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Formulation, Development And Evalution Of Roflumilast Psoriasis Gel

Payal Binnar[1], Sujit A. Jadhav[2], Khanderao Jadhav[3], Rishikesh Bachhav[4], Pravin P Gadakh[5], Prajakta Thete[6], Kapil Phulwani[7]

[1]Research Scholar, Department of Pharmaceutics, KCT's R.G Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.
[2*,3]Associate Professor, Department of Pharmaceutics, KCT's R.G Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.
[4]Professor, Department of pharmacology, KCT's R.G Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.
[5]Assistant professor,Department of Pharmaceutical Quality Assurance, KCT'S R G Sapkal college of Pharmacy Anjaneri Nashik Maharashtra India
Maharashtra, India.
[6]Assistant professor,Department of pharmaceutical Chemistry, KCT's R.G Sapkal College of Pharmacy, Anjaneri , Nashik, Maharashtra ,India
7 Assistant professor, Department of pharmaceutics, KCT'S R G Sapkal college of Pharmacy Anjaneri Nashik Maharashtra India

***Corresponding Author:** Dr. Sujit Appasaheb Jadhav
*Department of Pharmaceutics, KCT's R.G Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.
Email- sujitpharma29@gmail.com,

Abstract:
Effective symptom management for psoriasis, a chronic, immune-mediated inflammatory skin condition, necessitates tailored and consistent medication delivery. The formulation, creation, and assessment of a topical gel based on Roflumilast for the treatment of psoriasis using an emulsion-based delivery system are the main objectives of this study. Roflumilast is a viable topical treatment option because it is a selective phosphodiesterase-4 (PDE4) inhibitor with strong anti-inflammatory effects. In order to improve drug solubility, stability, and epidermal penetration, an oil-in-water emulsion gel was created. The generated gel's physicochemical properties, including its drug content, pH, viscosity, and spreadability, were evaluated. In vitro drug release tests were performed to assess the formulation's efficacy.
Consistency, homogeneity, and controlled drug release were all excellent outcomes of the optimized emulgel, suggesting that it could be a successful topical treatment for psoriasis. To assess the effectiveness and safety of the treatment, more in vivo research is advised.

Keywords: *Psoriasis, Roflumilast, Emulgel, Carbopol 940.*

INTRODUCTION:

Drugs must be delivered precisely, continuously, and with little systemic side effects in order to effectively treat chronic inflammatory diseases like psoriasis. Conventional dose forms, such as tablets, capsules, and injectables, may result in systemic exposure and frequently fail to produce localized action. Because topical drug delivery systems can circumvent first-pass metabolism and enable site-specific action, they present a viable alternative, especially for dermatological disorders. Psoriasis is a long-term skin disorder caused by the immune system that is typified by keratinocyte hyperproliferation and aberrant differentiation, which leads to erythematous, scaly plaques. Even though it affects 2–5% of people worldwide, present medicines frequently only offer modest alleviation, and unfavourable formulation features make patient compliance difficult.
The creation of an emulsion-based gel (emulgel) containing Roflumilast, a strong anti-inflammatory selective phosphodiesterase-4 (PDE4) inhibitor, is the primary objective of this endeavor. The emulgel system is the perfect vehicle for topical drug delivery because it combines the benefits of gels (easier to apply, non-greasy, and more patient-acceptable) and emulsions (greater solubility of hydrophobic medicines). Creating and testing a stable, efficient, and patient-friendly Roflumilast emulgel to treat psoriasis is the goal of this study.

MATERIALS AND METHOD:

MATERIALS:

Glenmark Pharmaceuticals Pvt. Ltd. provided a complimentary sample of Roflumilast. Every additional ingredient utilized was of analytical quality.

FORMULATION OF EMULGEL:

1. Weigh out the necessary amount of Roflumilast precisely, then dissolve it in a tiny amount of isopropyl myristate (oil phase) while stirring gently to create a transparent solution.
2. To prepare the aqueous phase, disperse Carbopol 940 (per batch requirement) in a portion of purified water in a separate beaker. Then, let it hydrate for one to two hours while stirring occasionally.
3. To guarantee consistent emulsification, add the appropriate amount of Tween 80 and Span 20 to the oil phase and mix well.
4. In a separate beaker, mix the necessary amounts of propyl and methyl paraben in propylene glycol over low heat, then add to the aqueous phase while stirring constantly.
5. After the aqueous and oil phases are ready, gradually mix the two phases together while stirring constantly at high speed to create a stable emulsion.
6. After the emulsion had formed, gradually add the hydrated Carbopol dispersion while stirring continuously to create a consistent gel basis.
7. To ensure a smooth and uniform emulgel, use triethanolamine dropwise to get the formulation's pH down to 5.5–6.5. Then, use purified water to bring the final weight down to 10 g. After that, the formulation was put into the proper containers for additional analysis.

Table 1: Formulation strategy

Sr. No.	Ingredients	Quantity (gm)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Roflumilast	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
2.	Isopropyl myristate	0.5	0.5	0.5	0.75	0.75	0.75	1	1	1
3.	Carbopol 940	0.03	0.05	0.07	0.03	0.05	0.07	0.03	0.05	0.07
4.	Tween 80	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2
5.	Span 20	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
6.	Propylene glycol	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
7.	Methyl paraben	0.018	0.018	0.018	0.018	0.018	0.018	0.018	0.018	0.018
8.	Propyl paraben	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
9.	Triethanolamine	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
10.	Water	q.s. to make 10 gm in each batch								
Total weight of formulation		10 gm								

EVALUATION OF EMULGEL:

1. pH

1 gram of the gel was precisely weighed and dissolved in 10 milliliters of distilled water to measure the pH. After a gentle stir, the resulting dispersion was left to equilibrate. A digital pH meter (Labman pH system LMPH-10), which had been calibrated using standard buffer solutions of pH 4.0 and 7.0, was used to measure the pH of this aqueous dispersion. Three separate measurements were made, and the average was noted.

2. Viscosity

A Brookfield viscometer (Amtech Model Number: LVDVE) equipped with the proper spindle (spindle no. 64) was used to measure the viscosity of the produced gel. To get rid of air bubbles, 10 g of the sample was put into a dry, clean beaker and let to stand for 30 minutes. Viscosity was determined at 50 rpm and a constant

temperature of 25 ± 1°C while the spindle was submerged in the sample without touching the bottom or sides. Three separate readings were made, and the average value in centipoises (cP) was noted.

3. Spreadability test

The slide and drag method was used to assess spreadability. Two pristine glass slides were sandwiched with a predetermined quantity (0.5 g) of the gel. To create a consistent film, a 500 g known weight was put on the top slide and left there for five minutes. A line fastened to a pulley system with a sliding weight was then used to draw the upper slide horizontally. Spreadability (S) was computed using the following formula after the time required to move the top slide a predetermined distance typically 5 cm was noted:

$S = ML/T$

where,

S = spreadability.

M = Pulley-tied weight (gm)

L=moved distance (cm)

T = Time (sec)

4. Drug content uniformity:

Gel containing 10 mg of Roflumilast (about 3.34 gm) was precisely weighed and transferred to a 100 mL volumetric flask with methanol to quantify the drug content. After 30 minutes of sonication to guarantee full drug extraction, the mixture was filtered using Whatman filter paper No. 41 to create a 1000 µg/ml dilution. A 0.1 ml aliquot was put into a 10 ml volumetric flask, and the volume was adjusted with solvent to create 10 µg/ml. A UV-visible spectrophotometer was used to detect the absorbance at 251 nm using methanol as a blank. A previously established Roflumilast calibration curve was used to quantify the concentration, and the percentage drug content was computed.

5. In vitro drug release (diffusion method):

A Franz diffusion cell was used to examine the in vitro release of Roflumilast from the gel. A diffusion membrane, also known as a cellophane membrane, was positioned between the donor and receptor compartments, which made up the cell. The cellophane membrane was immersed in phosphate buffer (pH 6.8) for 24 hours before to the test. Phosphate buffer was added to the receptor chamber, which was continuously stirred and kept at 37 ± 0.5°C. The donor compartment contained roughly 3.34 grams of the gel, which is equal to 10 milligrams of Roflumilast. To maintain sink conditions, 1 mL samples were taken out of the receptor medium and replaced with new buffer at predefined intervals of 1, 2, 3, 4, 6, and 8 hours. After filtering the removed samples, a UV spectrophotometer was used to detect absorbance at 251 nm. The percentage CDR of drug release was computed and shown against time.

6. Kinetic modelling study:

A kinetic modeling analysis was conducted by utilizing a variety of mathematical models to analyze the in vitro drug release data in order to ascertain the drug release mechanism from the optimized Roflumilast gel formulation. The Franz diffusion cell study was used to first compute the cumulative proportion of medication released at predefined time intervals. Microsoft Excel was then used to fit the data into five distinct kinetic models: Zero-order, First-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas. The cumulative percentage of drug released was displayed against time for zero-order kinetics, while the log of the remaining drug was shown against time for first-order kinetics. Plotting cumulative drug release against the square root of time was used to test the Higuchi model, and plotting the cube root of the percentage of medication left versus time was used to analyze the Hixson-Crowell model. The release exponent (n), which represents the mechanism of drug release in the Korsmeyer-Peppas model, was calculated by plotting the log of the fraction of drug released versus log time. Each model's correlation coefficient (R2) was determined, and the model that best captured the formulation's drug release behavior was determined to have the highest R2 value. Understanding whether the drug release occurred as a result of diffusion, erosion, or a mix of the two mechanisms was made easier by this approach.

7.Accelerated stability studies accordance with ICH Guidelines :

To ascertain the impact of formulation additives on medication stability and the formulation's physical stability under accelerated storage circumstances, stability studies were conducted for the optimized batch. The batch that was optimized was exposed to high temperatures and humidity levels of 40 ± 2oC and 75 ± 5% relative humidity. After 90 days, the samples were taken out and examined for drug concentration, pH, and physical appearance.

RESULT AND DISCUSSION:

All the formulated batches were examined for pH determination and results were found in range of 6.39 – 6.55 which complies the limit as per literature.

The viscosity of all nine batches of the Roflumilast gel were evaluated using a Brookfield viscometer. The results showed a gradual increase in viscosity with increasing concentrations of Carbopol 940, which acts as a gelling agent in the formulation. Isopropyl myristate also influenced viscosity to a minor extent by improving the solubility of roflumilast and slightly modifying its spreadability, but its effect was less as compare to Carbopol 940. Overall, the viscosity values across batches were within an acceptable range. Results were shown in table 2.

Spredability for all the formulated batches were examined and found to be in range to be in range of 0.1 – 14.7 gm.cm/sec. As the concentration of Carbopol 940 increases the viscosity increases and it results into decrease in spreadability of formulated gel. Table 2 displayed the spreadability results.

All nine batches of the Roflumilast gel were subjected to a drug content analysis utilizing UV-Visible spectrophotometry at 251 nm. The results demonstrated that the drug content in all formulations ranged between 98.25% and 101.15%, indicating uniform distribution of Roflumilast within the formulation. The results were expressed in table 2.

Table 2: pH, Viscosity, Spreadability, Drug content

Batches	pH	Viscosity (cP)	Spreadability (gm.cm/sec)	Drug content (%)
F1	6.42 ± 0.1	4436 ± 74	14.7 ± 0.2	98.25
F2	6.39 ± 0.1	5756 ± 55	12.6 ± 0.2	98.78
F3	6.45 ± 0.1	7158 ± 65	10.9 ± 0.1	99.14
F4	6.50 ± 0.1	4270 ± 82	13.6 ± 0.2	101.15
F5	6.47 ± 0.1	5553 ± 61	12.8 ± 0.2	99.55
F6	6.52 ± 0.1	6825 ± 49	11.2 ± 0.1	98.33
F7	6.55 ± 0.1	4155 ± 78	14.2 ± 0.1	100.32
F8	6.50 ± 0.1	5326 ± 72	13.5 ± 0.2	99.14
F9	6.55 ± 0.1	6552 ± 62	10.1 ± 0.1	100.55

DETERMINATION OF DRUG RELEASE (DRUG DIFFUSION):

Examining all of the formulated batches, it was discovered that the drug diffusion ranged from 81.28 to 94.04%. The medication diffusion process also slows down with time and exhibits a prolonged impact as formulation viscosity rises and penetration enhancer concentration falls. Table 3 and Figure 1 display the formulations' in vitro drug release studies. Based on the in vitro diffusion research, formulation F7 exhibited the highest release after eight hours.

Table 3: Determination of % drug diffusion

Time (Hrs.) ↓ / Batches →	% Cumulative Drug Release (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	12.13	13.42	14.55	14.85	14.45	13.62	12.55	11.62	11.52
2	21.29	21.71	22.16	23.18	24.18	22.71	20.18	19.38	20.71

3	34.98	35.4	35.85	36.87	37.87	36.4	33.87	33.07	34.4
4	49.63	50.05	50.5	51.52	52.52	51.05	48.52	47.72	49.05
6	76.62	77.04	77.49	78.51	79.51	78.04	75.51	74.71	76.04
8	88.91	84.78	81.28	90.52	87.18	84.49	94.04	91.32	87.91

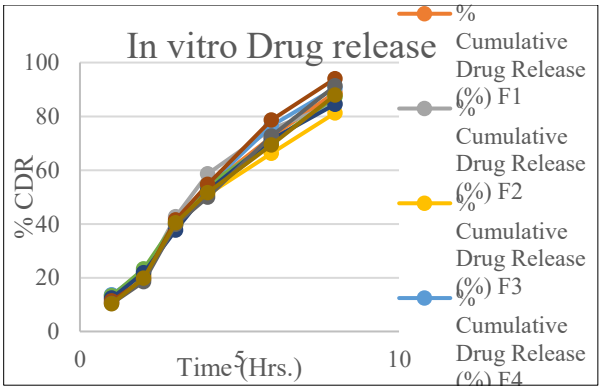

Figure 1: % CDR vs Time for drug diffusion

3. Kinetic modelling study:

The drug release mechanism from the optimized Roflumilast gel formulation (kinetic modeling study) was performed by analyzing the in vitro drug release data using various mathematical models and the results were as follows:

1. Zero Order Model:

Table 4: Zero order model for optimized batch

Time	% Drug release
1	12.55
2	20.18
3	33.87
4	48.52
6	75.51
8	94.04

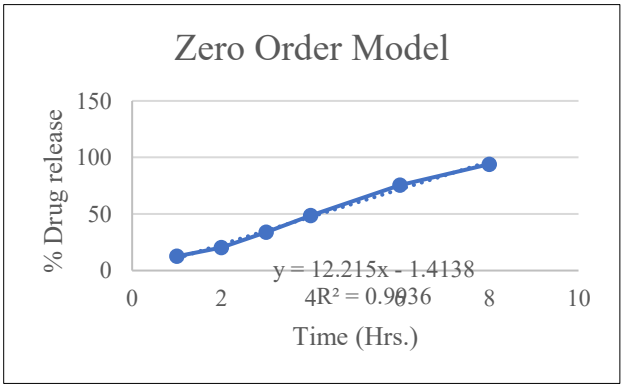

Figure 2: Zero order Model

1. First Order Model:

Table 5: First order model for optimized batch

Time	Log (% Drug release)

1	2.53
2	3.00
3	3.52
4	3.88
6	4.32
8	4.54

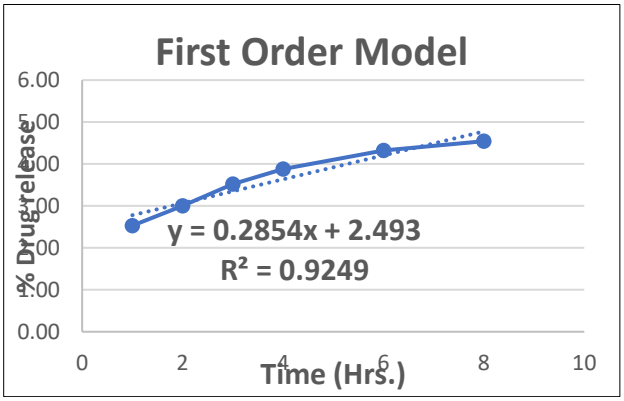

Figure 3: First Order Model

2. Higuchi Model:

Table 6: Higuchi model for optimized batch

Square root (Time)	% Drug release
1.00	12.55
1.41	20.18
1.73	33.87
2.00	48.52
2.45	75.51
2.83	94.04

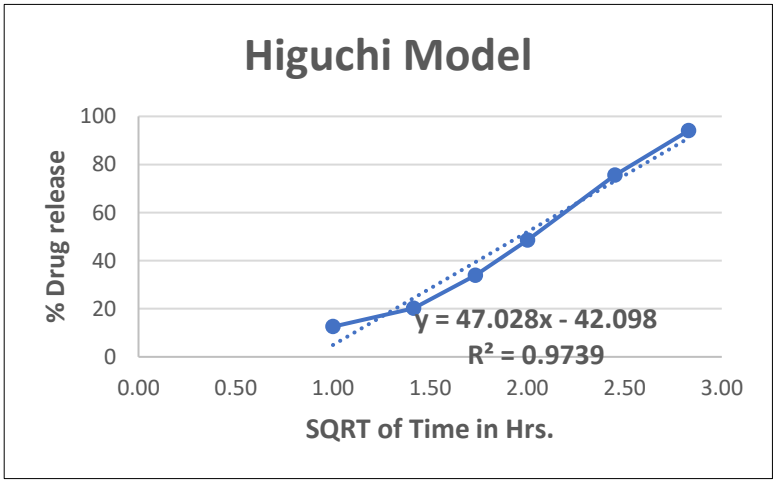

Figure 4: Higuchi Model

3. Krosmeyer-peppas Model:

Table 7: Krosmeyer-peppas model for optimized batch

Log (Time)	Log (% Drug release)

0.00	2.53
0.30	3.00
0.48	3.52
0.60	3.88
0.78	4.32
0.90	4.54

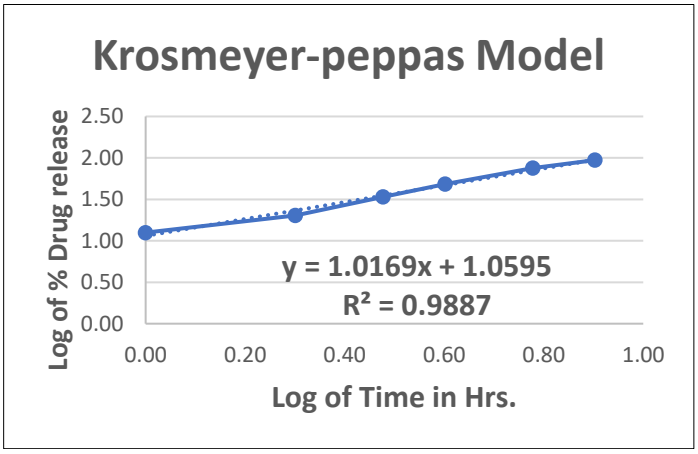

Figure 5: Krosmeyer-Peppas Model

3. Hixon Crowell Model:

Table 8: Hixon Crowell model for optimized batch

Time	Cube root of (% Drug release)
1	2.32
2	2.72
3	3.24
4	3.65
6	4.23
8	4.55

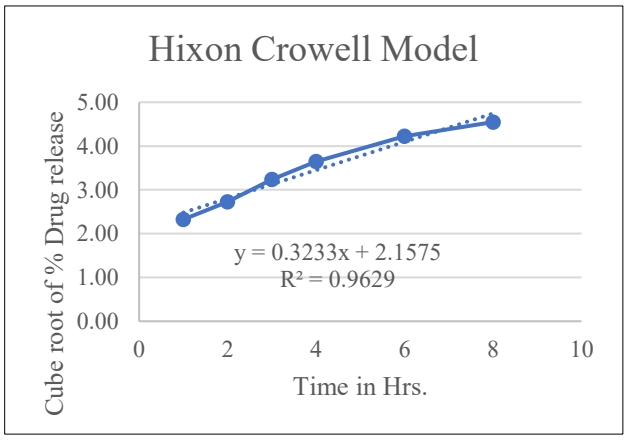

Figure 6: Hixon Crowell Model

4. Optimization of Roflumilast based gel:

Using Design Expert 7.0 software, the impact of independent variables on answers was examined. Table 9 displays the experimental design layout created for nine potential batches of Roflumilast gel. Software recommended

several models, including Linear, 2FI, Quadratic, and Cubic, which were tested for analysis of variance (ANOVA). After calculating regression polynomials for each dependent variable, one factor and perturbation graphs were produced for each dependent variable. For every single dependent variable or response (R), mathematical models were created and presented as coded equations.

Table 9: The layout of the Actual Design

Runs	Factor1	Factor 2	Response 1	Response 2
	A: % Isopropyl myristate	B: % Carbopol 940	Drug release %	Viscosity cP
1	7.5	0.5	87.18	5553
2	7.5	0.3	90.52	4270
3	5	0.3	88.91	4436
4	10	0.7	87.91	6552
5	7.5	0.7	84.49	6825
6	10	0.5	91.32	5326
7	5	0.7	81.28	7158
8	5	0.5	84.78	5756
9	10	0.3	94.04	4155

RESULTS FOR THE DRUG RELEASE:

1. **Fit Summary:**

Table 10: Fit summary table for drug release

Source	Sum of Squares	df	Square Mean	F Value	p-value Prob > F	
Mean vs Total	69419.95	1	69419.95			
Linear vs Mean	121.09	2	60.54	196.68	< 0.0001	Suggested
2FI vs Linear	0.56	1	0.56	2.19	0.1990	
Quadratic vs 2FI	0.85	2	0.42	2.90	0.1987	
Cubic vs Quadratic	0.39	2	0.19	3.76	0.3427	Aliased
Residual	0.05	1	0.05			
Total	69542.89	9	7726.99			

2. **ANOVA for Drug release:**

Table 11: ANOVA table for drug release

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	121.09	2	60.54	196.67892	< 0.0001	significant
A-Isopropyl myristate	55.82	1	55.82	181.32	< 0.0001	
B-Carbopol 940	65.27	1	65.27	212.04	< 0.0001	
Residual	1.85	6	0.31			
Cor Total	122.94	8				

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3. Fit Statistics for the Release of Drugs:

Table 12: Fit statistics for drug release

Std. Dev.	0.55	R-Squared	0.9850
Mean	87.83	Adj R-Squared	0.9800
C.V. %	0.63	Pred R-Squared	0.9641
PRESS	4.42	Adeq Precision	39.636

4. Final Formula Using Coded Drug Release Factors:

Table 13: Final equation in terms of coded factors of drug release

Drug release	=
+87.83	
+3.05	* A
-3.30	* B

5. Final Equation with Respect to Real Drug Release Factors:

Drug release = + 86.92 + 1.22*Isopropyl myristate – 16.49*Carbopol 940

6. Graphical Presentation: Diagnostics of drug release:

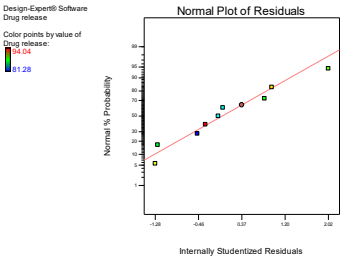

Figure 7: Normal % Probability for drug release

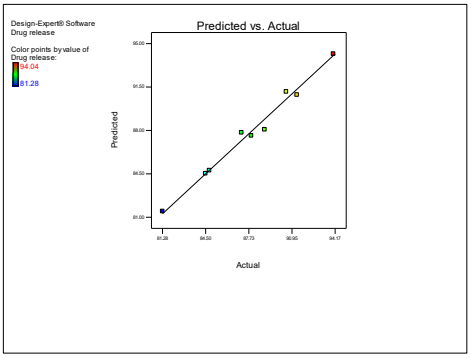

Figure 8: Predicted Vs Actual of drug release

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6. Model Graphs of drug release: One-factor Graphs of drug release

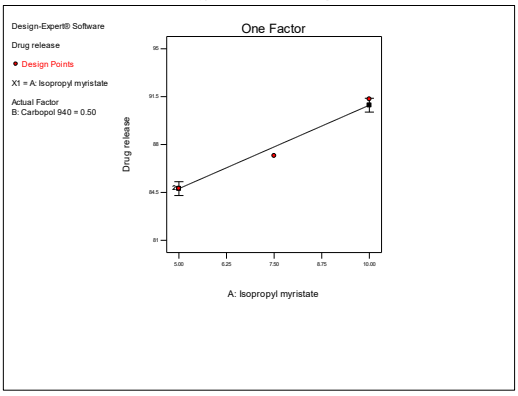

Figure 9: Effect of % Isopropyl myristate on drug release

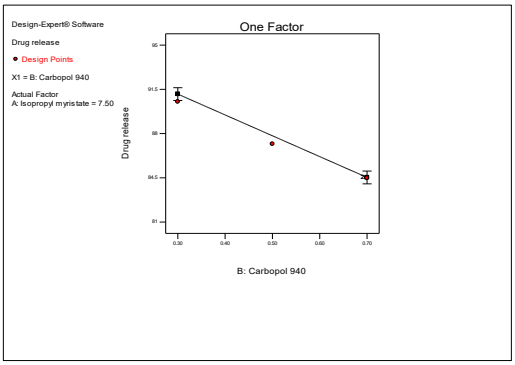

Figure 10: Effect of Carbopol 940 on drug release

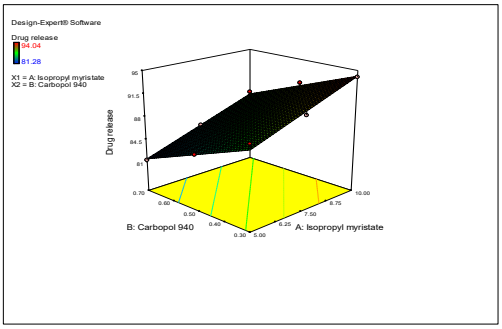

Figure 11: 3D plot for Drug release

RESULTS FOR THE VISCOSITY:

1. Fit Summary:

Table 14: Fit summary table for viscosity

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Mean vs Total	278122329	1	278122329			
Linear vs Mean	10104128	2	5052064	1064.40	< 0.0001	
2FI vs Linear	26406	1	26406	63.71	0.0005	Suggested
Quadratic vs 2FI	1303	2	651	2.54	0.2264	
Cubic vs Quadratic	68	2	34	0.05	0.9551	Aliased
Residual	702	1	702			
Total	288254935	9	32028326			

2. ANOVA for viscosity:

Table 15: ANOVA table for a viscosity

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	10104128	2	5052064	1064	< 0.0001	significant
A-Isopropyl myristate	289082	1	289082	60.91	0.0002	
B-Carbopol 940	9815046	1	9815046	2067.89	< 0.0001	
Residual	28479	6	4746			
Cor Total	10132606	8				

4. Fit Statistics for viscosity:

Table 16: Fit Statistics for viscosity

Std. Dev.	68.89	R-Squared	0.9972
Mean	5559.00	Adj R-Squared	0.9963
C.V. %	1.24	Pred R-Squared	0.9910
PRESS	90932.64	Adeq Precision	75.347

5. Final Equation in Terms of coded Factors for viscosity:

Table 17: Final equation in terms of coded factor for viscosity

Viscosity	=
+5559.00	
-219.50	* A
+1279.00	* B

6. The final equation for viscosity in terms of actual factors:

Viscosity = +3020.00 – 87.800*Isopropyl myristate + 6395.00*Carbopol 940

7. Graphical Presentation: Diagnostics of viscosity

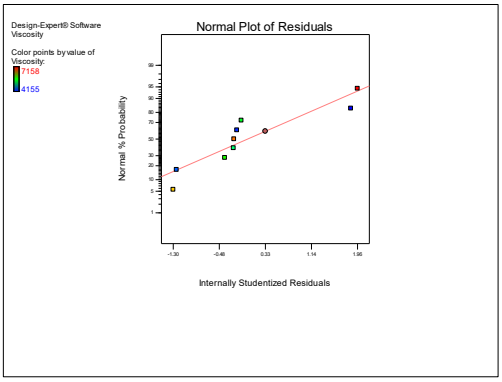

Figure 12: Normal % Probability for viscosity

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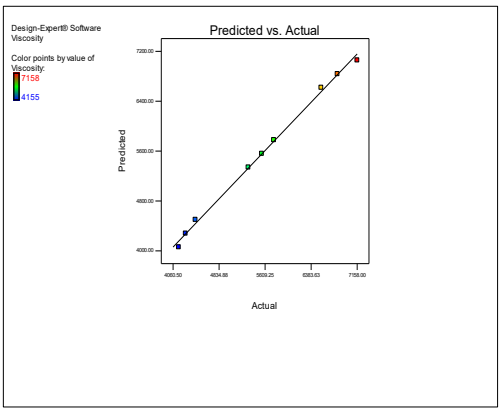

Figure 13: Predicted Vs Actual for viscosity

6. Model Graphs for viscosity: One-factor Graphs of viscosity:

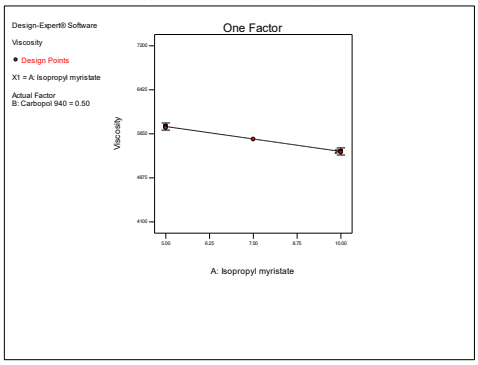

Figure 14: Effect of % Isopropyl myristate on viscosity

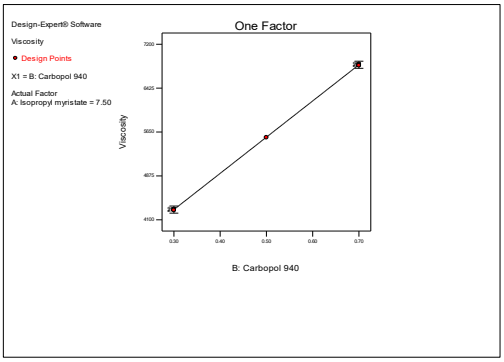

Figure 15: Effect of Carbopol 940 myristate on viscosity

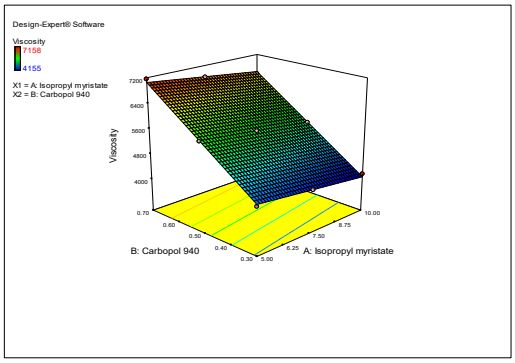

Figure 16: 3D plot for viscosity

Table 18: Summary of effect of independent variable on dependent variables

Sr. No.	Independent variables	Drug release (Diffusion)	Viscosity
1	% Isopropyl myristate in formulation	Directly proportional (As Isopropyl myristate increases, Drug release also increases)	Inversely proportional (As Isopropyl myristate increases, viscosity decreases)
2	% Carbopol 940 in formulation	Inversely proportional (As Carbopol 940 increases, Drug release decreases)	Directly proportional (As Carbopol 940 increases, viscosity also increases)

Table 19: Summary of Evaluation parameters for optimized batch

Sr.no.	Evaluation parameters	Selected batch
1.	Physical evaluation	Smooth
2.	pH	6.49 ± 0.1
3.	Viscosity	4292 ± 41
4.	Spreadability	14.0 ± 0.2
5.	Drug content	99.31%
6.	Drug release (% CDR)	95.29 %

CONCLUSION:

Using Carbopol 940 and Span 20, an optimized Roflumilast oil in water emulgel was created to improve the hydrophobic PDE4 inhibitor's distribution for topical psoriasis treatment. Strong compatibility and stability in line with available literature were validated by pre-formulation evaluations, which included organoleptic characteristics, melting point, solubility, UV spectroscopy, and FTIR.

The following important conclusions were reached after a thorough analysis of the formulations: Reliable dosage was indicated by the drug content homogeneity, which varied from 98.25% to 101.15%

• Performance was strongly impacted by formulation variables: o A higher concentration of carbopol 940 increased viscosity, which had a detrimental effect on spreadability and decreased diffusion. ·Drug diffusion was improved without sacrificing stability by raising Span 20.

• The formulation that achieved the best balance between viscosity, spreadability, and diffusion was batch F7.

• At 8 hours, sustained release with approximately 94.04% drug release was attained in vitro diffusion experiments for F7.

• Three months of accelerated stability testing revealed no appreciable alterations in performance or physical attributes, confirming robustness.

Batch F7 presents a possible substitute for traditional topical forms by exhibiting the perfect balance between rheological characteristics and release kinetics. The emulgel platform improves solubility and diffusion, extends skin contact, and may lessen the frequency of applications when compared to conventional formulations.

7. Stability study of Optimized batch (F7):

Roflumilast gel's optimum formulation batch was placed in an appropriate container and kept in a stability chamber for three months at 40 ± 20C and 75 ± 5% relative humidity. The formulation was examined for drug concentration, pH, viscosity, and physical evaluation. The ICH Q1A(R2) criteria were followed when conducting stability studies.

RESULTS:

Evaluation parameters	Results
Physical Appearance	White, Smooth
pH	6.42 ± 0.05
Viscosity	4102 ± 35
Drug content	99.36 %

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