Formulation And Evaluation of Ointment Using Novel Drug Apremilast for The Treatment of Psoriasis

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Abstract

This study was undertaken to formulate and optimize a topical Apremilast ointment with enhanced drug release and suitable pharmaceutical properties for effective dermal application. Multiple ointment batches (F1–F6) were developed using different base compositions and evaluated for parameters such as visual appearance, uniformity, spreadability, drug content, diffusion characteristics, microbial contamination, and storage stability. The comparative assessment showed that formulations prepared with polyethene glycol (PEG) bases performed better than traditional oleaginous preparations, particularly in texture, ease of application, and release behaviour. Optimisation of the formulation was achieved using a two-level factorial design in Design Expert® software. PEG 400 and dimethyl isosorbide (DMI) were selected as formulation factors to assess their effects on spreadability and drug diffusion. Response surface and contour plot analyses were used to determine the optimum composition. Among the prepared formulations, batch F6 containing Apremilast (2%), PEG 400 (124%), PEG 4000 (55%), PEG 6000 (5%), and DMI (14%) demonstrated the most desirable characteristics.

The optimized ointment exhibited a smooth and uniform consistency with good homogeneity and satisfactory spreadability. Drug diffusion studies revealed a controlled and prolonged release profile, with approximately 94.6% drug release observed over a period of 8 hours. Microbiological evaluation confirmed that the formulation was free from harmful microbial growth, indicating acceptable safety for topical use. Stability studies conducted under accelerated conditions further demonstrated that the optimized formulation maintained its physical integrity and performance without noticeable changes during storage. The overall results indicate that the developed PEG-based Apremilast ointment has strong potential as a stable and efficient topical drug delivery system, capable of enhancing therapeutic efficacy and improving patient acceptability.

Keywords

Ointment, Polyethene glycol (PEG), Spreadability, Apremilast, Psoriasis

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Introduction: -

Psoriasis is regarded as an autoimmune disease in which genetic and environmental factors play a significant role. The name of the disease is derived from the Greek word „psora", which means „itch". Psoriasis is a non-contagious, dry, inflammatory and ugly skin disorder, which can involve entire system of a person [1].

Psoriasis is a chronic, inflammatory skin disease that affects 3.2% of US adults and has a substantial effect on quality of life. In addition to skin manifestations, psoriasis is associated with many comorbidities, including psoriatic arthritis, cardiometabolic disease, gastrointestinal disease, and mood disorders [2].

Treatment selection is based upon the degree and classification of PsO, in addition to patient-specific considerations such as medical history, preferences, and previous treatment outcomes. Current treatment modalities include conventional methods such as topical treatments, phototherapy, systemic medicines, and biologic medications [3].

Recent advancements in drug delivery systems have focused on improving the effectiveness, safety, and targeting of drugs in the body [4]. Recent advancements in ointment-based drug delivery systems have mainly focused on improving drug penetration through the skin and enhancing therapeutic effectiveness. Topical drug administration is a localized drug delivery system anywhere in the body through vaginal, ophthalmic, rectal and skin as topical routes [5]. A dermatological delivery system is applied to the skin by injection, spraying or dusting. The topical or dermatological preparations are applied to the skin for their physical effects, i.e. for their ability to act as skin protectants, cosmetics, lubricants, rubifacients, counterirritants, astringents, cleansing agents, keratolytics, depilatory agents, altering pigmentation, sclerosing agents, etc [6].

Ointments are homogeneous, viscous semisolid preparations, most commonly a greasy, oily (Oil-80%, Water-20%) with high viscosity that is intended for external application to skin or mucous membranes. They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purposes and where a degree of occlusion is desired. Ointments are used topically on a variety of body surfaces. These include the skin and the mucous membrane of the eye (an eye ointment), chest, vulva, anus and nose [7],[8],[9].

Apremilast, an oral phosphodiesterase-4 inhibitor, was approved by the US Food and Drug Administration in September 20141 and the Drug Controller General of India in October 2017 for the management of moderate to severe psoriasis and psoriatic arthritis [8]. Apremilast has immunomodulatory activity, which partially blocks the expression of proinflammatory cytokines and induces the expression of anti-inflammatory cytokines that have a pathogenic role in psoriasis [10],[11]. Although the efficacy and safety of apremilast have been extensively documented in clinical trials, as well as in real-world studies on the management of both psoriasis and psoriatic arthritis, little is known about its real-world use, such as the correct positioning as monotherapy and combination therapy, titration practices, and variations in dosage [12],[13].

Materials and methods:

Apremilast (Cipla Pvt. Ltd., India); chlorocresol (Loba Chemicals); propylene glycol (Merck Specialities Pvt. Ltd., Mumbai, India); glyceryl monostearate (S.D. Fine Chemicals Ltd., Mumbai, India); cetostearyl alcohol (S.D. Fine Chemicals Ltd., Mumbai, India); white wax (Loba Chemicals Pvt. Ltd., India); dimethyl sulfoxide (DMSO) (Merck Specialities Pvt. Ltd., Mumbai, India); butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) (HiMedia Laboratories Pvt. Ltd., Mumbai, India); disodium EDTA (Merck Specialities Pvt. Ltd., Mumbai, India); polyethylene glycol 400 (PEG 400), polyethylene glycol 4000 (PEG 4000), and polyethylene glycol 6000 (PEG 6000) (Clariant India Pvt. Ltd., India); dimethyl isosorbide (DMI) (Sigma-Aldrich Chemicals Pvt. Ltd., India); and purified water (in-house) were used in the study. Apremilast was employed as the active pharmaceutical ingredient, while the remaining materials were utilised as preservatives, solvents, penetration enhancers, emulsifying agents, ointment bases, antioxidants, stabilisers, humectants, and vehicles during formulation development [14, 15],[16].

Pre-Formulation Studies

Pre-formulation studies of Apremilast were carried out to assess its physicochemical properties, including organoleptic characteristics, melting point, solubility, and UV spectroscopic analysis (λmax). Drug–excipient compatibility was evaluated using FTIR and DSC techniques. Based on these findings, the formulation variables were optimized using a Design of Experiments (DoE) approach [17], [18].

Formulation and Development of Apremilast Ointment:

Various formulation batches of Apremilast ointment were prepared, and six trial batches were developed to optimize the concentrations of excipients and evaluate formulation characteristics. Accurate quantities of Apremilast and excipients were weighed according to the formulation design. The ointments were prepared using the fusion method, wherein the base components were melted under continuous stirring, followed by incorporation of the drug and other ingredients to obtain a homogeneous mixture [19],[20]. The formulations were homogenized, cooled to room temperature, and filled into suitable containers. All batches were evaluated for physical appearance, homogeneity, spreadability, consistency, and stability, and the optimized formulation was selected based on the evaluation results [21].

Table No.1: Composition of Apremilast Ointment (F1–F6)

Ingredients	F1	F2	F3	F4	F5	F6
Base Type	Oleaginous	Oleaginous	PEG-based	PEG-based	PEG-based	PEG-based
Apremilast (%) / g	1 g	2g	1g	1g	1g	2g
White Wax (g)	1.5	3	-	-	-	-
Glyceryl	7.5	15	-	-	-	-

Monostearate (g)						
Cetostearyl Alcohol (g)	7.5	15	-	-	-	-
PEG 400 (%)	-	-	10	37	62	124
PEG 4000 (%)	-	-	68	50	27.50	55
PEG 6000 (%)	-	-	5	5	2.5	5
Propylene Glycol (g)	55	110	-	-	-	-
DMI (%)	-	-	16	7	7	14
Disodium EDTA	50mg	100mg	-	-	-	-
BHA	40mg	80mg	-	-	-	-
BHT	10mg	20mg	-	-	-	-
Chlorocresol	0.075 gm	0.15gm	-	-	-	-
Water (ml)	25ml	48.65 ml	-	-	-	-

Evaluation of Apremilast ointment

Clarity

The prepared ointment was visually examined for its clarity and appearance by observing against black and white backgrounds. The formulation was checked for uniformity, smoothness, grittiness, and any sign of phase separation [22].

Odour

The odour of the ointment formulation was evaluated by sensory perception. The formulation was observed for the presence of any characteristic or unpleasant smell [23].

pH

The pH of the prepared ointment was determined using a calibrated digital pH meter. About 1 g of ointment was dispersed in distilled water and kept aside for a few minutes to obtain uniform dispersion. The pH was then measured, and the readings were recorded [24].

Spreadability

Spreadability of the ointment was determined by the glass slide method. A small quantity of ointment was placed between two glass slides, and a specific weight was applied over the upper slide. The time taken by the upper slide to move over a fixed distance was noted, and spreadability was calculated using the standard formula [25].

$$S = \frac{M \times L}{T}$$

Where:

- S = Spreadability
- M = Weight applied on the slide
- L = Length moved by the slide
- T = Time taken

Viscosity

The viscosity of the ointment formulation was measured using a Brookfield viscometer at an appropriate spindle speed and room temperature. The viscosity was recorded to evaluate the consistency and flow behaviour of the formulation [26],[27].

Drug Content: A known quantity of ointment was dissolved, filtered, and suitably diluted. The absorbance was measured at 230 nm using a UV–Visible spectrophotometer to determine the drug content of Apremilast [28].

In Vitro Diffusion Study: The in vitro diffusion study was performed using a Franz diffusion cell with a dialysis membrane and phosphate buffer as the receptor medium. Samples were withdrawn at predetermined intervals and analyzed at 230 nm using a UV–Visible spectrophotometer to determine drug diffusion [29].

Microbial Study

The microbial study of the prepared ointment was carried out to evaluate its antimicrobial activity and microbial stability. The formulation was tested against selected microbial strains using standard microbiological techniques, and the zone of inhibition was measured after incubation [30].

Stability Study: The optimized Apremilast ointment formulation was subjected to accelerated stability studies as per ICH guidelines. The formulation was stored at 40 ± 2°C and 75 ± 5% RH for one month and evaluated periodically for its physical appearance, pH, drug content, and stability characteristics [31],[32].

RESULT AND DISCUSSION

Preformulation Study

Before initiating the formulation development, it is essential to assess the identity and purity of the active pharmaceutical ingredient (API) to ensure the reliability of the process. Various analytical methods were utilized to evaluate the drug's purity and structural integrity, with the results discussed in the following sections.

Organoleptic Properties.

Table No. 2: Physical appearance of Drug

Parameters	Observed
Colour	White to pale yellow crystalline powder
Odour	Odourless or practically odourless
Taste	Slightly bitter

Texture	Fine crystalline powder

Melting Point:

Table No.3: Reported and experimentally observed melting points Apremilast of using Melting point apparatus.

Drug Name	Reported melting point	Observed melting point	Inference
Apremilast	150 - 158 °C	156.3°C	Complies with IH specifications

Solubility

The solubility study of Apremilast showed that the drug is soluble in DMI, methanol, Acetonitrile, DMSO and Acetone, while it is insoluble in purified water. These results indicate that Apremilast has better solubility in organic solvents than in aqueous media.

Determination of λ max of Apremilast

The λ-max of Apremilast was determined by spectrometric scanning using methanol as the solvent. The drug exhibited a sharp and distinct absorption peak at 230 nm, which was identified as the maximum absorbance wavelength (λ-max) of Apremilast.

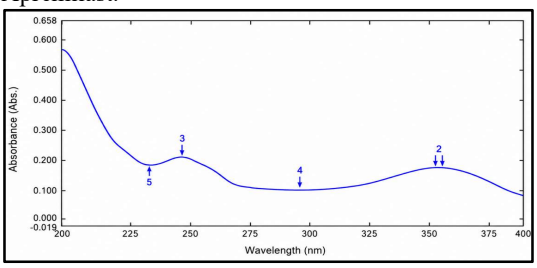


Figure No. 1: λmax of Apremilast

Table No. 4: Concentration and Absorbance value for Apremilast in Acetonitrile

Sr. No.	Concentration *µg/ml*	Absorbance λ max 230nm
1	2	0.214
2	4	0.430
3	6	0.607
4	8	0.809
5	10	1.011

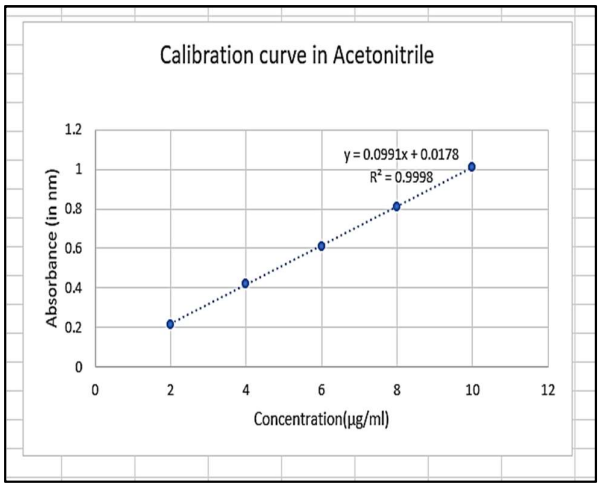


Figure No. 2: Calibration curve of Apremilast in Acetonitrile

DRUG – EXCIPIENTS COMPATIBILITY STUDY

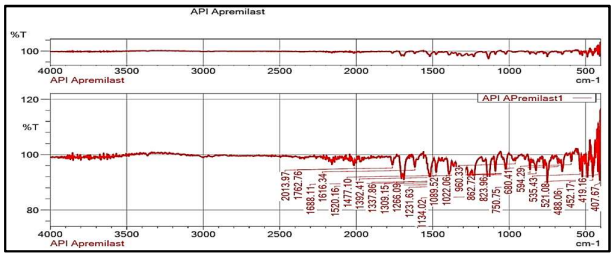


Figure No.3: FTIR spectrum of Apremilast showing characteristic functional group peaks confirming its structural identity and purity.

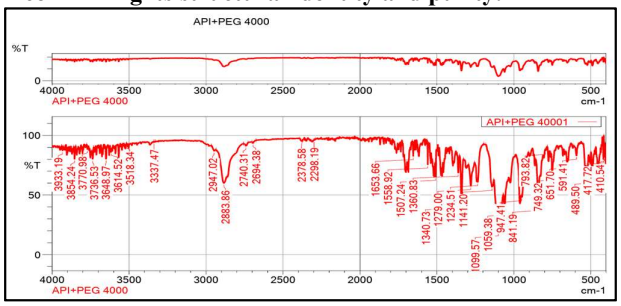


Figure No .4: FTIR spectrum of Apremilast with PEG 4000 showing characteristic functional group peaks and drug–excipient compatibility.

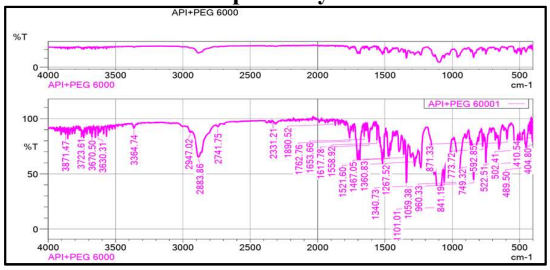


Figure No. 5: FTIR spectrum of Apremilast with PEG 6000 showing characteristic functional group peaks and drug–excipient compatibility.

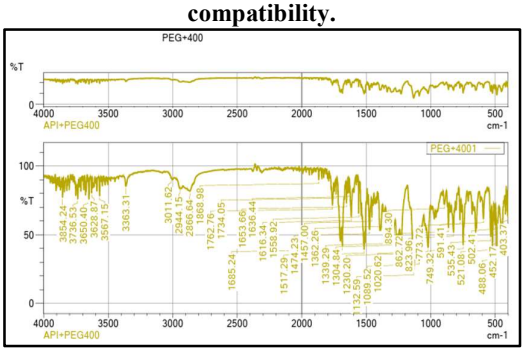


Figure No. 6: FTIR spectrum of Apremilast with PEG 400 showing characteristic functional group peaks and drug–excipient compatibility.

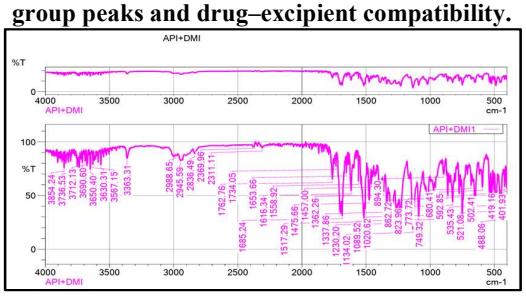


Figure No. 8.11: FTIR spectrum of Apremilast with DMI showing characteristic functional group peaks and drug–excipient compatibility.

Table No.5: Composition of drug and excipients for Physical observation (Compatibility study)

Sr. No.	Drug + Excipient	Initial Colour	After 4 Weeks
1	APR: Chlorocresol (1:0.5)	White	No Change
2	APR: Propylene Glycol (1:10)	White	No Change
3	APR: Purified Water (1:10)	White	No Change
4	APR: Cetostearyl Alcohol (1:5)	White	No Change
5	APR: Glyceryl Monostearate (1:5)	White	No Change
6	APR: White Wax (1:5)	White	No Change
7	APR: DMSO (1:5)	White	No Change
8	APR: DMI (1:5)	White	No Change
9	APR: BHA (1:10)	White	No Change
10	APR: BHT (1:10)	White	No Change
11	APR: Disodium EDTA (1:0.5)	White	No Change
12	APR: PEG 400 (1:10)	White	No Change
13	APR: PEG 4000 (1:10)	White	No Change
14	APR: PEG 6000 (1:10)	White	No Change

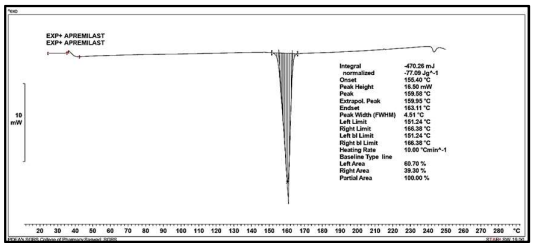


Figure No.7: DSC Curve of Physical mixture

Physicochemical evaluation of apremilast ointment formulations

All formulations (F1–F6) were white, odourless, and stable with no phase separation. F1 and F2 had a hard, gritty texture due to poor dispersion, while F3–F6 were smooth and homogenous, indicating better suitability for topical use and higher patient acceptability.

Table No.6: Physicochemical evaluation of apremilast ointment

Formulation Code	Physical appearance	Texture	Odour	Phase Separation	Homogeneity	Immediate skin feel
F1	White	Rough and Hard	Odourless	No	Homogeneous	Little grittiness was observed and no greasiness
F2	White	Rough and Hard	Odourless	No	Homogeneous	Little grittiness was observed and no greasiness
F3	Whi	Sm	Od	No	Hom	No

	te	ooth	ourless		ogeneous	grittiness or greasiness
F4	White	Smooth	Odourless	No	Homogeneous	No grittiness or greasiness
F5	White	Smooth	Odourless	No	Homogeneous	No grittiness or greasiness
F6	**White**	**Smooth**	**Odourless**	**No**	**Homogeneous**	**No grittiness or greasines**

Evaluation of Apremilast ointment

Table No.7: pH of Formulations F1–F6

Sr. No.	Formulation code	pH	Viscosity (CPS)	Spreadability g.cm/s	Drug content
1	F1	6.5	1850	2.7	NA
2	F2	6.8	1940	3.0	NA
3	F3	6.9	2280	5.0	97.3 %
4	F4	7.0	2450	6.6	97.8 %
5	F5	7.2	2750	8.1	98.0 %
6	F6	7.4	3200	9.3	98.1 %

In Vitro -Diffusion Study (optimized formulation F6)

The in vitro drug release profile of formulation F6 was evaluated over 8 hours. An initial release of 25.0% at 1 hour indicated the start of drug diffusion. This increased to 40.7% at 2 hours and 45.7% at 3 hours, suggesting ongoing availability. After 3 hours, the release rate accelerated significantly, reaching 69.6% at 4 hours, 70.3% at 5 hours, and 74.65% at 6 hours. By 7 hours, drug release was 80.04%, peaking at 94.6% after 8 hours. This profile indicates good drug availability and a controlled release suitable for topical applications.

Table No.8: *In -vitro* drug release table

Sr. No	Time (hr)	% Drug Released	% Drug Remaining	√Time	Cube Root of % Remaining (Wt)
1	1	25.0	75.0	1.000	4.22
2	2	40.7	59.3	1.414	3.89
3	3	45.7	54.3	1.732	3.79
4	4	69.6	30.4	2.000	3.14
5	5	70.3	29.7	2.236	3.10
6	6	74.65	25.35	2.449	2.96
7	7	80.04	19.96	2.646	2.72
8	8	94.6	5.4	2.828	1.76

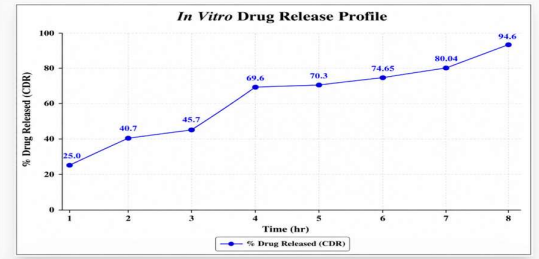


Figure No.8: In-vitro release of F6 Formulation

Table No.9: Shows microbial counts and the absence of specified pathogens, confirming the formulations are within acceptable limits for topical use.

Sr. No.	Test Parameter	Result	Limit
1	**Total bacterial counts**	40cfu/gm	NMT 100 cfu/gm
2	**Total fungal counts**	0cfu/gm	NMT 1000 cfu/gm
3	**Pathogens**		
a	**Staphylococcus aureus**	Absent	Absent
b	**Pseudomonas aeruginosa**	Absent	Absent
c	**Salmonella species**	Absent	Absent
d	**Escherichia coli**	Absent	Absent

OPTIMIZATION DATA ANALYSIS

Design of Experiments for F6 Aprimilast Ointment

To optimise F6 Apremilast ointment, a 2-level factorial design was employed using Design Expert® software (Version 8.0.7.1). Two independent variables, PEG 400 (%) (X_1) and DMI (%) (X_2), were selected to design four experimental formulations. The influence of these variables was evaluated for two dependent responses: % drug release (Y_1) and spreadability (Y_2). This statistical approach helped in understanding the effect of formulation variables and identifying the optimized composition with improved drug release and suitable spreadability characteristics.

A. Factors and Levels

Table No.10: Independent variables and their levels

Sr. No	Independent Factor	Unit	Low (-1)	High (+1)
1	PEG 400	%	27.5	124
2	DMI	%	7	14

B. Summary of Regression Analysis

All responses were fitted to multiple models using Design Expert software. Quadratic models were the best fit. The regression summary is shown in the Table.

Table No.11: Regression analysis for Y1 & Y2

Response	Model	R^2	Adjusted R^2	Predicted R^2	SD	% CV
Y1 (% Drug Release)	Quadratic	0.998	0.9976	0.912	1.25	2.10
Y2 (Spreadability)	Quadratic	0.995	0.9957	0.901	0.42	4.5

Table No.12: ANOVA for Y1 (% Drug Release)

Source	Sum of Squares	df	Mean Square	F Value	P Value	Significance
Model	145.32	3	48.44	15.12	0.028	Significant
A – PEG 400	65.87	1	65.87	20.56	0.017	Significant
B – DMI	49.45	1	49.45	15.44	0.022	Significant
Residual	9.88	1	9.88	–	–	–
Cor Total	155.20	3	–	–	–	–

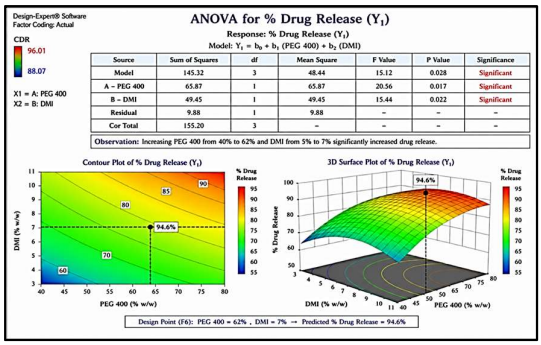
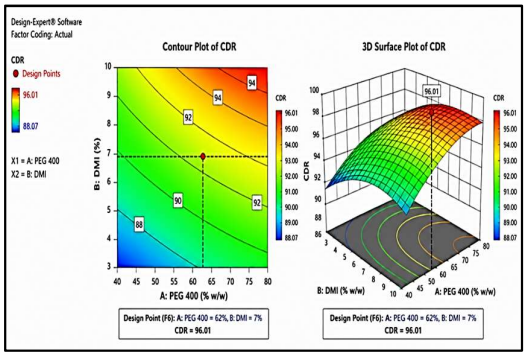


Figure No.9: Illustrates these observations: Y1 (% Drug Release): Increases with higher PEG 400 and DMI concentrations.

TableNo.13: ANOVA for Spreadability (Y2)

Source	Sum of Squares	df	Mean Square	F Value	P Value	Significance
Model	1.152	3	0.384	27.14	0.004	Significant
A – PEG 400	0.624	1	0.624	44.00	0.001	Significant
B – DMI	0.280	1	0.280	19.73	0.009	Significant
Residual	0.056	1	0.056	–	–	–
Cor Total	1.208	3	–	–	–	–



Figures No.10: Y2 (Spreadability): Improves with higher PEG 400, while DMI has a minor negative effect.

Stability Studies

The assay values across the stability conditions and time points (1 month and 2 months) remained within the ICH limit of 90.0%–110.0% of the label claim. The initial assay value was 98.1%. Under long-term conditions (25°C/60%RH), the assay values were 98.0% (1 month) and 97.6% (2 months), indicating excellent stability with negligible degradation of about 0.5%.

Table No.14: Assay (%) data of ointment formulation under different stability conditions

Time Point	Condition	Temp	Humidity	Assay

		(°C)	(%RH)	(%)
Initial	—	—	—	98.1
1 Month	Long-term	25	60	98.0
1 Month	Intermediate	30	65	97.8
1 Month	Accelerated	40	75	94.6
2 Months	Long-term	25	60	97.6
2 Months	Intermediate	30	65	97.1
2 Months	Accelerated	40	75	92.4

Conclusion

The study successfully developed an optimized PEG-based Apremilast ointment formulation (F6) with desirable pharmaceutical properties. The formulation exhibited satisfactory spreadability, controlled drug release, good physical stability, and acceptable microbiological quality. The enhanced diffusion profile and stable nature of the ointment suggest its potential as an effective topical delivery system for Apremilast. Therefore, formulation F6 may serve as a promising approach for improving topical therapy and patient compliance.

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