RESEARCH PAPER

In Vivo Anti-Psoriatic Activity and Dermal Safety Evaluation of Optimized Topical Halobetasol Propionate Systems in an Imiquimod-Induced Rat Model

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ABSTRACT

Psoriasis is a chronic immune-mediated inflammatory skin disorder requiring long-term topical therapy, where safety and effective dermal drug delivery remain major challenges. The present study aimed to evaluate the in-vivo anti-psoriatic activity and dermal safety of previously optimized microemulsion and microsponges loaded topical Halobetasol propionate systems in comparison with a marketed gel using an imiquimod-induced psoriasis model in rats. Dermal safety was initially assessed through an acute dermal irritation study in accordance with OECD 404 guideline. Psoriasis-like lesions were induced by topical application of imiquimod, followed by treatment with optimized topical systems and the marketed formulation. Anti-psoriatic efficacy was evaluated using Psoriasis Area and Severity Index (PASI) parameters, including erythema and skin thickness, along with histopathological examination of skin tissues. Dermal toxicity assessment demonstrated no evidence of erythema, oedema, or corrosive reactions, indicating good dermal tolerability of the optimized topical systems. In the imiquimod-induced psoriasis model, treatment with optimized formulations resulted in a marked reduction in PASI scores and epidermal thickness compared with disease control animals. Histopathological evaluation further confirmed restoration of normal skin architecture, with reduced hyperkeratosis and inflammatory cell infiltration. The therapeutic response observed with the optimized systems was better than the marketed conventional Halobetasol gel.

Keywords: Psoriasis; Halobetasol propionate; Imiquimod-induced psoriasis; In vivo evaluation; Dermal toxicity; Topical delivery.

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1. INTRODUCTION:

Psoriasis is a chronic, immune-mediated inflammatory skin disorder distinguished by epidermal hyperproliferation, altered differentiation of keratinocytes, and infiltration of activated T cells (Th1/Th17) releasing pro-inflammatory cytokines such as IL-17, IL-22, and TNF-α. These cytokines perpetuate a pathological feedback loop between keratinocytes and immune cells, leading to thickened, erythematous, and

scaly plaques characteristic of psoriatic lesions. The dysregulated synergy between IL-17 and TNF-α plays a central role in driving epidermal proliferation and sustained inflammation in psoriasis (e.g., synergistic cytokine interaction in keratinocytes contributes significantly to disease pathogenesis).[1-3]

The pathophysiology of psoriasis involves a complex interplay between innate and adaptive immunity. Antigen-presenting cells activate naïve T cells, prompting differentiation into Th17 and Th1 subsets, which release IL-17 and IFN-γ. These cytokines induce keratinocytes to proliferate rapidly and produce additional inflammatory mediators, including IL-6, IL-8, and chemokines that recruit more immune cells into the skin. This cycle exacerbates skin thickening and plaque formation.[3]

Conventional topical corticosteroids (TCS) have been the mainstay first-line therapy for mild-to-moderate plaque psoriasis because of their potent anti-inflammatory, immunosuppressive, and antiproliferative effects. They reduce local cytokine production and vascular dilation, providing symptomatic relief. TCS molecules such as clobetasol and Halobetasol have been widely prescribed due to their efficacy in attenuating psoriatic inflammation and keratinocyte hyperplasia.[4]

Despite their clinical utility, conventional topical corticosteroids have notable limitations. In addition to side effects, traditional gel, cream, and ointment bases often suffer from poor skin penetration and insufficient drug retention at the disease site. The hyperkeratotic and thick stratum corneum of psoriatic lesions acts as a formidable barrier, reducing the percutaneous absorption of therapeutic agents and diminishing their clinical effectiveness. This barrier, combined with the complex physicochemical environment of the diseased skin, results in suboptimal drug delivery using conventional vehicles.[5]

The need for improved dermal delivery and safety has driven extensive research into advanced topical delivery technologies Advanced topical delivery systems have been explored to enhance localized drug action and improve therapeutic outcomes. In earlier studies, optimized Microemulsion-based gel (MEBG) and Microsponge-based gel (MSBG) systems of halobetasol propionate were developed and characterized.[6-7] Building on those findings, the present study focuses exclusively on the in-Vivo anti-psoriatic efficacy and dermal safety evaluation of these optimized systems in comparison with a marketed halobetasol gel using an imiquimod-induced psoriasis rat model.

Collectively, there remains a significant clinical need for safer, more effective topical therapies for psoriasis that combine potent anti-inflammatory action with improved dermal delivery and minimized risk of local or systemic side effects. The present investigation aims to address this gap by evaluating the therapeutic performance and safety profile of optimized topical halobetasol propionate systems in a validated in vivo model.

2. MATERIALS AND METHODS

2.1 Material and test systems

Halobetasol Propionate was purchased from Clickchem research lab., Ankleswar. Commercially procured IMQ cream (5%) (Imiquad; Glenmark). HPMC K 100M was supplied by Loba Chemie Pvt. Ltd. (Mumbai, India). All the other chemicals used for formulation development were of analytical grade.

Experimental Animals

Female Wistar rats aged 7–9 weeks and weighing 180–210 g were used for the present study. Animals were obtained from an approved animal breeding facility and were specific pathogen free (SPF) at the time of arrival and were maintained under good conventional hygienic conditions throughout the study period. All experimental procedures were conducted in accordance with the guidelines of the Institutional Animal Ethics Committee (IAEC) and complied with CPCSEA regulations.

Ethical statement:

Ramanbhai Patel College of Pharmacy, Changa, Gujarat Institutional Animal Ethics Committee (IAEC) approve this protocol (RPCP/IAEC/2024-25/R24) with 24 Rat model and found it to be in accordance with provisions of the Committee for the Purpose of Control and Supervision on Experiments on Animals (CCSEA) guideline for laboratory animal facility**.**

Identification of Animals

Animals were identified using cage labelling. Each cage was tagged with details including cage number, animal identification number, study number, group number, sex, route of administration, and experiment start and end dates to ensure proper traceability during the study.[8]

Housing Conditions

Animals were housed individually in SS 304 stainless steel cages to prevent cross-interference during topical application. Cages were maintained under good conventional hygienic conditions. The bottom stainless-steel trays were cleaned daily to maintain cleanliness and minimize stress or infection.[8-9]

Environmental Conditions

Animals were maintained under controlled environmental conditions with a temperature of 22 ± 3 °C and relative humidity of 50–60%. A 12 h light / 12 h dark cycle was maintained using artificial lighting. Environmental parameters including temperature and humidity were continuously monitored and controlled using a regulated air-conditioning system, and all parameters were maintained within the protocol-specified limits.[8-9]

Feed and Drinking Water

Animals were provided free access to a standardized laboratory rat pellet diet throughout the study period. RO-treated drinking water was supplied ad libitum using polycarbonate drinking bottles. [8-9]

Acclimatization Period

All animals were acclimatized to laboratory conditions for 7 days prior to initiation of the experimental procedures. During this period, animals were observed daily for general health and behaviour. [8-9]

Randomization

After the acclimatization period, animals were randomly assigned to different experimental groups. Randomization was performed using a computer-generated randomization table to minimize selection bias. [8-9]

2.2 Methods:

2.2.1 Acute Dermal Irritation and Dermal Safety Study

Healthy, nulliparous and non-pregnant female Wistar rats were selected based on body weight and physical examination and randomized into the study. Animals were uniquely identified using cage cards following randomization. Acute dermal irritation and corrosion potential of the test formulations was evaluated in accordance with OECD guideline 404.

Approximately 0.5 g of the test formulation was applied uniformly to a shaved dorsal skin area of about 1 cm² and covered with a sterile gauze patch secured using non-irritating adhesive tape to ensure good contact with the skin. Care was taken to prevent animals from accessing or ingesting the applied formulation. After an exposure period of 4 h, the patch was removed and any residual formulation was gently cleaned using water without disturbing the skin integrity.

A sequential patch testing approach was followed in the initial animal, with exposure durations of 3 min, 1 h, and 4 h, applied at different sites. In the absence of corrosive reactions, additional animals were treated with a single 4-h exposure patch for confirmation. Animals were observed for signs of dermal irritation or corrosion immediately after patch removal and subsequently at 1, 24, 48, and 72 h, and up to 14 days to assess reversibility of any observed reactions.

Dermal responses, including erythema and oedema, were scored according to the standardized grading scale described in OECD 404. Animals showing severe pain or distress were humanely withdrawn from the study. The absence or presence of irritation was determined based on the cumulative dermal reaction scores.[8-13]

All experimental animals were kept under daily observation for clinical signs throughout the course of study:

Symptoms, Mortality, Body weight, Food consumption

2.2.2 Anti Psoriatic Activity:

Experimental Design:

Rats were randomly divided into control and experimental groups. The psoriasis-like condition was induced in the experimental groups using topical application of Imiquimod, while control animals received vehicle treatment.

Induction of Psoriasis-like Lesions[14]:

all animals divided into 6 groups. each group contain (n=4) animal. A commercially available 5% Imiquimod (IMQ) cream was used. To induce psoriasis-like skin inflammation, approximately 62.5 mg of IMQ cream + test formulations was topically applied once daily on a shaved area of 4 cm² on the dorsal skin of each rat for 6 consecutive days. The control group received a similar amount of vehicle cream (e.g., Vaseline or aqueous cream base) applied on the same area and duration.

Assessment Parameters [14-16]:

Clinical Scoring (Psoriasis Area Severity Index - PASI):

The severity of skin inflammation was assessed daily using a modified PASI scoring system, evaluating: **Erythema and Skin thickness**

Erythema scored on a scale from 0 to 4 (0 = none; 1 = slight; 2 = moderate; 3 = marked; 4 = very marked), and the cumulative score was used to quantify inflammation.

Skin thickness is measured by digital vernier calipers.

Statistical Analysis [17]:

The experimental result are expressed as mean ± SD with 4 animals in each group followed by one way ANOVA. Multiple comparison of each group is followed by **Dunnett's test**. statistical analysis performed by using graph pad prism software 10.6.1

Histopathological study [16-18]:

On the 7th day, animals were euthanized, and skin samples from the treatment site were excised and All the tissue samples were collected and fixed in 10% neutral buffered formalin for 72 Hrs. before processing for histopathology examination. Later on, thin slices (1-2 cm) of the tissues were kept in plastic cassettes and subjected for processing for tissue histopathology study as pert the method described by **Luna, L.G. (1968).**

All the tissues were embedded in paraffin blocks, sectioned at 5 microns, mounted on glass microscopic slides and stained with hematoxylin and eosin (H & E)**.** The stained slides were mounted with DPX (Dibutyl phthalate Polystyrene Xylene) and allowed to dry. The sections of all slides were observed under light microscope for ascertaining histopathological changes at various magnifications ranging from 20X to 800X (microscope eyepiece digital camera (Model: CatcamScopetekDCM130E, Make: Catalyst Biotech) and software ScopePhoto86x to assess characteristic features such as:

- **Acanthosis (epidermal hyperplasia)**
-
- **Inflammatory cell infiltration**

3. RESULT AND DISCUSSION:

3.1 Acute Dermal Irritation and Dermal Safety Study

Dermal irritation assessment performed at 3 min, 1 h, and 4 h exposure intervals, followed by observations at 24 h, 48 h, and 14 days, showed no evidence of erythema, oedema, or eschar formation at any time point. All dermal reaction scores remained zero throughout the observation period, indicating that the formulations were non-irritant and non-corrosive. The absence of delayed or progressive skin reactions further confirms the good dermal tolerability of the formulations and supports their suitability for repeated topical application. Result shown in Table 1 & 2.

Table 1: Grading represents removal of formulation after 3min, 1 hr. & 4 hr. interval

Name of Test	Female group					
	111-F (MSBG)	111-F (MEBG)	112-F (MSBG)	112-F (MEBG)	113-F (MSBG)	113-F (MEBG)
After 3 min.						
Erythema Formation	0	0	-	-	-	-
Oedema Formation	0	0	-	-	-	-
After 1 hr.						
Erythema Formation	-	-	0	0	-	-
Oedema Formation	-	-	0	0	-	-
After 4 hr.						
Erythema Formation	-	-	-	-	0	0

Oedema Formation	**-**	**-**	**-**	**-**	**0**	**0**

Table 2: Grading represents after removal observation at 24 hr., 48 hr. & 72 hr. interval & delayed reaction

Name of Test	**Female group**					
	111-F (MSBG)	**111-F (MEBG)**	**112-F (MSBG)**	**112-F (MEBG)**	**113-F (MSBG)**	**113-F (MEBG)**
After 24 hrs.						
Erythema Formation	**0**	**0**	**0**	**0**	**0**	**0**
Oedema Formation	**0**	**0**	**0**	**0**	**0**	**0**
After 48 hrs.						
Erythema Formation	**0**	**0**	**0**	**0**	**0**	**0**
Oedema Formation	**0**	**0**	**0**	**0**	**0**	**0**
After 72 hrs						
Erythema Formation	**0**	**0**	**0**	**0**	**0**	**0**
Oedema Formation	**0**	**0**	**0**	**0**	**0**	**0**
After 14 days (For delay reaction)						
Erythema Formation	**0**	**0**	**0**	**0**	**0**	**0**
Oedema Formation	**0**	**0**	**0**	**0**	**0**	**0**

Experimental Design:

All the animal were divided in six groups and four Rat in each group as mentioned in **Table 3** of treatment groups and control group.

Table 3: Group division of Animals for Anti Psoriatic activity:

Treatment Groups-	**Control**	**Disease Control**	**Standard**	**Test-1**	**Test-2**	**Test-3**
Dose	Vaseline	5% Imiquimod	5% Imiquimod + Psoricort-H gel (0.05% w/w) for 6 consecutive days	5% Imiquimod + T-1 (Blank gel) for 6 consecutive days	5% Imiquimod + T-2 (MSBG) for 6 consecutive days	5% Imiquimod + T-3 (MEBG) for 6 consecutive days
No. of animal	04	04	04	04	04	04

Psoriasis Area Severity Index – PASI:

After six days of treatment, the disease control group exhibited pronounced erythema, scaling, and thickened psoriatic plaques, confirming sustained inflammatory response. In contrast, animals treated with the standard formulation showed visible improvement, with reduced redness and scaling. The optimized formulations, particularly **MEBG**, demonstrated marked restoration of normal skin appearance, with minimal erythema and scaling, closely resembling the normal control group. These visual findings corroborate the quantitative PASI scores and skin thickness measurements, indicating effective suppression of psoriatic inflammation following topical treatment. Result for Erythema scaling and skin thickness shown in **Table 4 & 5** and skin appearance after 6 days of treatment shown in **figure 1.**

Table 4: Result of Erythema Scaling

No. of Animals	Control	Disease Control	Standard	Test-1 (Blank gel)	Test-2 (MSBG)	Test-3 (MEBG)
1	0	4	1	3	0	1
2	0	3	1	3	1	0
3	0	4	2	4	1	0
4	0	4	1	4	1	1

Table 5: Result of Skin thickness (in cm)

No. of Animals	Control	Disease Control	Standard	Test-1 (Blank gel)	Test-2 (MSBG)	Test-3 (MEBG)
1	0.10	0.23	0.17	0.21	0.12	0.11
2	0.11	0.21	0.15	0.19	0.11	0.10
3	0.11	0.22	0.16	0.20	0.11	0.11
4	0.10	0.25	0.15	0.22	0.15	0.15

Each group rat skin appearance after 6 days treatment:

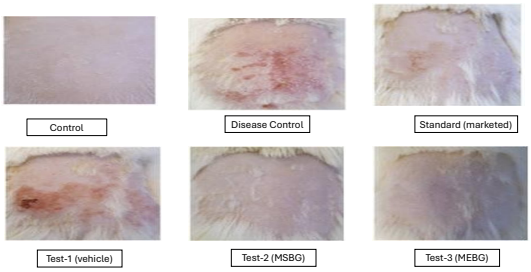

Figure 1: The psoriasis-like symptoms of experimental rat in each group were evaluated after 6 days of topical application of ME gel and MS gel.

Statistical Analysis:

1) Erythema score:

One way ANOVA followed by Dunnette's multiple comparison test

Imiquimod application significantly increased erythema scores in the disease control group compared with normal control, confirming successful induction of psoriasis. Treatment with optimized formulations significantly reduced erythema compared with disease and blank gel groups (****$p < 0.0001$). Among all treatments, MEBG showed the lowest erythema score, followed by MSBG, indicating superior anti-inflammatory efficacy shown in **figure 2.** Multiple comparison and ANOVA summary shown in **Table 6 & 8** respectively.

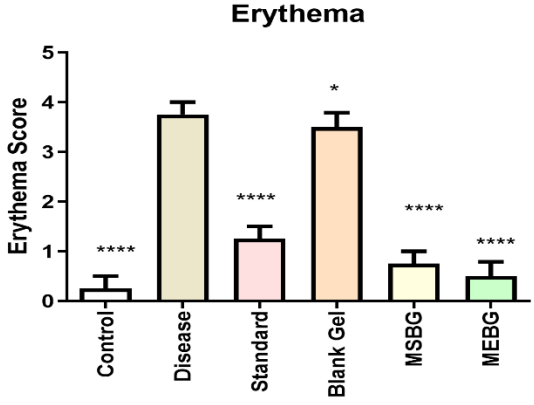

Figure 2: One way ANOVA for erythema score

Table 6: Dunnett's multiple comparisons test for Erythema score

Dunnett's multiple comparisons test	Mean diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value
Disease vs. Control	3.500	2.471 to 4.529	Yes	****	<0.0001
Disease vs. Standard	2.500	1.471 to 3.529	Yes	****	<0.0001
Disease vs. Blank Gel	0.250	-0.7792 to 1.279	No	Ns	0.9393
Disease vs. MSBG	3.000	1.971 to 4.029	Yes	****	<0.0001
Disease vs. MEBG	3.250	2.221 to 4.279	Yes	****	<0.0001

2) Skin Thickness:

one way ANOVA followed by Dunnette's multiple comparison test

Imiquimod treatment resulted in a significant increase in skin thickness in the disease control group compared with the normal control, confirming psoriasis induction. One-way ANOVA revealed a statistically significant difference among group means ($F = 42.6$, $p < 0.0001$; $R^2 = 0.9221$), indicating a strong treatment effect. Dunnett's multiple comparison test showed that the standard formulation, MSBG, and MEBG groups exhibited a significant reduction in skin thickness compared with the disease control (****$p < 0.0001$), whereas the blank gel did not show a statistically significant difference ($p > 0.05$). Notably, MEBG and MSBG demonstrated greater reduction in skin thickness, approaching normal control values, suggesting superior suppression of epidermal hyperplasia and enhanced anti-psoriatic efficacy shown in **figure 3.** Multiple comparison and ANOVA summary shown in **Table 7 & 8** respectively.

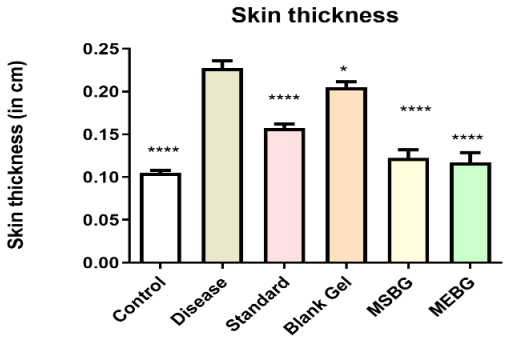

Figure 3: One way ANOVA for Skin Thickness

Table 7: Result of Dunnett's multiple comparisons test for skin Thickness

Dunnett's multiple comparisons test	Mean diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value
Disease vs. Control	0.12225	0.09232 to 0.1527	Yes	****	<0.0001
Disease vs. Standard	0.07	0.03982 to 0.1002	Yes	****	<0.0001
Disease vs. Blank Gel	0.02225	-0.007681 to 0.05268	No	ns	0.1877
Disease vs. MSBG	0.1005	0.07482 to 0.1352	Yes	****	<0.0001
Disease vs. MEBG	0.111	0.07982 to 0.1402	Yes	****	<0.0001

Table 8: Result of ANOVA summary

ANOVA summary	Erythema score	Skin Thickness
F	34.8	42.6
P value	<0.0001	<0.0001
P value summary	****	****
Significant diff. among means (P < 0.05)?	Yes	Yes
R squared	0.9063	0.9221

Histopathological study:

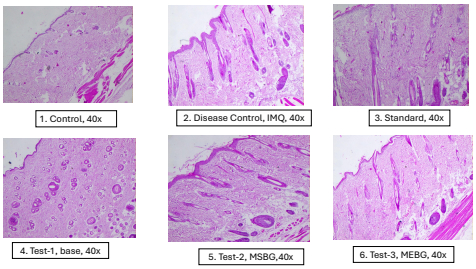

Figure 4: Effect of optimized Halobetasol formulations on IMQ-induced histological alternations in rat skin (H&E staining, 40 ×). (1) The normal control group shows normal skin structure. (2) A lack of epidermal thickness is seen with obvious inflammatory cell infiltration in the disease control group. (3) group treated with standard marketed gel (4) The group treated with (blank gel) vehicle (5) The group treated with optimized MSBG formulation of halobetasol propionate **(**6) The group treated with optimized MEBG formulation of halobetasol propionate.

Histopathological observations:

Group 1 – Control (Normal Skin):

The epidermis exhibited normal thickness without evidence of acanthosis or rete ridge elongation. The stratum corneum appeared compact and well-keratinized, with no retention of nuclei, thereby excluding parakeratosis. The dermis appears normal with intact hair follicles and glands.

Group 2 – Disease Control (IMQ):

Very thickened epidermis shows evidence of acanthosis with Dense stratum corneum indicating hyperkeratosis. Marked Elongation and widening of dermal papillae. There are dense clusters or perivascular (around blood vessels) or periadnexal (around hair follicles or glands) accumulations shows heavy inflammatory infiltration in dermis, indicating severe psoriatic changes.

Group 3 – Standard (Marketed gel of HBT):

Noticeable recovery of epidermal structure with reduced acanthosis and Keratin layer appears more compact shows minimal parakeratosis.

Group 4 – Test 1 (Vehicle)

Slight decrease in epidermal thickness compared to disease control, partial decrease in acanthosis and inflammatory infiltration, Mild persistence of Munro's microabscesses, suggesting minimal therapeutic influence.

Group 5 – Test 2 (MSBG):

Evident reduction in hyperkeratosis and parakeratosis with near-normal epidermal thickness. Dermal papillae appear less elongated. indicating good restoration toward normal skin.

Group 6 – Test 3 (MEBG):

Prominent improvement with marked decrease in epidermal hyperplasia and the fibrous connective tissue (stroma) was healthy, and skin structures like hair follicles and sebaceous glands were intact and undamaged. There was only a small number of scattered inflammatory cells, and no major inflammation around blood vessels or skin glands, comparable to the standard group.

Conclusion:

During dermal toxicity study No mortalities were recorded in rats over 14 days of Test formulation treatment. None of the rats showed any obvious morbidity or symptoms of toxicity after exposure of test formulations. No significant toxic effect was found on body weight of rats. The given test formulations had no significant effect on grading of skin reactions. Based on these findings, optimized both Test formulations when applied to rat skin, over a period of 14 days, was found to be non-irritant and non-corrosive.

No mortalities were recorded in entire study of anti-psoriatic activity. Imiquimod induces psoriatic dermatitis (psoriasis like symptoms) and optimized test formulations improves the imiquimod-induced psoriasis in rats. Based on these findings, the optimized Test formulations MEBG and MSBG loaded with Halobetasol Propionate were found to possess anti-psoriatic activity in the imiquimod-induced rat model.

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