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INNOVATIVE NANOSTRUCTURED LIPID CARRIER GEL FOR ENHANCED TOPICAL DELIVERY OF ROFLUMILAST IN PSORIASIS MANAGEMENT

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ABSTRACT

Background: Psoriasis is a chronic immune-mediated skin disorder marked by keratinocyte hyperproliferation, inflammation, and oxidative stress, causing erythematous, scaly plaques that impair quality of life. Current therapies have side effects and poor solubility, highlighting the need for improved topical delivery systems. **Methodology:** An NLC-based gel encapsulating the PDE4 inhibitor roflumilast was developed for enhanced topical delivery. NLCs were prepared by high-pressure homogenization with oleic acid, glycerol monostearate, and Tween 80, and incorporated into a Carbopol 934 gel. The physicochemical properties, encapsulation efficiency, in vitro release, and in vivo efficacy of imiquimod in imiquimod-induced psoriatic rats were evaluated. **Results:** The developed gel was homogeneous, white, and transparent, with a dermally compatible pH (5.36-5.85), optimal viscosity (3.5-14.5 Pa·s), and good spreadability (4.3-7.2 g/cm/s). Formulation F3 showed high encapsulation efficiency (90.38 ± 2.91%) and sustained drug release (~90% over 24 hours). Drug content ranged from 72% to 95%. Ex vivo skin permeation studies demonstrated enhanced roflumilast penetration. In vivo application led to a significant reduction in psoriasis area and severity index (PASI) scores from 6.5 on Day 1 to 1.6 on Day 9. No signs of erythema, edema, or rashes were observed during the 72-hour skin irritation study, confirming excellent dermal compatibility. Histopathology confirmed decreased inflammation, reduced hyperkeratosis, and restored epidermal architecture. **Discussion:** The NLC-based roflumilast gel showed favorable physicochemical and biopharmaceutical properties, offering improved delivery and sustained release over conventional psoriasis therapies. **Conclusion:** Roflumilast-NLC gel is a promising topical therapy for psoriasis with controlled release and enhanced skin retention.

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INTRODUCTION

The limitations of traditional therapeutic techniques have drawn a lot of attention to the development of innovative drug delivery systems in recent years. Although in vitro experimental results are typically promising, they are often followed by less-than-ideal results in clinical or in vivo settings [1]. These difficulties are caused by factors such as poor drug solubility, high toxicity due to widespread distribution, insufficient drug concentration resulting from rapid metabolism, and notable inter-subject variability in plasma drug levels. Drug-carrier systems at the nanoscale have been investigated as potential remedies for these problems. A potential medication delivery method is nanostructured lipid carriers (NLCs), which are made of a matrix of liquid and solid lipids. Compared to conventional carriers, NLCs have several benefits, including better solubility, greater bioavailability, improved storage stability, fewer side effects, longer half-life, and tailored tissue delivery. In particular, when applied topically, NLCs have occlusive qualities that improve skin moisture and facilitate medication absorption by dissolving or fluidizing the stratum corneum's lipid bilayers. These characteristics have made NLCs a potentially effective therapy option for long-term skin conditions, especially those caused by oxidative stress and inflammation. The quality of life is greatly impacted by psoriasis, a chronic inflammatory skin condition marked by keratinocyte hyperproliferation and immunological dysregulation that results in red, scaly plaques. Conventional therapeutic approaches, such as systemic treatments and corticosteroids, sometimes have drawbacks including unreliable effectiveness and unfavourable side effects. In order to maximize medication delivery and reduce systemic exposure, there is an increasing interest in creating tailored topical medicines [2], [3].

For the treatment of diseases like psoriasis, roflumilast, a selective phosphodiesterase-4 (PDE4) inhibitor, has demonstrated strong anti-inflammatory properties. By blocking PDE4, roflumilast raises intracellular cAMP levels, which decreases the synthesis of pro-inflammatory cytokines such as interleukin-17 (IL-17), interleukin-23 (IL-23), and tumor necrosis factor-α (TNF-α) and downregulates inflammatory pathways. Despite being licensed for chronic obstructive pulmonary disease (COPD) for a long time, roflumilast has shown promise for use in dermatology [4]. Roflumilast cream's promise as a localized therapy with fewer systemic adverse effects is demonstrated by the FDA's recent approval of the product for plaque psoriasis [5], [6]. Despite its effectiveness, roflumilast's physicochemical characteristics, such as its high metabolism and limited water solubility, make creative administration methods necessary to maximize its therapeutic potential. 60 %-70 % of the new drug molecules on the market belong to the Biopharmaceutical Classification System (BCS) class II drugs (low solubility, high permeability). Poor water solubility of these drugs restricts their oral bioavailability. Various solid dispersion techniques, such as fusion method, melting method, kneading method, co-grinding (micronization) method, co-precipitation method, lyophilization method, congealing method, hot extrusion method, solvent evaporation method, supercritical fluid method, etc. have been successfully employed to enhance the dissolution of poorly water-soluble drugs in the bio-media of the body and hence improve bioavailability [7]. This solid dispersion technology enables a fast production process of poorly water-soluble drugs via improving drug loading, wettability, removal of crystallinity, and compressibility [8]. Amalgamation of the drug moiety with a polymeric solution improves stability, solubility, and bioavailability of the drug [9].

NLCs provide a solution by increasing skin penetration, guaranteeing regulated release, and promoting drug stability through their capacity to encapsulate lipophilic medications such as roflumilast. Recent research has shown that NLC-based formulations can efficiently administer anti-psoriatic drugs, reducing systemic absorption and enhancing therapeutic results. The objective of this study is to create and describe an NLC gel loaded with roflumilast that may be used topically to treat psoriasis.

This formulation is intended to decrease systemic toxicity, improve patient compliance by reducing the frequency of doses, and enable targeted distribution to psoriatic lesions by utilizing the sophisticated drug delivery capabilities of NLCs. To determine its potential as a unique and successful treatment for psoriasis, thorough assessments of its physicochemical characteristics, in vitro drug release, skin penetration, and therapeutic effectiveness are carried out.

MATERIAL AND METHODS

Materials

Roflumilast was obtained from Zydus Life Science Ltd, Sanand, Ahmedabad, India, and Glycerol monostearate, oleic acid, tween

80, triethanolamine, and carbopol 934 were available in the Central store of Teerthanker Mahaveer College of Pharmacy, TMU. Every other chemical and solvent utilized in the research was of the caliber of an analytical reagent.

Methods

Preparation of Roflumilast-loaded NLCs-based Gel

Preparation of NLCs was done as reported previously [10], High-pressure homogenization was used to develop NLC formulations that contained roflumilast. A translucent mixture was created by carefully melting a liquid lipid and a solid lipid, and then measuring roflumilast at 70 ± 2°C while stirring constantly. Tween-80 was prepared separately by dissolving it in water at 100 °C and maintaining the temperature at 70 ± 2°C. The aqueous phase was progressively added to the lipid phase using a high-speed homogenizer that was constantly agitated at 2000 rpm. Then, to create NLCs, this mixture was run through a high-pressure homogenizer (Unigenetics Instruments Pvt. Ltd, India) at 20,000 rpm.

The resultant NLC dispersion was then gently stirred and allowed to cool for five minutes. After that, carbopol was used to manufacture the optimum roflumilast-NLC dispersion into the gel [11]. In short, Carbopol 934 was mixed vigorously with a stirrer at 500 rpm until the gelling agent was evenly distributed in the roflumilast-NLC dispersion. Triethanolamine was also used to neutralize this dispersion to create the desirable and homogenous viscous gel.

To determine the ideal concentration, two distinct concentrations of carbopol-based gels (1 and 2% w/v) were made and assessed for several factors [12].

Characterization of Roflumilast-loaded NLCS-based gel

Homogeneity

Each designed gel formulation based on Roflumilast NLCs was described for the purpose of evaluating homogeneity. This was accomplished by visually inspecting the gel after it had settled in the appropriate containers. Gels were examined to see whether any clogs were present [13].

pH

Both the direct technique and the dilution method were used to measure the formulation's pH. In the direct procedure, a pH electrode was dipped in a sample after 10g of the sample was placed in a glass vial. After it steadied, the reading was noted. 10% of the product is dissolved in purified water using the dilution process. With repeated shaking, a 10% dispersion is achieved by diluting 1g of the sample formulation with 10g of purified water. The produced dispersion was used to dip the pH electrode. After it settled, the reading was recorded [14].

Viscosity

The viscosities (Rheological analysis) of the formulations were measured using a Brookfield digital viscometer (Cone and Plate, Model 2000+ Brookfield Engineering Laboratories Incorporate, United States of America) equipped with a 25 cm3 capacity sample container. Spindle number 62 was used to test each sample, using a 100 mg bulk sample at 100 RPM for one minute. The mentioned digital reader showed the readings [15].

Spreadability

A glass slide apparatus and a wooden block were used to gauge the gels' spreadability. About 2 grams of the roflumilast gel that had been produced was added to the pan. The time it took for the upper slide to detach from the fixed slides fully was recorded. This equation was used to assess the gel spreadability: [12][13].

$$S = \frac{ML}{T}$$

Where S = spreadability, M = weight tied to upper slide, L = length of glass slide, and T = time taken by the slide to separate from.

Drug content

After weighing, 0.5g of topical nanogel was diluted in 50mL of methanol. The Roflumilast was fully dissolved in the methanol by sonicating it for fifteen minutes. Whatman filter paper was used to filter the mixture, then methanol was added to the filtrate. Drug content was determined by scanning the aliquot with a UV spectrophotometer (Shimadzu1900i, Japan) at a wavelength of 248 nm [18], [19].

In-vitro drug release

Using Franz diffusion cells, the drug release profile of the gel based on Roflumilast-NLCs was assessed for 24 hours at skin temperature and pH. A semi-permeable cellulose membrane (MW 12,000-14,000 Da) with pores sized at 2.4 nm was affixed between the donor and receptor compartments following a full night of soaking in PBS (pH 7.4). 3.14 cm2 was the surface area of the releasing membrane. After adding PBS, the receptor

compartment, which was maintained at 37±0.5°C, was agitated with a magnetic stirrer at 700 rpm. 0.5 milligrams of Roflumilast were included in 1 milliliter of Roflumilast-NLCs-based gel, which was placed in the donor area. Methanol was included as a cosolvent in the PBS within the receptor compartment to maintain sink conditions throughout the experiment.

This decision was substantiated by literature indicating that modest doses of methanol (0.5–2%) enhance the solubility of hydrophobic medicines such as Roflumilast without impairing membrane function or physiological significance. This investigation demonstrated that the incorporation of 1% methanol efficiently preserved the sink condition. From the receptor compartment, aliquots (3 ml) were extracted at regular intervals (15, 30, 45, 60 min, and 2, 4, 8, 12, 24 h).

Immediately after the volume was removed, an equivalent volume of PBS was added to replace it. Using a UV-visible spectrophotometer (UV-1900i, Shimadzu) set at 248 nm, the concentration of the drug released at different times was measured [10], [20].

IN-VIVO STUDY

Animal

This study aimed to determine whether healthy adult male Wistar rats were utilized in the antipsorasis investigation. They weighed between 150 and 200g and were between two and three months old. The rats were kept in the prescribed environment. The recommended atmosphere had a temperature range of 25±2°C and a humidity of 45–55% for 12 hours of light and 12 hours of dark. Rat pellets and water were given to the rats as part of their daily diet. The Teerthanker Mahaveer Medical College & Research Center's Institutional Animal Ethical Committee gave its approval to the project (TMMC & RC), Teerthanker Mahaveer University, Moradabad, India (CCSEA/1205/2024/ 13).

Skin irritation study

The purpose of this investigation was to ascertain whether Roflumilast NLC-loaded gel may cause skin irritation. For this investigation, albino Wistar rats were divided into three groups. To prevent variance, each group consisted of three rats. A sterile razor and hair removal lotion were used to cut the hair from a 2x2 cm2 area that had been demarcated on the body's dorsal surface. To check for any negative consequences, the animals were kept at room temperature for a full day after their hair was removed.

NLC-laden Roflumilast gel was administered to the first group, Roflumilast loaded on gel basis (control) was administered to the second group, and marketed cream was administered to the third group. According to the groups assigned, 1g of the formulation was applied to each rat, and at 24 and 72 hour intervals, the skin was checked for rashes, erythema, or edema [21].

Anti-Psoriasis Activity

Imiquimod-Induced Psoriasis Rat Model

Healthy adult male Wistar rats were selected, and each rat's dorsal region was shaved to remove any hair. Each group of the four animal groups (Table 1) had six rats. In order to cause psoriasis in all groups except group 1, 100 mg of topical Imiquimod cream (5% w/w) was administered to the animal's shaved back and right ear in succession during a 10-day period. After ten days with the formulation, the therapy will begin and last for seven days [22], [23].

Table 1: Formulation samples and animal group

Group	Details	Formulation	Animals
Group I	**Normal control**	(no disease)	6 Wistar Rats
Group II	**Negative Control**	Having Disease + Blank NLCs-based gel Formulation	6 Wistar Rats
Group III	**Standard/ Positive Control**	Having Disease + Standard Formulation	6 Wistar Rats
Group IV	**Test Control**	Having Disease + Testing Roflumilast-loaded NLCs-based gel Formulation (0.3%)	6 Wistar Rats

Scoring the severity of skin inflammation

The PASI score, vision examination of the erythema and edema, thickness of the right ear, and skin histology are used to assess the antipsoriatic formulation potential. Thickness, erythema, and scaling are the three manifestations that make up the Psoriasis Severity Index. The PASI scores are as follows: 0 for no, 1 for slight, 2 for moderate, 3 for marked, and 4 for very marked. The vernier calipers are used to measure the right ear's thickness. The

animal was euthanized 24 hours after the treatment was finished, and the skin samples (a piece of skin cut to a thickness of 4 µm) were obtained and preserved in 10% formalin before being examined under a microscope for histological analysis.

The imiquimod (IMQ)-induced mouse model of psoriasis replicates several skin characteristics and inflammatory conditions that are comparable to psoriatic inflammation in humans, such as thickening of the epidermal layer and elongation of the rate-like ridges and he condition of hyperkeratosis [22], [24].

Histopathology

Skin samples were taken from the affected areas (usually the dorsal skin) when the rats were put to sleep at the end of the experiment, and the psoriasis-like lesions had fully appeared or resolved. Immediately after, the samples were preserved for 48 hours in 10% neutral buffered formalin. Following fixation, the tissues underwent paraffin embedding processing. Samples with underlying bone (such as skin tissues) were decalcified for 4–6 weeks in a 10% EDTA solution, depending on the degree of calcification. A graded ethanol series was used to dehydrate each sample, followed by xylene clearing and paraffin block embedding. A microtome was used to create 5 µm-thick serial sections. Sections were taken such that thorough histological and histometric investigations at different tissue levels could be performed at various depths (e.g., 100 µm intervals).

Stability study

In accordance with ICH Q1A (R2) criteria, the optimized topical Roflumilast-loaded NLCs-based gel (F3) was tested for accelerated stability. To evaluate the stability of the topical nanogel, a three-month stability research was conducted in an environmental stability chamber at 25 ±2°C and 60 ±5% relative humidity. After being transferred to amber-colored glass vials, the topical nanogel was sealed and stored in the stability chamber. After three months, measurements were made of the physical appearance, homogeneity, medication content, spreadability, and pH [25].

RESULT AND DISCUSSION

Physical Examination

It was discovered that the NLC-based gel was white in color and had a distinct smell. The translucent appearance of the nanostructured lipid carriers within the gel matrix indicated their high homogeneity and uniform dispersion. Crucially, no phase separation was noted during the investigation, suggesting the formulation's exceptional physical stability. Indicating its capacity to create a protective layer on the skin, the gel's occlusive qualities may promote drug penetration and skin hydration. Furthermore, it was discovered that the formulation was washable, suggesting that it may be easily removed from the skin's surface, improving patient comfort and compliance.

pH

All formulations' pH levels were determined to be within the permissible cutaneous range (5.36 to 5.85), guaranteeing skin compatibility and lowering the possibility of irritation. The pH values of F3 (5.85±0.01) and F7 (5.36±0.02) were the highest and lowest, respectively. The narrow pH variation shows good formulation stability and consistency in the preparation process.

Viscosity

Viscosity (Rheological Analysis) measurements ranged from 3.5 Pa·S to 14.5 Pa·S, which is a significant variation. Formulations with higher viscosities, such as F2 (14.5±0.1 Pa·S) and F6 (13.4±0.4 Pa·S), may have a longer skin residence time, which could improve drug absorption. On the other hand, F3 had the lowest viscosity, suggesting that it was easier to spread but might have less skin retention. For both medicinal efficacy and patient compliance, viscosity and spreadability must be balanced.

Spreadability

For application consistency and patient acceptance, spreadability is an essential metric. The spreadability varied between 4.3 and 7.2 g·cm/sec (F2 and F7). With the highest spreadability, F7 and F6 may be simpler to apply to broader skin regions. Despite its high viscosity and drug concentration, F2 had the lowest spreadability, suggesting a thicker gel consistency that would be more difficult to apply.

Drug content

The range of the drug concentration in the gel formulations based on NLC was 72.46% to 95.43%. F8 had the most excellent drug content (95.43±1.73%) of any formulation, suggesting excellent drug entrapment effectiveness and little drug loss during formation. The drug content of formulations F2, F3, F6, and F8 was over 85%, which is advantageous for effective therapeutic administration. The lowest drug contents were found in F1 and F4, which may indicate inadequate drug loading or potential degradation during preparation.

Table 2: Characterization of gel formulations

Formulation	Drug content (%)	pH	Viscosity (Pa.S)	Spreadability (g.cm/sec)
F1	72.46±2.21	5.55±0.01	7.9±0.2	5.7±0.47
F2	85.9±3.32	5.81±0.02	14.5±0.1	4.3±0.81
F3	90.38±2.91	5.85±0.01	3.5±04	5.9±0.91
F4	75.37±3.78	5.66±0.03	6.9±0.2	5.2±0.4
F5	78.43±3.36	5.72±0.02	5.2±0.1	6.5±0.57
F6	90.99±3.11	5.54±0.01	13.4±0.4	6.8±0.69
F7	76.6±2.28	5.36±0.02	6.5±0.2	7.2±0.79
F8	95.43±1.73	5.73±0.03	7.6±0.3	5.8±0.21

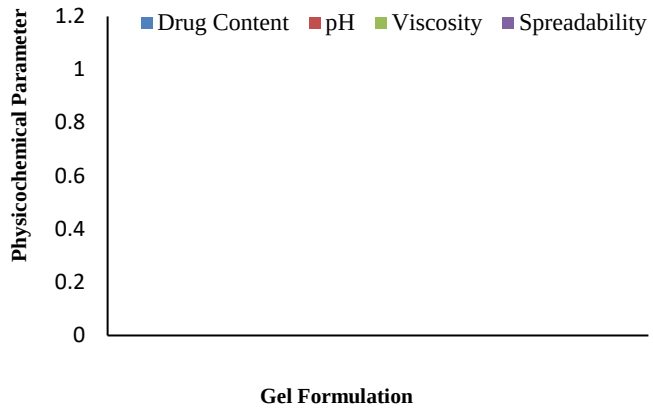

Figure 1: Graphical representation of the characterization of the Gel formulation

In-vitro drug release

In vitro drug release characteristics of eight distinct NCL-based gel formulations (F1–F8) during 24 hours (up to 1440 minutes) are depicted in the figure. The release pattern of all formulations is biphasic, with a burst release during the first 200 minutes and a slow, continuous release phase that lasts until the completion of the research. About 60% to 70% of the medication is released during the first phase by formulations F1, F2, F3, and F7, suggesting rapid drug diffusion. This could be because of surface-associated drug molecules and a more porous or weakly crosslinked gel matrix. A denser or more viscous gel matrix that prevents instantaneous diffusion is probably the cause of F4 and F8's slower initial release, with drug release values below 50%.

The majority of formulations maintain a steady release of the medication throughout time. By 1440 minutes, formulations F1, F3, and F7 attain the maximum cumulative drug release, approaching 90%, indicating potential matrix erosion and effective drug diffusion. With a cumulative release of around 85%, F2 and F5 follow closely, whereas F4, F6, and F8 exhibit a more regulated and extended release, reaching roughly 75% to 80%, suggesting stronger gel matrices or greater crosslink densities that restrict drug migration. The error bars in the graph represent standard deviation, indicating excellent data repeatability and experimental dependability. The modest discrepancies in release profiles amongst formulations suggest that gel composition, crosslinking density, and polymer content all have a substantial impact on drug release kinetics.

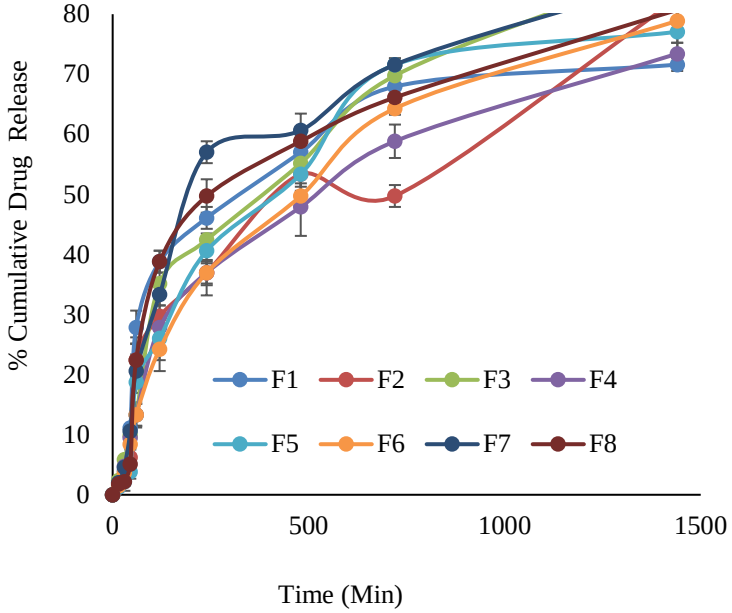

Figure 2: In vitro drug release profile

Release Kinetics

The in vitro drug release profile of the nanogel formulation was evaluated using Zero-order, First-order, Higuchi, and Korsmeyer–Peppas kinetic models. Among these, the Korsmeyer–Peppas model demonstrated the best fit (R^2=0.9945), indicating that the release mechanism follows Fickian diffusion (n = 0.1754, n < 0.45). The First-order model also showed a high correlation (R^2=0.98), suggesting that the

release rate is concentration-dependent. The Higuchi model (R^2=0.9618) further confirmed that drug release is governed predominantly by a diffusion-controlled mechanism through the gel matrix. The Zero-order model exhibited the lowest correlation (R^2=0.8401), indicating that the system does not maintain a constant release rate. Overall, the release kinetics data support a diffusion-driven, concentration-dependent drug release from the nanogel formulation.

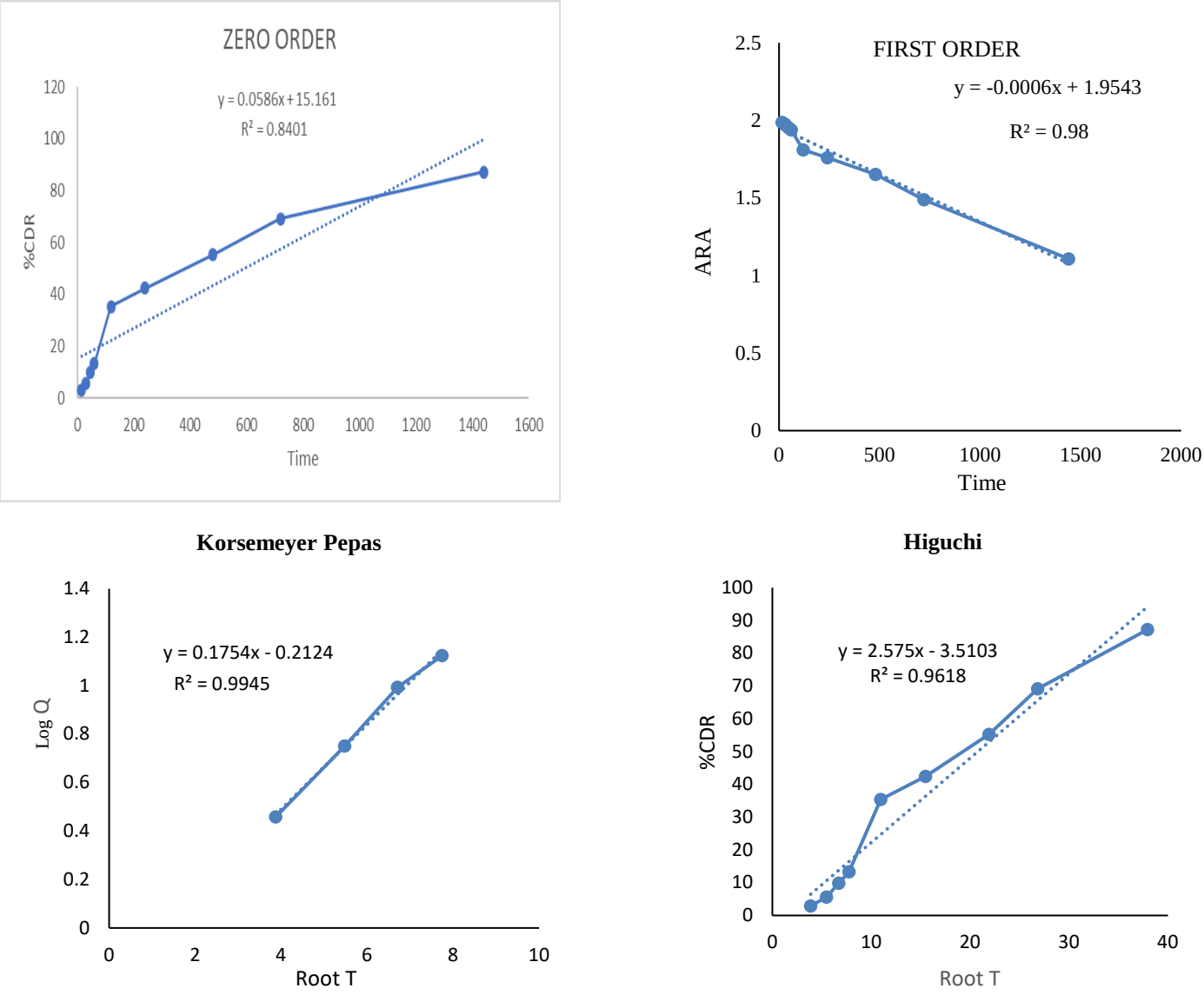

Figure 3: *In vitro* release kinetics of Optimized formulation

***IN VIVO* STUDY**

Skin Irritation Study: Topical formulations should not cause skin irritation; hence, a skin irritation test was undertaken on the improved NLC gel. There was no evidence of irritation potential, such as erythema, edema, or rashes, with the optimized NLC formulation after 24, 48, and 72 hours.

Anti-Psoriasis Activity: Based on the PASI score, the result was determined. Erythema or desquamation scores range from 0 (no sign), 1 (slight sign), 2 (moderate sign), 3 (marked sign) & 4 (immensely marked sign). After 24 hours, no symptoms of skin irritation were seen.

Following the display of the cumulative PASI score, the results were created based on the characteristic symptoms of erythema and desquamation. In comparison to the illness control group, the test control group was determined to be statistically significant.

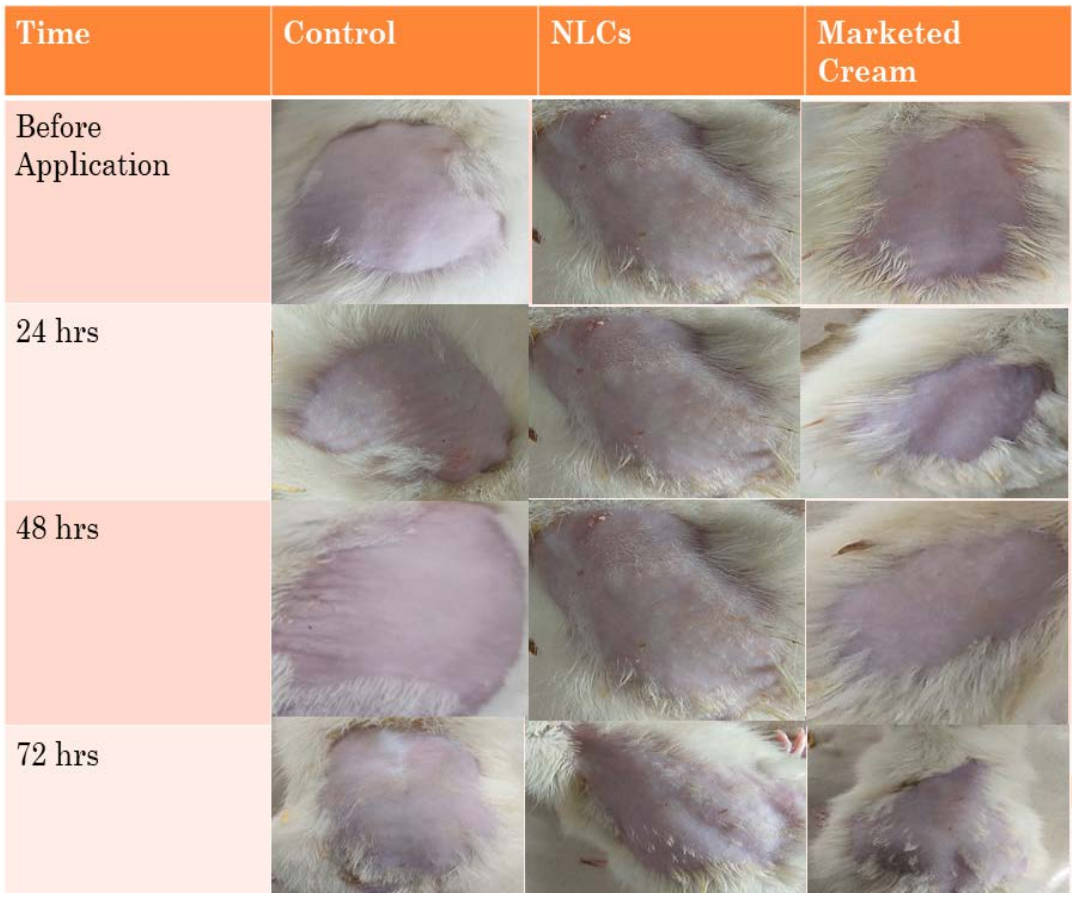

Figure 4: Skin irritation studies of roflumilast NLC-loaded gel after topical application on the dorsal side of the rat.

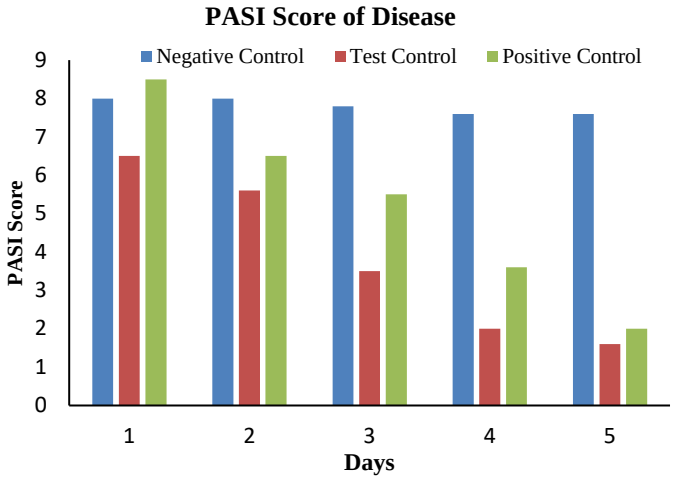

Figure 5: PASI Scores of Disease Control, Negative Control, Positive Control, and Test Control at treatment Days 1st, 3rd, 5th, 7th, and 9th. The data is analysed by using ANOVA. The dashed line represents the comparison between the disease control group and the test control group. While *p < 0.005 & **p < 0.001 indicates the statistical significance of both groups (Test control and Positive control, respectively) from the disease control group.

Table 2: PSAI score data for the negative control, Test Control, and Positive Control on different days

Day	Negative Control	Test Control	PositiveControl
1	8	6.5	8.5
3	8	5.6	6.5
5	7.8	3.5	5.5
7	7.6	2	3.6
9	7.6	1.6	2

For the in vivo investigations where the optimized formulation (F3) was used in the test control group, the optimized F3 formulation was further investigated (Figure 24). The cumulative psoriasis area and severity index (PASI) scores for each group on the first, third, seventh, and ninth days have been displayed. On the ninth day of treatment, the test control group's cumulative PASI score had significantly decreased, according to the data. While the test control group and positive control group showed a decrease in desquamation and erythema, the negative control group did not show any discernible decrease in these conditions, indicating that the blank Nano-gel formulation (F3) lacked any therapeutic moiety. Table 2 and Figure 4 illustrate that the PASI score for the test group (administered roflumilast-

loaded NLC gel) markedly decreased from 6.5 on Day 1 to 1.6 on Day 9, signifying a distinct therapeutic advantage. This was statistically significant ($p<0.005$) in comparison to the disease control group. ANOVA is used to examine the data in Figure 4. The dashed line shows the comparison between the test control group and the disease control group. However, the statistical significance of both the test control & positive control groups from the illness control group is shown by *$p<0.005$ & **$p< 0.001$, respectively.

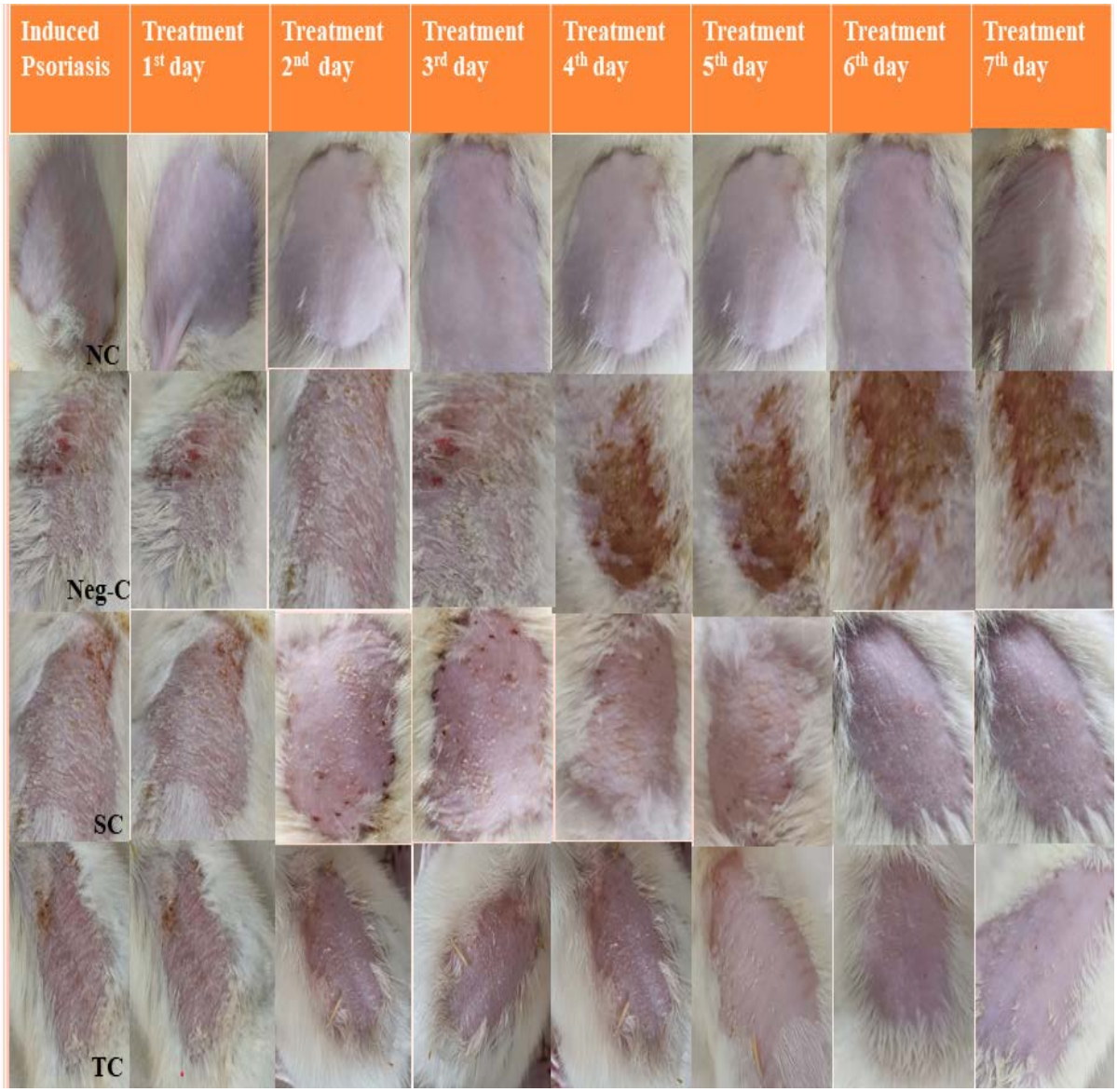

Figure 6: Representation of gross skin characteristics of rats in different groups (Normal Control, Negative Control, Positive Control, and Test Control) on Day 1 and Day 7, giving a clear visual comparison of erythema, scaling & lesion size.

Body Weight Monitoring for Systemic Toxicity Assessment

During the in vivo investigation, the body weight of all animals was documented at baseline (Day 0), mid-treatment (Day 5), and at the conclusion of the therapy (Day 9) to evaluate any potential systemic toxicity resulting from the topical administration of the formulations. All groups, including the test group administered Roflumilast-loaded NLC gel, exhibited stable body weight with no significant fluctuations in weight. This indicates that the topical therapy did not cause systemic toxicity. These data further corroborate the local safety and acceptability of the NLC-based roflumilast gel formulation.

Histopathology: A semi-quantitative grading system for essential histological criteria such as parakeratosis,

inflammatory cell infiltration, acanthosis, and epidermal hyperplasia. Each parameter was evaluated on a scale ranging from 0 to 3, as shown below: 0 denotes Absent, 1 signifies Mild, 2 indicates Moderate, and 3 represents Severe. The normal control group showed no symptoms of keratosis, indicating undamaged and normal skin. The negative group demonstrated hyperkeratosis and parakeratosis indications, which might be linked to increased skin sensitivity, implying disease induction. The standard formulation-treated group exhibited few mild and parakeratosis symptoms. In contrast, the Roflumilast-NLC gel-treated group showed normal skin with very light keratosis, likely due to the greater penetration and gradual release of the NLC gel. (10X, with Hematoxylin and Eosin (H&E).

The histological investigation of skin sections from four groups, Normal Control, Negative Control, Standard Control, and Test Control (treated with roflumilast-loaded NLC gel), sheds light on the structural alterations related to psoriasis and its treatment. In the Normal Control group, the skin had intact epidermal and dermal architecture, no evidence of inflammation, keratinocyte overgrowth, or edema, and no keratosis or hyperkeratosis, indicating healthy skin morphology.

The Negative Control group, on the other hand, which was psoriasis-induced and untreated, showed notable pathological alterations, such as acanthosis, thickness of the stratum corneum, and considerable epidermal hyperplasia, all of which were signs of severe keratosis. Psoriatic diseases are characterized by dilated blood vessels and inflammatory cell infiltration in the dermis. In comparison to the Negative Control group, the conventional Control group, which received conventional treatment, showed mild to severe keratosis and decreased epidermal thickness. Reduced inflammation and a discernible improvement in skin structure point to the therapeutic benefit of conventional therapy. After receiving treatment with roflumilast-loaded NLC gel, the Test Control group displayed a restoration of normal epidermal structure with very little keratosis. Compared to the Negative Control group, the dermis showed less inflammation, edema, and vascular congestion. Overall, the Test group's skin morphology was quite similar to the Normal Control group's, suggesting that their psoriatic symptoms had significantly improved.

In summary, by considerably enhancing the histological characteristics of psoriatic skin, the roflumilast-loaded NLC gel showed significant therapeutic efficacy that was both superior to untreated skin and comparable to standard treatment. Effective medication delivery, decreased inflammation, and skin structure normalization were probably facilitated by the nanostructured lipid carriers' improved penetration and sustained release capabilities. These findings lend credence to the possibility of NLC-based gel formulations as a minimally harmful topical treatment for psoriasis.

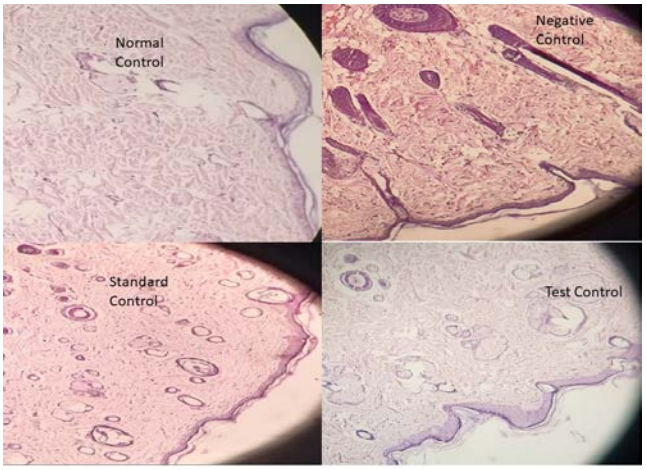

Figure 7: Representation of histopathological characteristics of rats' skin in different groups. (A) Normal Group (B) Negative Control Group (C) Test Control Group (D) Positive Control Group [standard], Images captured at 10× magnification, stained using Hematoxylin and Eosin (H&E).

Stability Study

In the stability study, we conducted routine physical inspections of the improved formulation (F3) over a 3-month duration under ICH-recommended settings (25 ± 2°C / 60 ± 5% RH and 40 ± 2°C / 75 ± 5% RH). The gel retained a white and smooth appearance, with no alterations in color or odor noted over the research period, signifying the lack of visual or olfactory indicators of deterioration. The in vitro drug release profiles for the freshly manufactured formulation (F3) do not expressly address release patterns upon storage. Nonetheless, the drug conc. consistently remained elevated (95–98%) after 3 months under both storage settings (Table 3), indicating little degradation & probable retention of drug release properties. Each batch was assessed according to the evaluation criteria. Batch F3 underwent a 3-month stability test after being optimized based on the maximal release being displayed in 24 hours. Table 3 shows the results for the first, second & third months, respectively. The Nanogel formulation of Roflumilast, which was exposed to 25°C/60% RH & 40°C/75%RH for 3

months, demonstrated good stability, according to the stability study result.

Table 3. Stability studies result of optimized (F3) formulation

Stability Period	25 ± 2°C/ 60 ± 5% RH				40± 2°C/75 ± 5% RH			
	pH Value	Spreadability	Physical appearance	Drug Content	pH Value	Spreadability	Physical appearance	Drug Content
Initial	5.59	5.01	White smooth Cream	94.98%	5.59	5.52	White smooth Cream	95.90%
1st Month	5.53	5.01	White smooth Cream	94.23%	5.67	5.89	White smooth Cream	97.21%
2nd Month	5.63	5.12	White smooth Cream	97.74%	5.50	6.12	White smooth Cream	98.20%
3rd Month	5.67	5.89	White smooth Cream	95.78%	5.62	6.12	White smooth Cream	96.31%

CONCLUSION

This study effectively developed and characterised a nanostructured lipid carrier (NLC) based gel for the topical administration of roflumilast, intended to enhance therapeutic outcomes in psoriasis. The optimised formulation exhibited exceptional physicochemical stability, skin compatibility, elevated drug encapsulation, and prolonged drug release over a 24-hour period. *In vivo* results showed a significant improvement in PASI scores, less inflammation, and standard epidermal architecture without any signs of skin irritation. This was backed up by histopathological analysis. According to a study, NLC-based gel can get around common drawbacks of traditional topical and systemic psoriasis treatments, such as frequent dosing, systemic side effects, and poor drug penetration. The work's dependence on preclinical models, however, limits it. To verify translatability in human subjects, more clinical trials are necessary.In the current context, where there is an increasing need for targeted, safe, and patient-friendly dermatological therapies, this nanocarrier-based approach represents a significant advancement. For chronic skin conditions like psoriasis, it provides a potentially superior alternative to corticosteroids and immunosuppressants, and it aligns with current development in personalised therapy.

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FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

The study was conceptualized and designed by Abhishek Singh, who also performed the experimental procedures, gathered and analyzed the data, and drafted the initial version of the manuscript. Anurag Verma and Prashant Kumar provided support in developing the methodology, oversaw the progress of the project, contributed to data interpretation, and thoroughly revised the manuscript for critical intellectual content. All authors have reviewed & approved the final manuscript & take full responsibility for the integrity & accuracy of the work.

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