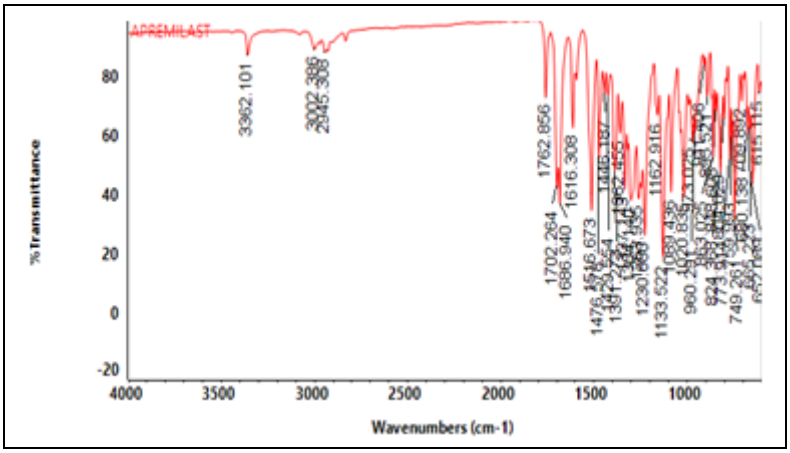

FIG. 6: ATR SPECTRA OF APREMILAST

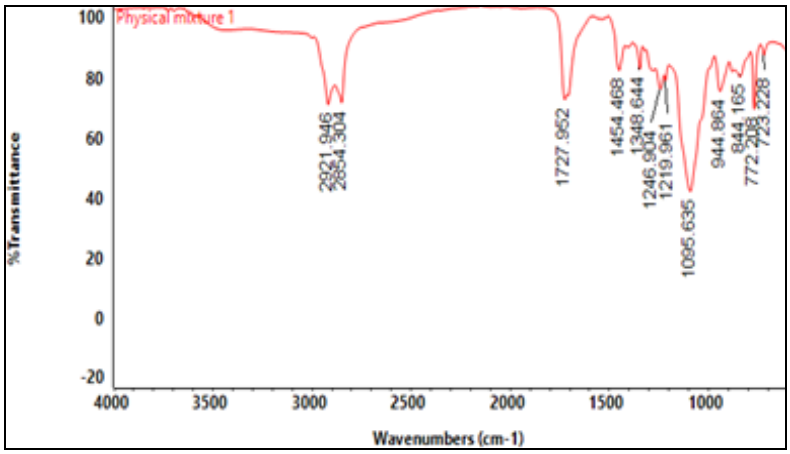

FIG. 7: ATR SPECTRA OF PHYSICAL MIXTURE

Particle Size and PDI: The average particle size of all batches lies within the range of 84 nm-151. The PDI of all the batches lie within the range of 0.454-0.935. Both Smix ratio and concentration of oil plays a vital role in particle size distribution in microemulsion formulations.

From **Table 2**, it is seen that batch F14 as particle size of 84±0.75 nm which was found to have the optimum particle size. The PDI of F14 formulation was found to be 0.454. F14 formulation was chosen for further studies and evaluated.

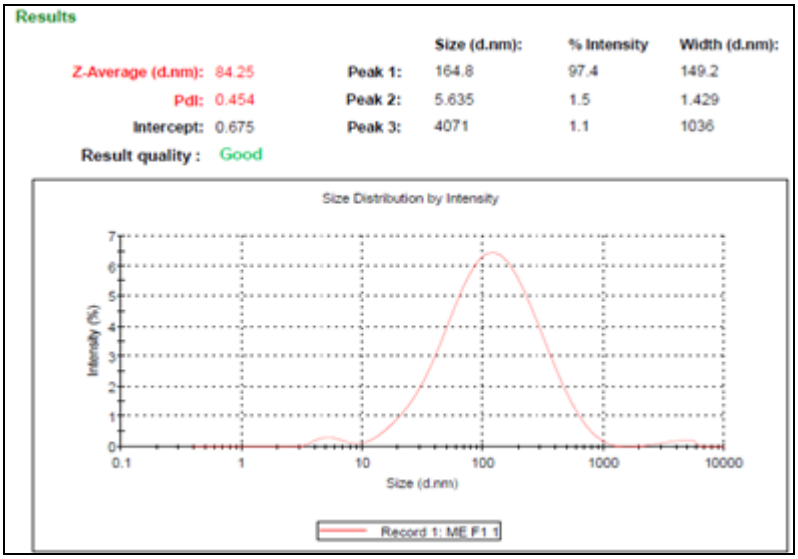

FIG. 8: PARTICLE SIZE AND PDI OF OPTIMIZED MICROEMULSION

Zeta Potential: Zeta potential indicates the stability of the batches. Greater the zeta potential greater is the stability. The zeta potential of F14 formulation was found to be -35.5 mv. Zeta potential between greater then +25mv or less than -25mv are stable. Zeta potential of -35.5 mv indicate strongly anionic and stable.

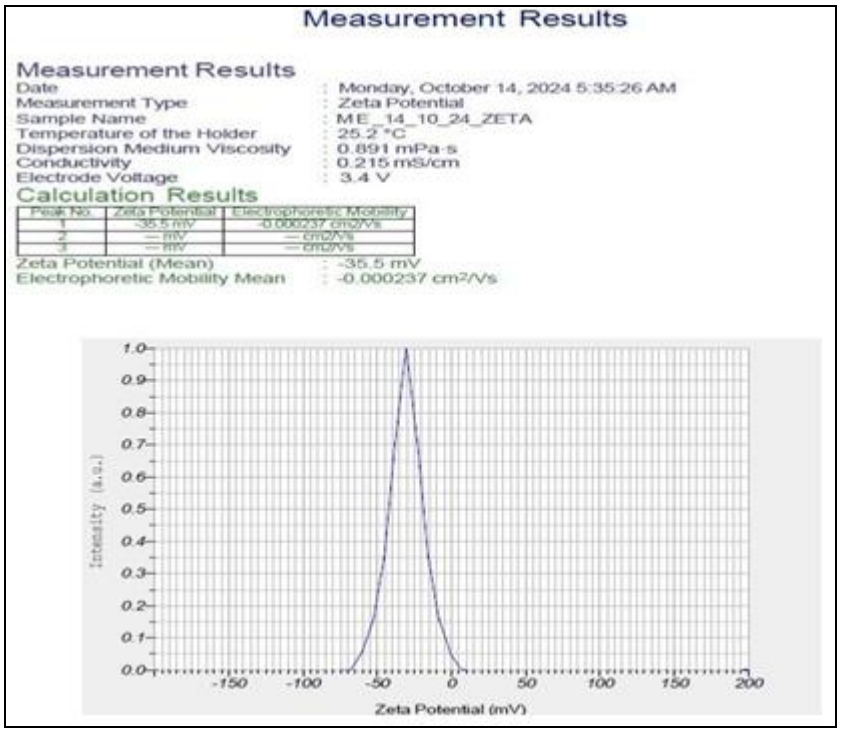

FIG. 9: ZETA POTENTIAL OF SELECTED OPTIMIZED MICROEMULSION

Response Surface Analysis: The mean particle size (Y1) and PDI (Y2) of apremilast loaded microemulsion showed R^2 values at 0.8476 and 0.8904, respectively as shown in **Table 4** and **5**, indicating good fit and it was concluded that the second order model adequately gives the values for true surface. From Table it is concluded that P-values less than 0.0500 indicate model terms are significant and the model F-value of 2.77 and 5.42 implies the model is significant.

TABLE 4: REGRESSION ANALYSIS DATA FOR MEASURED RESPONSES FOR PARTICLE SIZE

Source	Std Dev	R^2	Adjusted R^2	Predicted R^2	P value	F value	Press	
Linear	21.08	0.0701	-0.1445	-0.8013	0.0309	7.91	11185.58	
2FI	18.85	0.4281	0.0849	-1.3348	0.0399	7.04	14498.54	
Quadratic	11.63	0.8476	0.6516	-0.7243	0.1747	2.77	10707.90	Suggested

TABLE 5: REGRESSION ANALYSIS DATA FOR MEASURED RESPONSES FOR PDI

Source	Std Dev	R^2	Adjusted R^2	Predicted R^2	P value	F value	Press	
Linear	0.1083	0.2364	0.0601	-0.5669	0.0093	15.24	0.3127	
2FI	0.0737	0.7282	0.5651	-0.2653	0.0341	7.71	0.2525	
Quadratic	0.0559	0.8904	0.7495	-0.4414	0.0681	5.42	0.2877	Suggested

Design expert software was used to generate 3D response surface plots, visually representing the regression equation for optimizing apremilast-loaded microemulsion. These plots effectively illustrate the impact of various factors on the responses, revealing the interactive effects between three independent variables and two dependent variables, as shown in **Fig. 10(A)** indicates that as the concentration of oil increases, generally particle size tends to decrease. This suggests that higher oil concentrations might lead to smaller particles and as the Smix Increases generally increases the particle size. This implies that higher mix ratios might result in larger particles. **Fig. 10(B)** indicates that as the concentration of oil increases, generally particle size tends to decrease. This suggests that higher oil concentrations might lead to smaller particles and as the Concentration of Water

Increases generally increases the particle size. This implies that higher water concentrations might result in larger particles. **Fig. 10(C)** indicates that as the SmixRatio Increases, generally particle size tends to decrease. This suggests that higher Smix ratios might lead to smaller particles and as the Concentration of Water generally increases the particle size. This implies that higher water concentrations might result in larger particles.

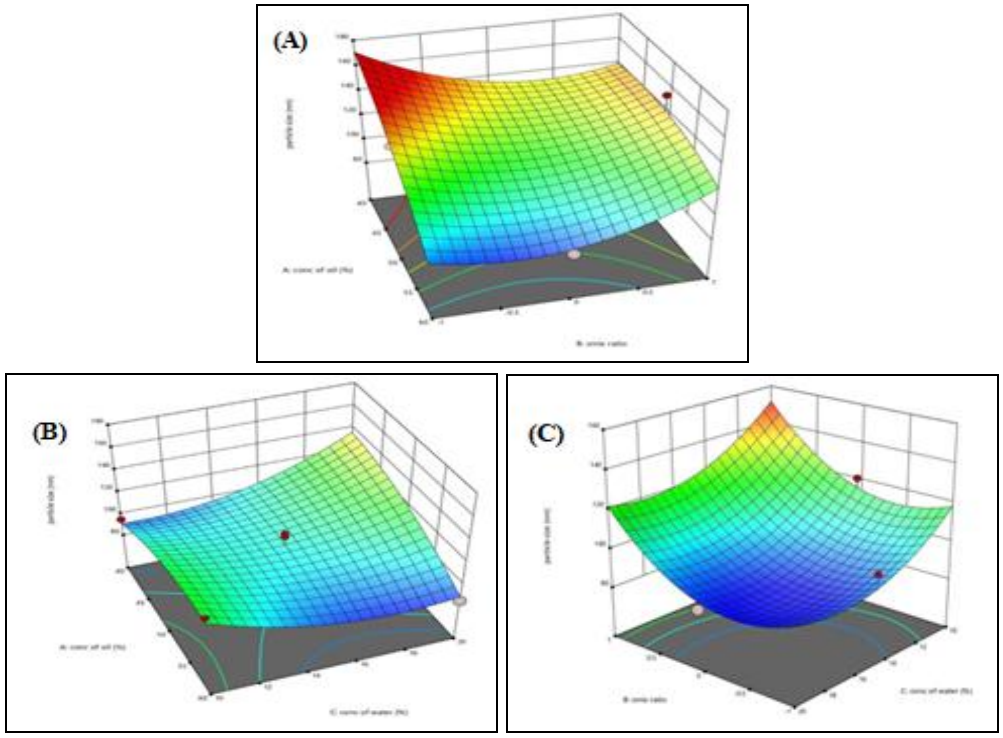

FIG. 10: RESPONSE SURFACE 3D PLOTS SHOWING THE EFFECT OF (A) CONCENTRATION OF OIL AND SMIX RATIO ON PARTICLE SIZE; (B) CONCENTRATION OF OIL AND CONCENTRATION OF WATER ON PARTICLE SIZE; (C) SMIX RATIO AND CONCENTRATION OF WATER ON PARTICLE SIZE.

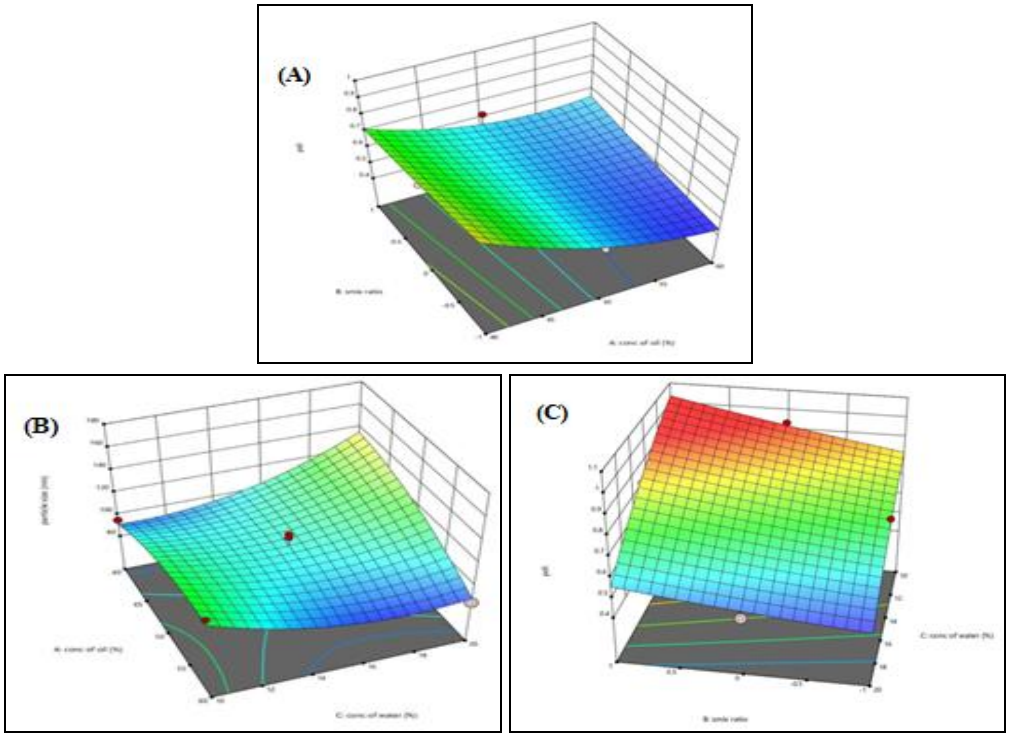

FIG. 11: RESPONSE SURFACE 3D PLOTS SHOWING THE EFFECTS OF (A) CONCENTRATION OF OIL AND SMIX RATIO ON PDI; (B) CONCENTRATION OF OIL AND CONCENTRATION OF WATER ON PDI; (C) SMIX RATIO AND CONCENTRATION OF WATER ON PDI.

Response surface 3D **Fig. 11(A)** indicates that as the concentration of oil increases, PDI value decreases. This suggests that higher oil concentrations might lead to a less dispersed system and Smix Ratio generally increases the PDI value. This implies that higher smix ratios might result in a more dispersed system. **Fig. 11(B)** indicates that as the concentration of oil increase, generally PDI value tends to decrease. This suggests that higher oil concentrations might lead to a less dispersed system, and as the Concentration of Water Increases the concentration of water generally increases the PDI value. This implies that higher water concentrations might result in a more dispersed system. **Fig. 11(C)** indicates that as the Smix ratio increases, generally PDI value tends to decrease. This suggests that higher smix ratios might lead to a less dispersed system and as the Concentration of Water Increases generally increases the PDI value. This implies that higher water concentrations might result in a more dispersed system.

Drug Content: The drug content of F14 Apremilast microemulsion was found to be 86.2±2.5%

***In-vitro* Drug Release Studies:** The pure drug and optimized F14 apremilast microemulsion were subjected to *in-vitro* drug release profile. PBS pH 5.5 was used as medium for evaluating the pattern of release of apremilast from the prepared microemulsion as in **Fig. 9.** The apremilast microemulsion showed 81.63% of drug release at the end of 24 hour. The higher Microemulsion formulation releasing profile can be due to its smaller particle size and higher drug solubilization potential. The pure drug showed 14.12 % of drug release at 24hr. The pure drug shows a slow and steady release over time, with minimal release compared to the microemulsion formulation. It indicates that the pure drug has a low permeability or limited diffusion rate in the medium used for the experiment. The apremilast microemulsion showing an initial burst release within the first few hours, quickly reaching a high percentage of drug release within approximately 5 hours. After this point, the release plateaus, indicating that the majority of the drug has been released and that further release is limited. The microemulsion achieves a much higher and quicker drug release compared to the pure drug, suggesting that the microemulsion system enhances drug solubility or diffusion, allowing for faster and more efficient drug release. The Higher F14 microemulsion drug release profile can be due to smaller particle size and high drug solubilization potential Hence, sustain release of apremilast microemulsion lotion formulation successfully can aid the delivery of the drug topically.

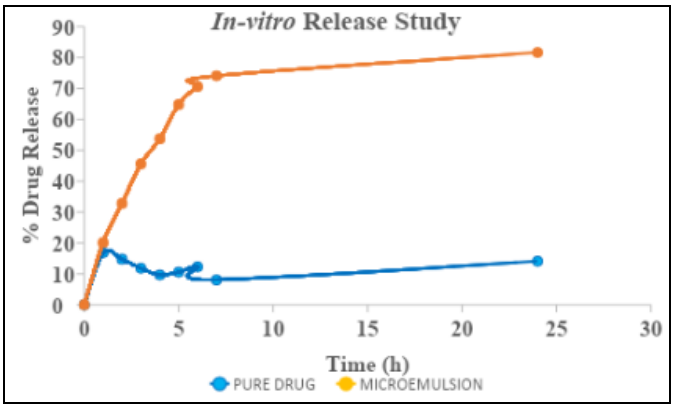

FIG. 12: COMPARISON OF *IN-VITRO* RELEASE PROFILE OF PUREDRUG, OPTIMIZED APREMILAST LOADED MICROEMULSION

Transungual Permeation Study: *Ex-vivo* permeation study of pure drug suspension, optimized microemulsion and microemulsion lotion was carried out using goat hoof membrane (section of goat hoof) in pH 7.4 was found to be 11.45% and 42.09% **Fig. 10** at the end of 24 hours respectively. This indicates that microemulsion formulations effectively improve drug delivery across the membrane, likely due to their smaller droplet size and better skin penetration properties, making them promising vehicles for enhanced drug absorption.

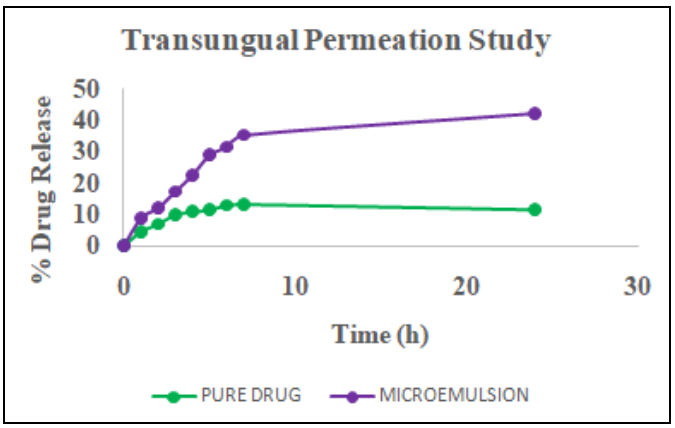

FIG. 13: COMPARATIVE TRANSUNGUAL PERMEATION STUDY OF PURE DRUG, OPTIMIZED APREMILAST LOADED MICROEMULSION

CONCLUSION: This study demonstrated that apremilast-loaded microemulsion offers a promising topical treatment for nail psoriasis, overcoming the challenges of nail penetration and enhancing drug delivery. Utilizing oleic acid, Tween 80, and PEG 600 enabled a stable microemulsion with optimal particle size, PDI, and zeta potential, indicating high stability and effective delivery. The formulation achieved significant *in-vitro* drug release (81.63% in 24 hours), significantly surpassing pure drug suspension. Additionally, *ex-vivo* permeation studies confirmed its potential for improved transungual delivery. This microemulsion system, by enhancing apremilast's bioavailability and controlled release, provides a novel approach to nail psoriasis management with minimized side effects, supporting future applications in topical therapy.

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