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FORMULATION DEVELOPMENT AND EVALUATION OF TOPICAL NANOEMULGEL OF APREMILAST

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ABSTRACT

In recent years, the use of topical nano-emulgels has gained significant attention due to their enhanced patient compliance. This is largely attributed to their non-greasy texture, ease of application, favorable spreadability, and strong therapeutic and safety profiles. Nano-emulgels are particularly promising for delivering lipophilic drugs through the skin, despite facing certain formulation challenges. Among various formulations studied, the nano-emulgel incorporating nano-emulsion prepared using Tween 80 and almond oil demonstrated superior drug diffusion capabilities. The optimized nano-emulsion exhibited a zeta potential of -32.0 mV, indicating thermodynamic instability in the dispersion system. Drug content within the formulation ranged from 64% to 96%, suggesting good content uniformity across samples. When evaluated against a commercially available product in terms of in-vitro drug release, the optimized formulation (Batch F1) exhibited a controlled release profile over 24 hours, with initial drug release starting at 12 hours. The release pattern followed the Higuchi kinetic model, indicating diffusion-controlled drug delivery. An accelerated stability study conducted over a three-month period showed no significant changes in the formulation, affirming its stability. In conclusion, the Apremilast-loaded nano-emulgel demonstrates strong potential as a novel percutaneous delivery system. Its ability to provide sustained drug release makes it a promising option for the long-term management of fungal infections, while also ensuring improved stability and therapeutic efficacy.

KEYWORDS: Apremilast, Topical Emulgel, Nanoemulsion.

INTRODUCTION

Apremilast, marketed under the brand name Otezla, is a phosphodiesterase 4 (PDE4) inhibitor commonly used in the management of several inflammatory autoimmune disorders. It shares its drug class with other PDE4 inhibitors such as Roflumilast and Crisaborole. Originally approved in 2014, Apremilast is distributed by Celgene. In July 2019, the FDA granted an additional approval for its use in treating oral ulcers associated with Behçet's disease—an autoimmune condition marked by recurrent inflammation affecting the skin, blood vessels, and central nervous system.

The objective of the present study was to develop a topical emulgel formulation containing 1% w/w Apremilast, incorporating the drug in nanoemulsion form to enhance its delivery and therapeutic effectiveness.

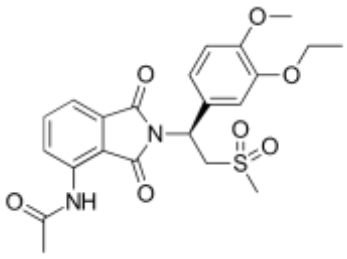


Fig 1: Structure of Apremilast

The exact mechanism by which apremilast exerts its therapeutic effects is not yet fully understood. Nonetheless, it is known to act as an inhibitor of the enzyme phosphodiesterase 4 (PDE4), which plays a key role in modulating intracellular levels of cyclic adenosine monophosphate (cAMP), a critical second messenger. By inhibiting PDE4, apremilast increases cAMP concentrations within immune cells. This rise in cAMP helps downregulate the inflammatory response by decreasing the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-23 (IL-23), among others.

These cytokines are implicated in the pathogenesis of various inflammatory conditions, including psoriatic diseases and Behçet's disease, contributing to clinical symptoms like oral ulcers, skin lesions, and joint inflammation. Through its modulation of inflammatory signaling, apremilast helps to mitigate these symptoms and improve patient outcomes.[1,2]

MATERIALS AND METHODOLOGY

Materials

Apremilast was obtained from Lupin Pharmaceuticals. Almond oil, propylene glycol, and Tween 80 were sourced from Research-Lab Fine Chem Industries, Mumbai. Carbopol 934 was procured from Molychem, Mumbai. All other chemicals and reagents used in the study were of analytical grade.

METHODOLOGY

High pressure homogenization methods are used for the formulation of nanoemulgel. There are three steps involved in the formulation of nanoemulgel which are given follows.

1. Preparation of Nanoemulsion.
2. Preparation of hydrogel and.
3. Finally, nanoemulgel will be produced by the incorporation of Nanoemulsion into gel with continuous stirring.

3^2 Full Factorial Design

In the current study, a 3^2 full factorial design was employed. This experimental design involved two independent variables, each assessed at three different levels, resulting in a total of nine experimental runs, as outlined in Table 1. The two factors selected for evaluation were the concentration of almond oil (X_1) and the homogenization speed (X_2).

Table 1: Composition of Nanoemulsion formulation.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredients	%								
Apremilast (w/w)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Almond Oil (v/v)	0.3	0.3	0.3	0.2	0.2	0.2	0.1	0.1	0.1
Tween 80 (v/v)	0.525	0.525	0.525	0.525	0.525	0.525	0.525	0.525	0.525
Propylene glycol (v/v)	0.175	0.175	0.175	0.175	0.175	0.175	0.175	0.175	0.175
Methyl Paraben (w/w)	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003
Propyl Paraben (w/w)	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
BHT	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Water Q.S (v/v)	100	100	100	100	100	100	100	100	100

METHOD OF PREPARATION FOR NANOEMULSION

Preparation of aqueous phase 'A': A precisely weighed amount of propylene glycol was added to distilled water. (80^0c).

Preparation of Oil phase 'B': A weighed amount of Almond oil and tween 80 were mixed together in a heated condition, then a weighed amount of Apremilast was added, followed by the addition of methyl paraben, propyl paraben, and BHT.

Incorporation of solution 'A' in dispersion 'B': Both the phases were mixed properly with the help of High-pressure Homogenizer maintaining the respective rpm.

Preparation of gel

The weighed quantity of carbopol 934 was mixed in distilled water (40^0c) further addition of triethanolamine to maintain the desired pH range of the solution. The uniformity in the stirring was maintained and then the gel was kept in the refrigerator for 24 hrs.

Table 2: Composition of gel.

Sr. No.	Ingredients (% w/w)	Quantity
1	Carbopol 934	1%
2	Triethanolamine	0.1%
3	Water (q.s.)	100

Preparation of Emulgel

Further incorporation of nanoemulsion containing 1% drug was incorporated to obtain emulgel.

Filling to container

The formulation was transferred into previously cleaned and dry containers.

EVALUATION OF NANOEMULSION

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) is a valuable technique for examining the surface morphology of nanoemulsions. It provides detailed three-dimensional images of the particles. During analysis, samples are observed under different magnifications using a suitable accelerating voltage, commonly around 20 kV.[3]

Particle Size Analysis

The hydrodynamic particle size of the formulated nanoemulsion needs to be evaluated. Typically, dynamic

light scattering (DLS) is employed to determine the particle size and analyze the particle size distribution in nanoemulsion systems.[3]

Zeta potential measurements

The zeta potential of the nanoemulsion was measured using a Zetasizer HAS 3000 (Malvern Instruments Ltd., UK). Measurements were carried out by placing the samples in transparent disposable zeta cells. Prior to each analysis, the cuvettes were thoroughly cleaned with methanol and rinsed with a portion of the sample before introducing the fresh sample for measurement.[4]

EVALUATION OF NANOEMULGEL

Physical Appearance

Visual examination of the produced nanoemulgel formulations was done to check for color, homogeneity, consistency, and pH.[3]

Determination of pH

With the use of a digital pH meter, the formulation's pH was determined. The pH meter electrode was cleaned with distilled water before being put into the mixture to test the pH.[5,6]

Measurement of viscosity

Viscosity of the formulated batches was measured using a Brookfield Viscometer (Model RVDV-I Prime, Brookfield Engineering Laboratories, USA) equipped with spindle number 63. The sample was transferred into a beaker and allowed to equilibrate for 30 minutes at the test temperature of 25 ± 1°C prior to measurement.[5,6]

Drug content study

To determine the drug content, an analysis was performed to quantify the amount of drug in a specific quantity of the formulation. One gram of the formulation was transferred to a 10 mL volumetric flask, and methanol was added. The mixture was thoroughly shaken to ensure uniformity and then allowed to stand for 2 hours while being continuously mixed on a shaker. Afterward, the solution was filtered through filter paper to remove any particulate matter. The absorbance of the resulting filtrate was measured at 229 nm using a spectrophotometer.[5,6,7]

In-vitro Drug release study

In-vitro drug release studies of the emulgel were carried out using diffusion cells with an egg membrane. The egg membrane was carefully secured to one end of the dialysis cell's hollow glass tube. A 1g sample of the emulgel was applied to the surface of the membrane. The receptor chamber was filled with freshly prepared PBS solution (pH 7.4). The total amount of gel used helped to solubilize the drug within the tube. The receptor chamber was stirred using a magnetic stirrer. At specific intervals, 1 mL aliquots were withdrawn, appropriately diluted, and analyzed for drug content using a UV-visible spectrophotometer at a wavelength of 229 nm.[5,6,8]

Release kinetics of selected formulation

The cumulative release data were analyzed by fitting them to different kinetic models: Zero-order (cumulative % drug release vs. time), First-order (log cumulative % drug retained vs. time), and the Higuchi model (cumulative % drug retained vs. square root of time) to evaluate the drug release kinetics and mechanism.[5,6]

Accelerated stability studies of Emulgel.[4,9]

Stability studies were conducted following established guidelines. The prepared emulgels were placed in 5 g aluminum collapsible tubes and stored for three months under different conditions: 5°C, 25°C/60% relative humidity (RH), 30°C/65% RH, 40°C/75% RH, and 60 ± 2°C. Samples were taken at 15-day intervals and evaluated for physical appearance, pH, rheological properties, and drug content.[10,11]

RESULT AND DISCUSSION

Determination of (λ_{max}) of Apremilast in Methanol

The UV spectrum of Apremilast solution (100µg/ml) scanned between 400-200 nm using UV spectrophotometer exhibited wavelength of absorbance maxima at 229 nm.

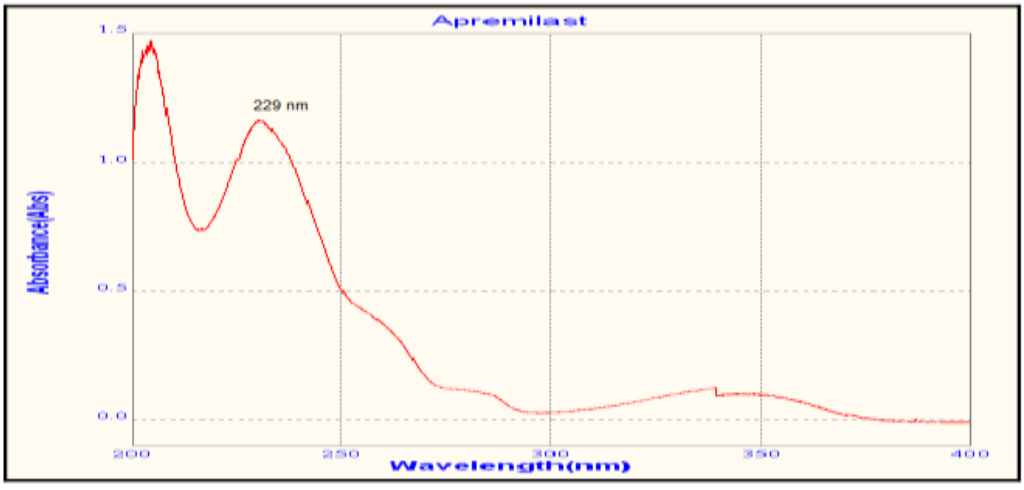


Fig 2: Ultraviolet Spectra of Apremilast in Methanol.

Calibration of Apremilast in Methanol

Apremilast calibration curve was produced in methanol because Apremilast is soluble in methanol. The drug solution in methanol was highly transparent and easily analyzed using a UV-visible spectrophotometer. The calibration curve was determined to be linear in the concentration range of 2-10 µg/ml, as shown in the table below.[12]

Table 3: Calibration Curve of Apremilast in Methanol.

Sr. No.	Conc.(ppm)	Absorbance
1	2	0.272
2	4	0.460
3	6	0.678
4	8	0.894
5	10	1.144

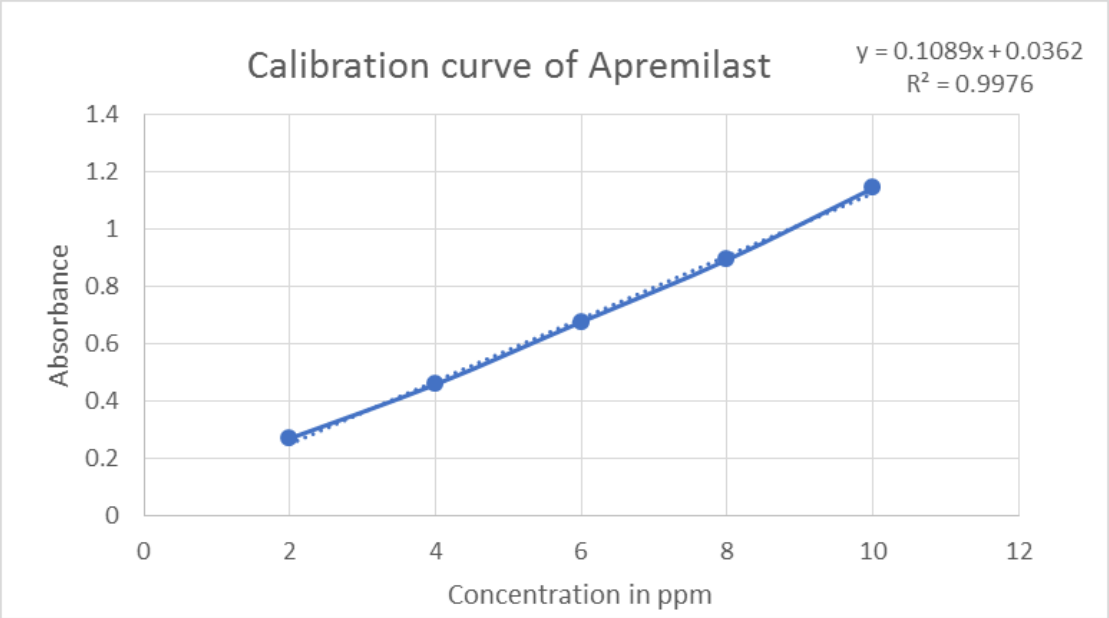


Fig 3: Calibration curve of Apremilast in Methanol.

Solubility study of drug in different oils

Table 4: Solubility of Apremilast in different oils.

Sr. No.	Oils	Solubility
1	Castor oil	10.33
2	Oleic acid	12.30
3	**Almond oil**	**31.03**
4	Liquid paraffin	9.33
5	Isopropyl myristate	20.66

Solubility determination of Apremilast in surfactants and co-surfactant

Table 5: Solubility of Apremilast in different surfactants and cosurfactant.

Sr. No.	Excipients	Solubility (mg/ml)
1	Tween 20	28.03
2	Span 20	3.02
3	Tween 80	37.33
4	Span 80	30.41
5	Propylene glycol	35.66

Fourier Transform Infrared Spectroscopy

The FTIR spectrum of Apremilast has been shown in below figure. The major peaks observed, and corresponding functional groups are given in below Table. The spectrum shows characteristic peaks for Apremilast.[13,14]

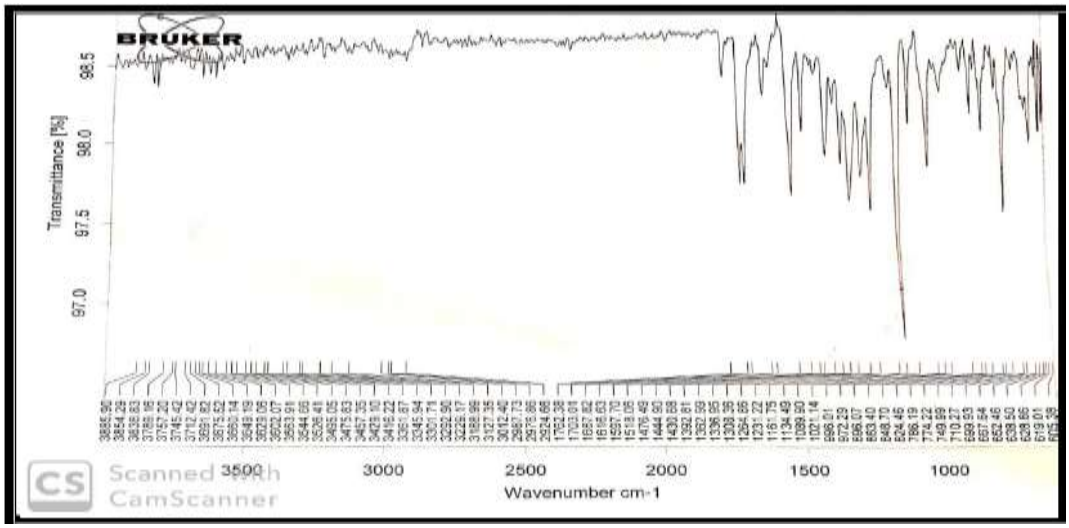


Fig 4: Representative IR spectrum of Apremilast.

The absorption bands shown by Apremilast are characteristics of the groups present in its molecular structure. The presence of absorption bands corresponding to the functional groups present in the structure of Apremilast confirms the identification and purity of the Apremilast sample used in the study.[15,16]

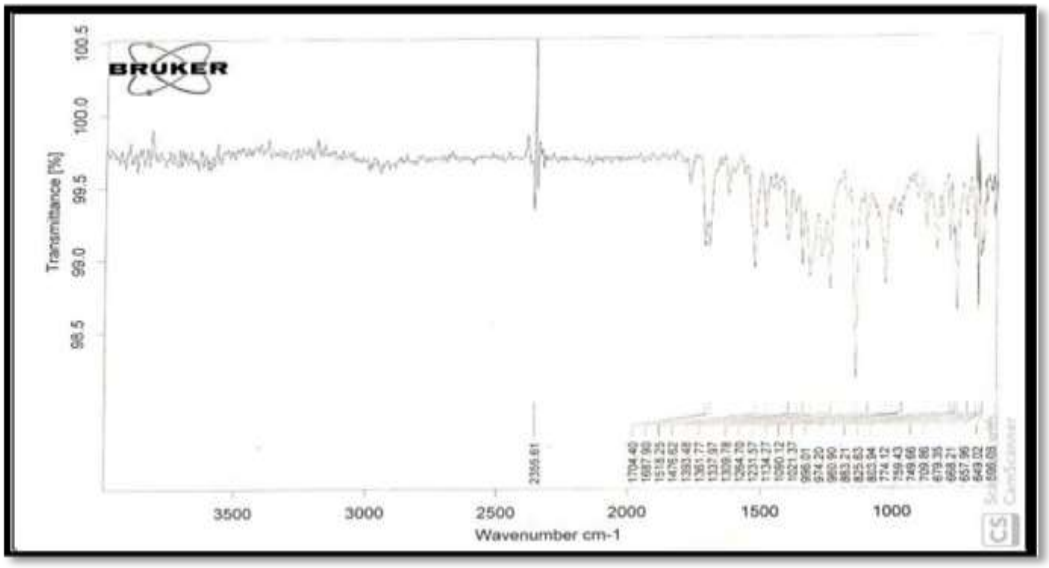


Fig 5: FTIR of Physical mixture.

Table 6: Interpretation of FTIR Spectrum of physical mixture.

Functional Group	Peaks	
	Pure Drug	Physical Mixture
NH Stretch	**Yes**	**Yes**
C=O Stretch	**Yes**	**Yes**
C-O Stretch	**Yes**	**Yes**
C-H Bending	**Yes**	**Yes**
C=C	**Yes**	**Yes**
S=O	**Yes**	**Yes**

Optimization of Nanoemulsion formulation

Table 7: Experimental design and Optimization study of In-Vitro drug release.

Formulation code	Factor X1 (Almond oil)	Factor X2 (Speed of homogenizer	Response Y1 (% in-vitro drug release)
F1	3	25000	96
F2	3	20000	90
F3	3	15000	87.42
F4	2	25000	78.94
F5	2	20000	72.09
F6	2	15000	69.99
F7	1	25000	65.05
F8	1	20000	61.19
F9	1	15000	58.45

Table 8: Analysis of variance for % in-vitro drug release.

Source	F-value	p- value Prob>F	Model significant/ Non- significant	Standard Deviation	R- squared
Model	13.61	0.0284	Significant	2.65	0.9578
A - Almond oil	1.97	0.0254			
B - Speed of homogenizer	33.95	0.0101			

The Surface response plot were analysed as shown in Figures.

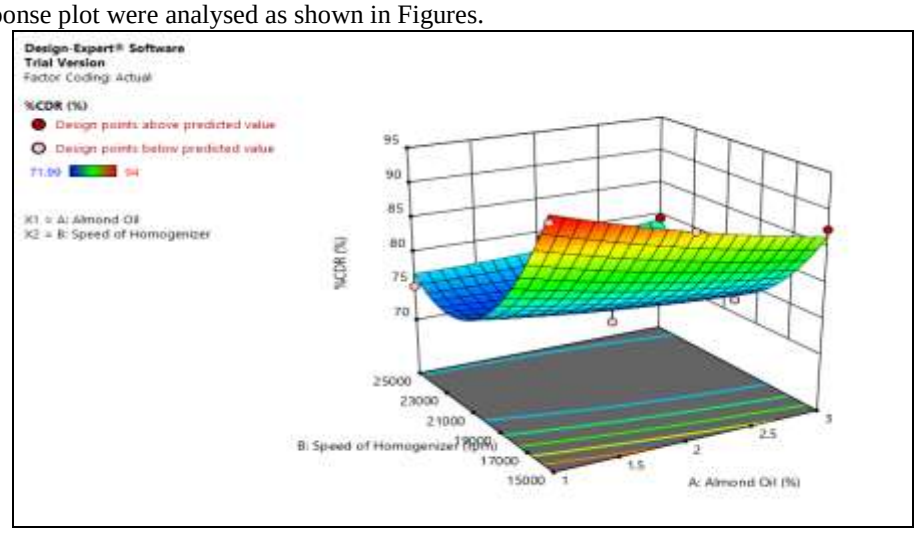


Fig 6: Surface response plot showing effect of Almond oil and speed of homogenizer on % drug release.

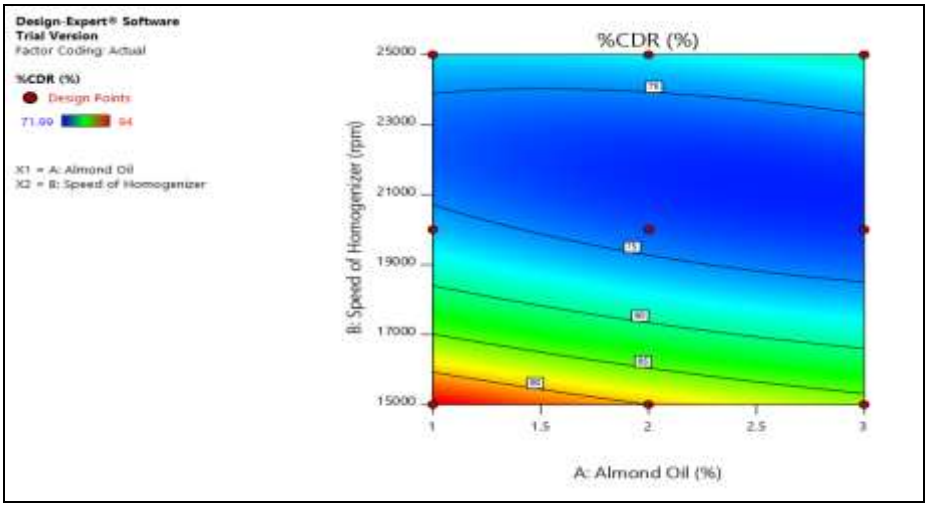


Fig 7: Counter plot showing effect of Almond oil and speed of homogenizer on % drug release.

EVALUATION OF NANOEMULSION

Scanning Electron Microscopy

Figure 8 presents the scanning electron microscopy image of the nanoemulsion. The nanoemulsion particles appeared spherical, with a size in the micrometer range. The micrograph also showed some degree of agglomeration, likely due to the evaporation of water from the formulation during sample preparation prior to SEM analysis. The particle size of the optimized nanoemulsion was found to be 100 nm. It was observed that an increase in the concentration of almond oil, along with a higher homogenizer speed, resulted in a decrease in particle size.[17-19]

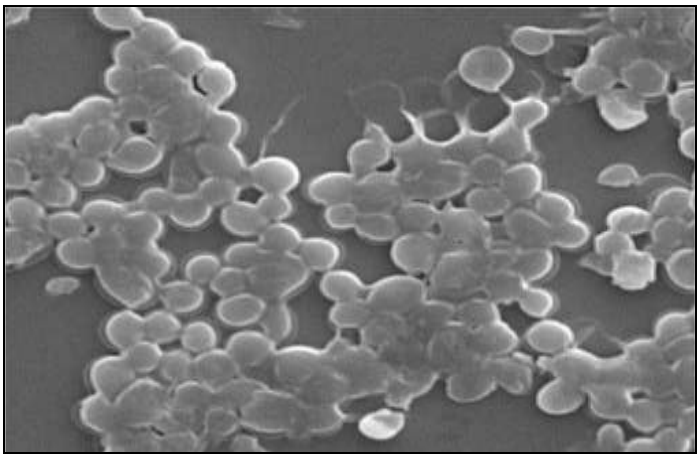


Fig 8: Scanning Electron Microscopy.

Particle size and polydispersibility index

The particle size of the optimized batch's nanoemulsion was determined to be 100 nm. It is observed that when the concentration of Almond oil increases with the speed of the homogenizer, the particle size decreases.

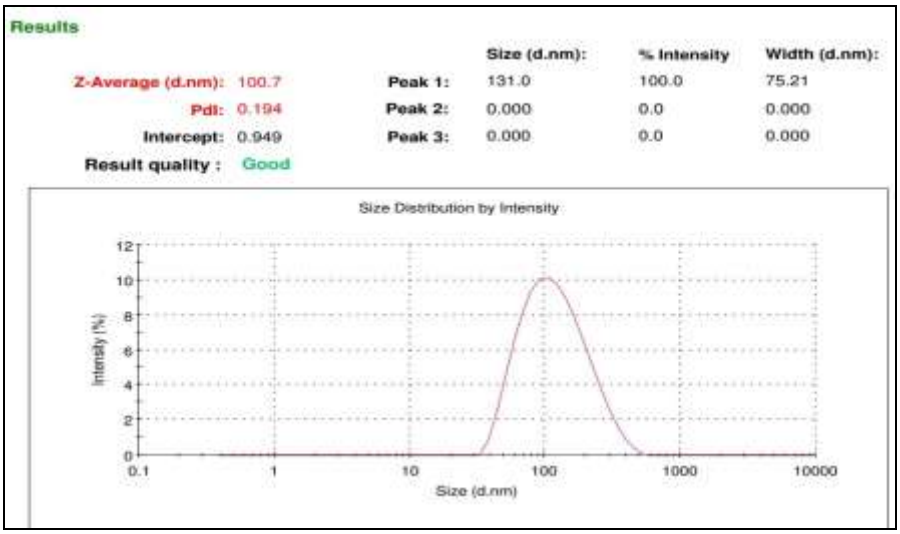


Fig 9: Particle Size of Optimized Formulation.

Zeta Potential

As per ICH guidelines for stability testing of pharmaceutical formulations, zeta potential serves as an indicator of the stability of colloidal dispersions, such as nanoemulsions, under stress conditions. The zeta potential is influenced by particle size, with the smallest particle size (around 100 nm) showing a zeta potential of -32 mV. This value suggests a degree of thermodynamic instability in the dispersion.

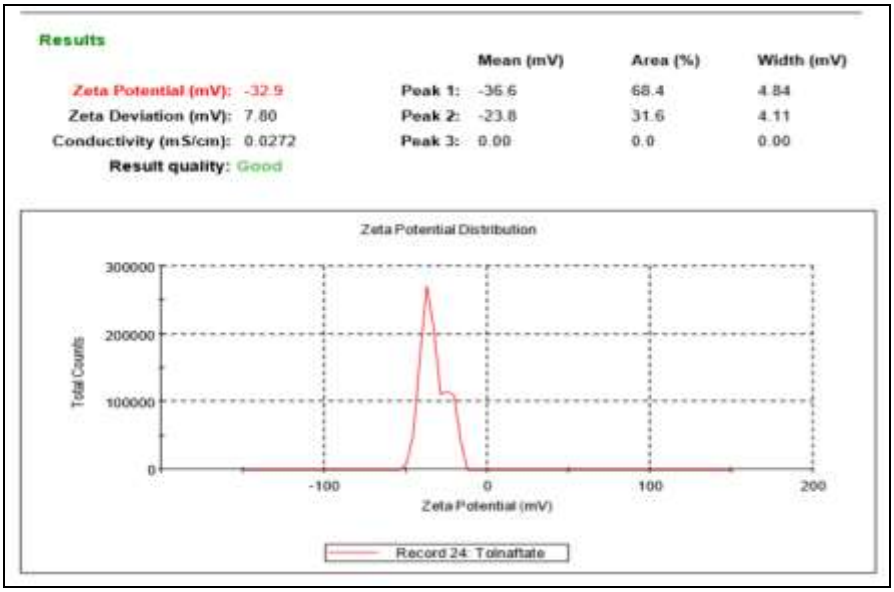


Fig 10: Zeta Potential of Optimized formulation.

EVALUATION OF NANOEMULGEL

Physical Appearance

The emulgel formulation's physical characteristics were determined to be transparent, homogenous, and consisten.[14]

pH

pH of various emulgel is shown in the following table 28 which was found to be in range of 6.31 to 6.75 pH values indicate the suitability of emulgel for topical application, so as to minimize discomfort or irritation due to acidic pH and microbial growth due to basic pH.

Viscosity

The viscosity values of formulations are shown in the Table 10.

Spreadability

Spreadability and emulgel viscosity exhibit an inverse connection. The spreadability of Formulation F1 is 17.77 gm.cm/sec, which is the formulation's ideal viscosity. Spreadability is shown in Table 11.

Drug Content

Table No. 12 displays the formulation's medication composition. All produced emulgel formulations were found to have a medication content that ranged from 64 to 96%.

In-vitro drug release

The in-vitro release of Apremilast from its various emulgel formula are represented in Table 13.

Table 9: pH values of formulation.

Sr. No.	Formulation code	Observed pH (± SD)
1	F1	6.60±0.025
2	F2	6.75±0.018
3	F3	6.55±0.011
4	F4	6.45±0.011
5	F5	6.43±0.0158
6	F6	6.33±0.011
7	F7	6.31±0.005
8	F8	6.40±0.018
9	F9	6.53±0.026

Table 10: Viscosity of formulations.

Rpm	Viscosity (cP) at Room Temperature								
	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	14960	13450	14500	13750	12500	13500	14500	13500	12000
20	14200	12390	14000	13400	12250	12440	14250	12500	11709
30	13050	12050	13445	12350	11200	12203	13900	12000	10500
40	13000	11500	12230	12010	11000	11253	12750	11500	9850
50	12350	10420	11520	11250	10950	10504	12520	11200	9230

Table 11: Spreadability values of formulation.

Sr. No.	Formulation code	Spreadability (g.cm/sec)± S.D.
1	F1	17.77 ± 0.025
2	F2	16 ±0.035
3	F3	15.38 ±0.028
4	F4	15.68 ±0.018
5	F5	15.09 ±0.032
6	F6	14.81± 0.012
7	F7	15.53± 0.012
8	F8	15.23± 0.011
9	F9	15.84 ±0.018

Table 12: Drug content of formulation.

Sr. No.	Formulation code	Drug content (%)± SD
1	F1	96±0.5
2	F2	91.91±0.7
3	F3	95±0.7
4	F4	93.91±0.7
5	F5	94±0.7
6	F6	72±0.7
7	F7	68±1.09
8	F8	82±1.07
9	F9	64.91±1.43

Table 13: Cumulative amount of Apremilast diffused (%) from all the emulgel formulations through egg membrane using Modified Franz diffusion cell.

Time hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	9	8.17	7.14	6.25	6.13	5.34	5.01	3.41	2.31
2	17	14.08	12.96	15.22	11.13	12.96	16.74	19.15	16.24
3	25	24.21	23.01	22.11	23.12	19.6	21.30	18.12	20.11
4	34	32.65	31.09	28.23	26.61	25.66	23.49	22.44	20.66
5	41	40.42	40.97	35.49	30.99	32.67	34.69	39.45	39.41
6	50	48.57	47.87	45.66	45.35	40.19	38.09	35.66	30.11
7	59	57.45	55.13	52.79	48.49	44.09	41.49	38.09	37.71
8	68	65.15	62.14	60.49	57.18	54.66	51.78	48.83	49.89
12	78	72.30	74.25	64.49	62.16	58.19	56.99	54.97	52.31
16	85	81.89	73.41	70.89	68.12	64.69	61.44	58.10	54.14
24	96	90	87.42	78.94	72.09	69.99	65.05	61.19	58.45

Drug release Kinetics

The drug release was studied in this work to determine the kinetics of the drug release mechanism. Figures 11 and 12 demonstrate the results for zero order model kinetics and Higuchi model kinetics, respectively.[20]

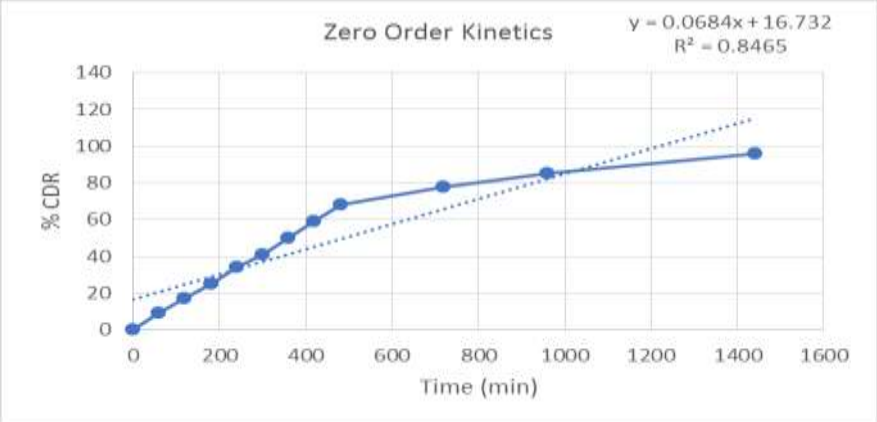


Fig 11: Model graph for comparative evaluation of Zero order Kinetics.

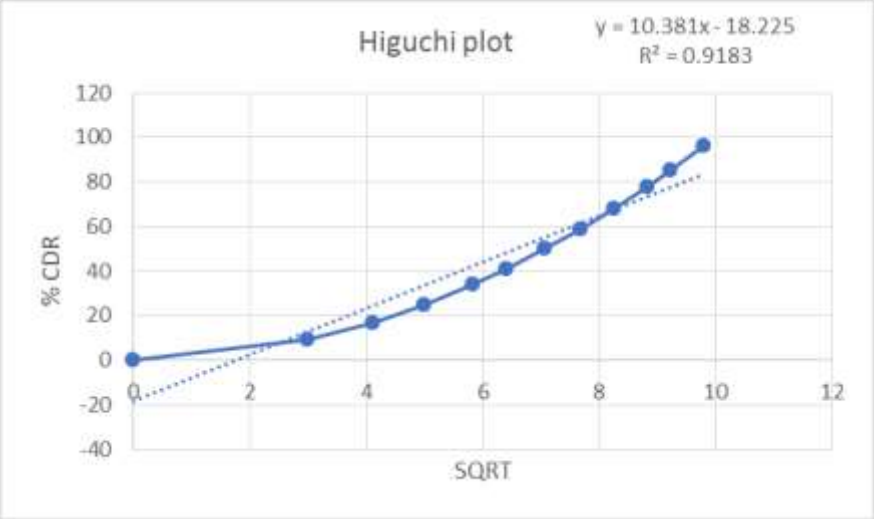


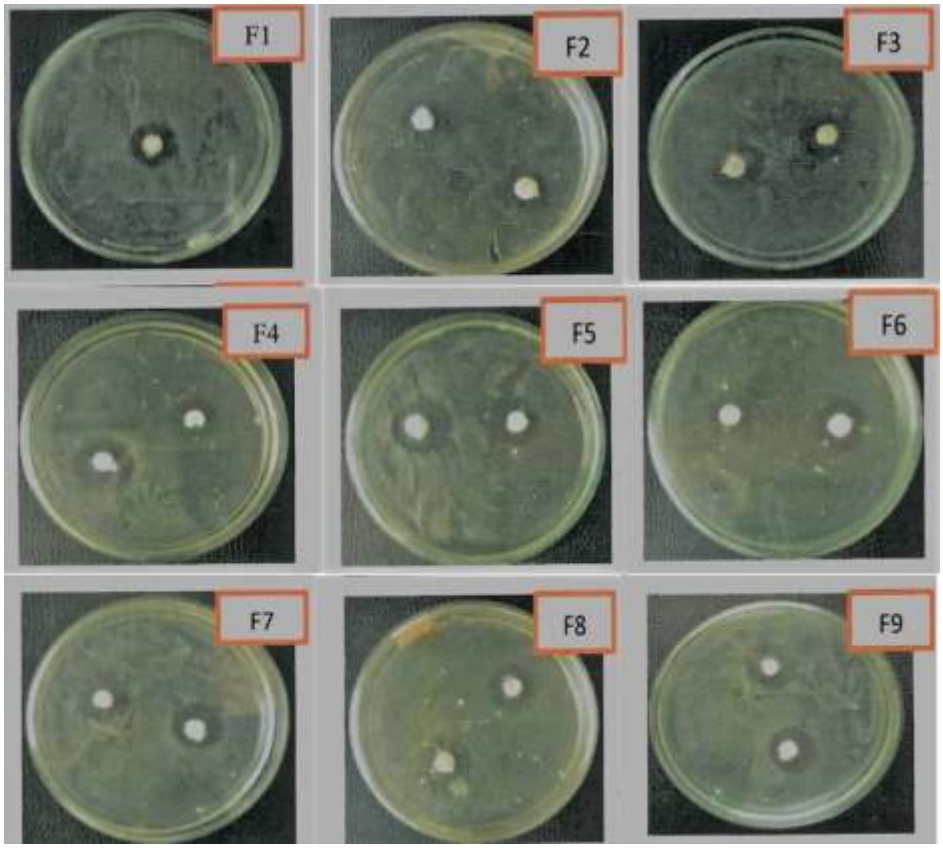
Fig 12: Model graph for comparative evaluation of Higuchi Kinetics.

Antimicrobial Activity

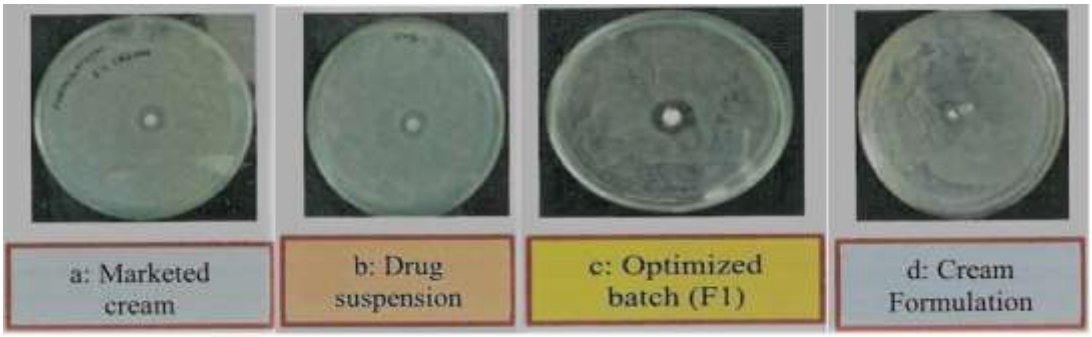
The observed zone of inhibition for Apremilast in drug suspension against Trichophyton rubrum (ATCC 28188) was 15 mm. This study demonstrates that Apremilast maintains its antimicrobial activity when incorporated into a nanoemulsion-loaded emulgel, showing effectiveness against the selected microorganism strain. Formulation F1 exhibited a zone of inhibition measuring 24 mm. The antimicrobial activity results of the formulation are presented in Table 14. The standard zone of inhibition for Apremilast in drug suspension against Trichophyton rubrum is 24 mm.

Table 14: Antimicrobial Activity of Formulation F1 to F9.

Sr. No.	Formulation code	Trichophyton rubrum
		Zone of inhibition (mm)
1.	F1	24
2.	F2	23
3.	F3	22
4.	F4	21
5.	F5	20
6.	F6	19
7.	F7	18.40
8.	F8	18
9.	F9	17
10.	0.1% Drug suspension	15
11.	Marketed formulation (Otezla cream 0.1%)	16.40
12.	0.1% Formulated cream	15



[A]



[B]

Fig 13: Zone of inhibition for all formulations (A: F1 to F9 Batches, B: Comparative study of antimicrobial activity).

Stability Study

The improved formulation was tested after accelerated storage and at room temperature. Stability experiments revealed that the formulation was stable at accelerated temperatures (40^0C± 2^0C, 75 % RH ± 5% RH). At room temperature, the stability of the optimized batch F1 was investigated.[15]

Table 15: Stability Study data for F1 formulation at Accelerated condition (40^0 C± 2^0 C, 75 % RH±5% RH).

Sr. No.	Observations		Before Stability Testing	During study 3rd month
1	Clearity		Translucent	Translucent
2	pH		6.84±0.006	6.80±0.008
3	% Drug content		96±0.5	95.97± 0.5
4	Viscosity	10	14960	14846
		20	14200	14152
		30	13050	12948
		40	13000	12794
		50	12350	12015

CONCLUSION

Prior to formulation, pre-formulation tests were conducted to characterize the drug, assess its purity, and evaluate compatibility with the excipients. The tests included evaluations of organoleptic properties, melting point, solubility, UV spectroscopy, and FTIR analysis. The Apremilast sample used in the formulation was found to be pure and compatible with the excipients. The drug-loaded nanoemulsions were assessed for particle size, polydispersity index, zeta potential, and scanning electron microscopy (SEM). The drug-loaded emulgel was further evaluated for physical appearance, pH, viscosity, spreadability, drug content, in vitro drug release (diffusion study), antibacterial activity, and accelerated stability. Following accelerated storage conditions and room temperature storage, the formulation's stability was assessed. Stability tests showed that the formulation remained stable under accelerated conditions (40°C ± 2°C, 75% RH ± 5%). The stability of the optimized batch (F1) was also evaluated at room temperature.

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