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PRELIMINARY DEVELOPMENT STUDIES OF HALOBETASOL PROPIONATE ORGANOGEL FOR MANAGEMENT OF ATOPIC DERMATITIS

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ABSTRACT: Halobetasol propionate (HP) is an ultra-potent corticosteroid used in management of severe and recurrent cases of Atopic Dermatitis (AD). The marketed cream formulations are based on synthetic surfactants which often aggravate AD. The present studies investigate biocompatible pluronic lecithin organogel (PLO) of Halobetasol propionate in management of AD. Organogels were prepared by aqueous titration method and preliminary ternary phase studies optimized the ratio of surfactant (phospholipon 90G) to co-surfactant (propylene glycol).The optimized organogel comprised of surfactant and co- surfactant in ratio of 2:1, which exhibited satisfactory morphology and rheology. Systematic analysis by employing statistical models revealed that increasing concentration of lecithin and pluronic enhanced the viscosity of formulation and inhibited drug release. The developed formulation showed enhanced drug retention in skin as compared to marketed HP cream in ex-vivo permeation studies across rodent skin. Increased and deeper layer permeation from the PLO was confirmed by confocal microscopy using a fluorescent marker. Histopathological evaluation of excised skin from treated rats revealed non-irritating nature of the PLO. The present studies indicate the possibility of non-irritating bio-compatible dosage form for potent steroids which increase drug permeation but does not aggravate AD. It is also expected to alleviate xerosis and has potential for dose reduction of the drug.

INTRODUCTION: Atopic dermatitis (AD) is one of the common, periodically relapsing, chronic inflammatory, allergic, non-contagious skin disease of unknown origin that occurs in all ages of people but mainly affects the children. Its most frequent symptom is itchy rashes accompanied with xerosis [1, 2]. The pathophysiology of AD is said to be due to defects in the skin barrier, environmental factors and infectious agents, genetic susceptibility and immunological abnormalities. The inflammatory cytokines like IL-4, IL-5, IL-10 and IL-13 are found to be elevated in AD [3].

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Xerosis is also a major observation in AD due to which barrier integrity is lost and leads to increased ingress of infectious agents and allergens [4].

Therapeutic management of AD aims to control the flares, reduce their duration and recurrence. The most commonly employed agents are emollients, topical corticosteroids and topical calcineurin inhibitors [2, 5]. Topical corticosteroids are very effective in the management of AD by virtue of their multipronged anti-inflammatory effects. However, local and systemic side effects of topical corticosteroids limit their duration and frequency of use [6]. The efficacy of available topical cream based preparation is limited due to inadequate penetration through stratum corneum. Researchers have attempted corticosteroid delivery through microemulsion, liposome, transferosome etc. with varying success [7, 8].

Research on improving dermal localization of corticosteroid has yielded mixed results in management of AD also because of higher concentration of synthetic surfactants in formulations which sometimes lead to aggravation of AD [9, 10]. Attempts for maximizing therapeutic benefits of ultrapotent corticosteroid halobetasol propionate (HP) have been attempted which indicate the possibility of dose reduction with enhanced dermal localization of drug [11, 12].

Lecithin organogels are thermodynamically stable, viscoelastic, biocompatible, and non-birefringent gels. They consist of a 3-dimensional network of entangled reverse cylindrical micelles which immobilizes the macroscopic external organic phase to a gel [13, 14]. Pluronic is incorporated in such systems to improve their gelling characteristics [15]. The formulations so developed exhibit enhanced skin penetration by preferential accumulation in skin layers, biocompatibility and biodegradability [16].

Use of topical preparation of lecithin, increases the moisture content of the skin, reduces wrinkling, and provides a rejuvenated appearance to the skin [17]. It is hypothesized that steroid like HP when incorporated in pluronic lecithin organogels (PLO) will exhibit enhanced penetration and present a possibility of dose reduction. It is also expected that such an occlusive and biocompatible system will also reduce the xerosis and irritation to give significant clinical benefits. Hence, the present studies investigate the utility of lecithin organogel of HP in management of AD.

2. MATERIALS AND METHODS:

2.1 Materials: Halobetasol Propionate (HP) was received as a gift sample from Lyka Ltd. (Ankleshwar, India). Phospholipon 90 G was received as a gift sample from Lipoid GmbH (Germany). Pluronic F-127 was received as a gift sample BASF Ltd (Mumbai, India). All others chemicals used in this study were of analytical grade.

2.2 Analytical Method: The detection and quantification of HP was done using a modified HPLC method. The analysis was performed at room temperature on a reverse phase C18 column (Hypersil C-18) (250×4.6 mm) with UV detection at 240 nm. The mobile phase used was Acetonitrile-Water (70:30 v/v) at a constant flow rate of 1.0 ml/min under isocratic conditions[18].

2.3 Preparation and Optimization of Organogel: Solubility studies were carried out to determine maximum solubility of drug in oils, surfactants and co-surfactants. Organogel was prepared by aqueous titration method wherein organic phase and surfactant mixture was titrated slowly and gradually with aqueous media till clear gel is formed. Preliminary screening included selection of co surfactant on the basis of viscosity and drug release. Optimization of ratio of surfactant to co surfactant was done using pseudo ternary phase diagram studies. Finally, central composite design was employed to optimize the PLO. In this study the effect of independent variables, i.e. concentration of lecithin, isopropyl myristate and pluronic on the dependent variables viscosity and cumulative drug release at 8 hours (Q8) was studied (**Table 1**).

2.4 Physico-Chemical Characterization of Organogel: The pH of the formulated organogels was measured using a calibrated pH meter (Welltronix, PM100). Washability was investigated by rubbing a small quantity of orgenogel on skin of the back of the hand, followed by washing with water. Spreadability was determined by modified glass slide apparatus, wherein the spreadability of gel was observed with increasing weight on the slide. Rheological studies were performed with a thermostatically controlled Brookfield programmable rheometer using spindle no. 96 at 25°C. Gel strength of optimized formulation was determined using texture analyzer (Brookfield, CT-3 10Kg) [19, 20, 21].

2.5 *In-vitro* diffusion study: *In-vitro* drug release study was carried out in a two compartment Franz diffusion cell through a previously activated dialysis membrane (Molecular weight cut off – 12000 to 14000 Daltons). The donor compartment contained HP PLO equivalent to 0.5 mg of HP while the receptor compartment was filled with diffusion media (25 ml, water: acetonitrile 7:3 v/v).The apparatus was thermo-stated at 32^{o}C and maintained under constant slow speed stirring. At pre-selected time points, aliquots were withdrawn from the receptor compartment for analysis of drug

released and replaced by equivalent fresh receptor media [22].

2.6 *Ex-vivo* drug permeation and skin retention study: *Ex-vivo* studies were carried out across full thickness rodent skin in a Franz diffusion cell. The whole skin, after removing fat with a scalpel, was mounted in the diffusion cell with stratum corneum on upper side and dermal side flushing to the receptor media. Receptor media (Water: Acetonitrile, 7:3 v/v) was selected so that sink conditions are maintained. A gel sample equivalent to 50mg HP was loaded on the skin in the donor compartment. Aliquots were withdrawn from the receptor compartment at 8 h and 24 h and replaced with fresh media. The amount of drug diffused across the skin was estimated by analyzing the drug concentration in receptor medium by HPLC. After 24 h of application, the skin was removed from the diffusion cell, cleaned with cotton soaked in methanol, and was cut in small pieces. It was homogenized in 5 ml of methanol, bath sonicated for 30 min, and kept overnight in methanol for extraction. The methanol extract was then filtered using a 0.45 µm membrane, and drug was assayed in the filtrate by HPLC [23].

2.7 Skin irritation and histopathological evaluation: Skin irritation study was performed on wistar rats under an approved animal ethical committe protocol (BIP/IAEC/2014/13), by removing the hair from the back and area on both sides of the back was marked. One side served as the control (Negative Control – 0.9% v/v Saline Solution) while the other side served as the test. The rats were grouped as optimized HP PLO, marketed preparation and positive control (0.8% formalin). Formulation was applied twice a day for 14 days. Skin irritation from the formulation was assessed by observations of any skin sensitivity reactions such as redness, edema, and skin rash for 14 days. The skin irritation effect of test formulations were graded as: 0-no reaction; 0.5-slight, patchy erythema; 1-moderate but patchy erythema; 2-moderate erythema, and 3-severe erythema with or without edema. Following skin irritation studies, the animals were humanely sacrificed and excised rat skin was fixed in 10% formalin. Sections were prepared and stained with hematoxylin and eosin and observed for signs and symptoms of inflammation [24].

2.8 Confocal Microscopy: Formulations containing lipophillic fluorescent marker, 6-coumarin were prepared to visualize the penetration of organogel and cream into the skin. Fluorescent dye containing formulations were applied on backs of rat and secured with a gauze bandage. The animals were humanely sacrificed after 24 hours. The excised skin was then cryodermatomed at -20˚C and ultrathin sections were cut and observed under laser scanning confocal microscope (Zeiss, LSM 710) [24].

3. RESULT AND DISCUSSION: Solubility studies showed that HP was more soluble in isopropyl myristate (IPM), polyethylene glycol (PEG200), transcutol HP® and propylene glycol (PG) (data not shown). Based on the solubility data, preliminary batches of PLO were prepared by aqueous titration using PEG200, PG and transcutol HP® as co-surfactants and phospholipon 90G as a surfactant. They were evaluated for appearance, viscosity, drug content and drug diffusion. Preliminary studies favoured the use of PG as a co-surfactant. Various ratio of surfactant to co-surfactant were explored by constructing pseudoternary phase diagram for the clear microemulsion region and the PLO was optimized for 2:1 ratio of surfactant to co-surfactant (PL 90G: PG). The ratio of surfactant to co-surfactant was kept constant at 2:1 for all further investigations.

Further optimization of PLO was carried out by central composite design wherein the effect of independent variables, concentration of lecithin, IPM and pluronic was studied on viscosity and drug release (Table 1). The optimized formulation of PLO contained halobetasol propionate (0.05% w/w), phospholipon 90G (15.16% w/w), propylene glycol (7.58%w/w), isopropyl myristate (10% w/w), pluronic F-127 (5.01%w/w), potassium sorbate (0.1%w/w), and purified water (q.s.). The optimized formulation exhibited a viscosity of 2224.7 cps and 93.88% cumulative % drug release in 8 hours. The kinetic modelling of in-vitro drug release data showed best fit for higuchi kinetic model. This indicates that drug diffusion was proportional to square root of time. Response surface plots (**Fig. 1** and **2**) indicated that increasing the concentration of lecithin and pluronic increased viscosity and decreased drug diffusion.

On the other hand, increasing the concentration of IPM increased drug diffusion and decreased viscosity. The interaction effects between independent variables were found to have no significant effect. The *in-vitro* diffusion studies also showed that the system could give a sustained drug release. These trends indicate that lecithin and pluronic increases the gel strength and viscosity and thus a sustained release is expected. This could also be indicative of higher affinity of drug towards lecithin. Increasing the IPM concentration, although decreases the concentration gradient, but the lower viscosity offsets it and ultimately, higher drug diffusion is observed. The similarity factor (f2) was used to compare optimized formulation and marketed formulation. The similarity factor was found to be 28.75. The value of similarity factor less than 50 signified that the optimized formulation and marketed preparation were statistically dissimilar and the marketed preparation showed an incomplete drug release in 8 hours. The developed formulation showed a faster but controlled drug release for 8 hours.

TABLE 1: INDEPENDENT VARIABLES, VARIABLE LEVELS AND DEPENDENT VARIABLES USED IN THE CENTRAL COMPOSITE DESIGN FOR OPTIMIZATION OF PLO

Independent variables	Variable levels		Dependent variable
	Low Level (-1)	High level (+1)	
Lecithin (% w/w)	15	30	Viscosity
IPM (% w/w)	10	30	*In vitro* drug release (Q8)
Pluronic F-127 (% w/w)	5	10	

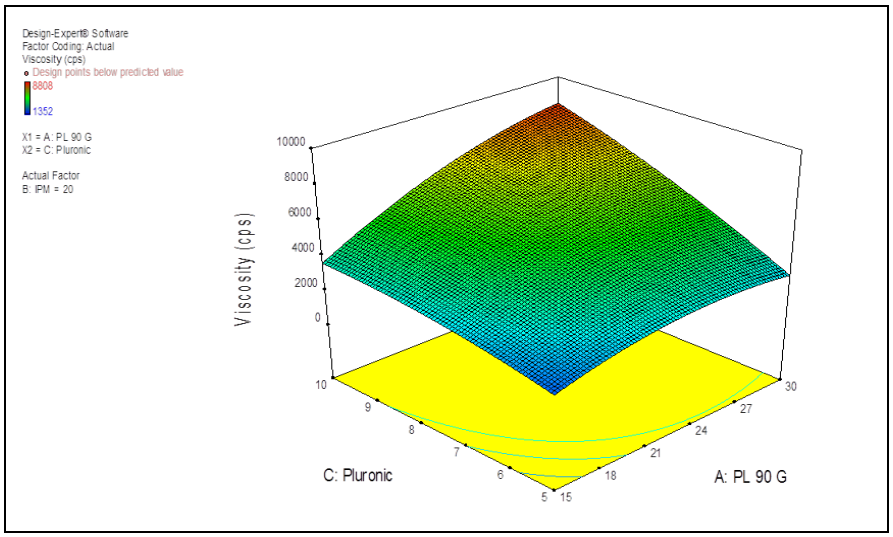


FIG. 1: RESPONSE SURFACE PLOT FOR VISCOSITY

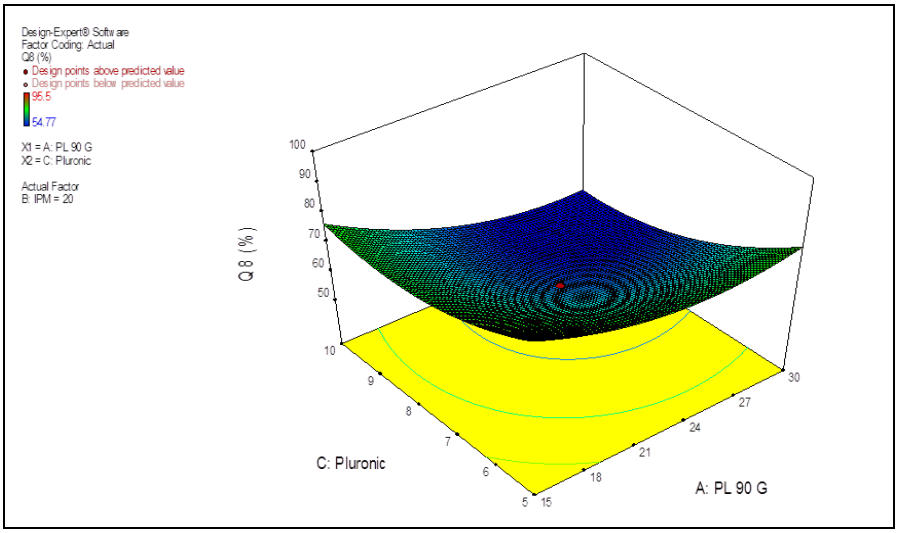


FIG. 2: RESPONSE SURFACE PLOT FOR Q8

The developed PLO had a translucent appearance and was not easily washable. The pH of the PLO was 6.8, which was compatible with the skin. The formulation displayed good spreadability and sufficient gel strength. From the spreadability study it was observed that the formulation with low viscosities showed comparatively more spreadability than the highly viscous formulations. As the concentration of lecithin increased, the time required for plunger to sink in through the gel also increased and hence gel strength increased. The rheological studies showed that the structure of gel was altered in presence of stress, as the stress increases, the viscosity decreases. Formulation was not easily washable which indicates that the developed formulation will be retained on the skin for a longer time (**Table 2**). Increased adherence of an occlusive lecithin film on the skin is expected to increase the hydration of skin. Xerosis is said to be one of the very significant parameter in AD pathophysiology, which has both cause and effect dimensions to it. Formulations which increase skin hydration are expected to useful in management of AD [10, 25].

TABLE 2: CHARACTERIZATION OF OPTIMIZED PLO

Parameter	Observation
Appearance	Translucent
Washability	Not easily washable
pH	6.8
Spreadability (gm.cm/sec)	23.25
Drug content (% w/w)	97.2
Viscosity (cps)	2224.7
Q8 (%)	93.88

Ex-vivo studies across rodent skin in a Franz diffusion cell demonstrated that less than 10% drug permeates transdermally into the receptor compartment from optimized formulation as well as marketed cream preparation. These studies showed that drug showed a preferable dermal localization. Skin retention studies showed that the developed formulation had significantly higher skin retention (50.92%) as compared to the marketed formulation (22%) (p value < 0.05%). Mass balance studies confirmed the validity of the studies (**Fig. 3**). The target receptors and the pathological condition in AD are topical, so dermal localization is expected to improve the effectiveness of therapy [26]. It is suggested that the drug transport across the skin from organogel may follow various routes. It is well reported that the increased hydration leads to opening of pores and improves drug transport, the same phenomenon may be observed with PLOs also [27]. The presence of amphiphillic lipid like lecithin also drives the drug across the skin barrier by virtue of its surfactant action. There is another possible mechanism operating to increase the dermal transport of the drug, the solvent drag effect of propylene glycol [28]. Together, these mechanisms are proposed to account for the higher dermal retention of drug from PLO.

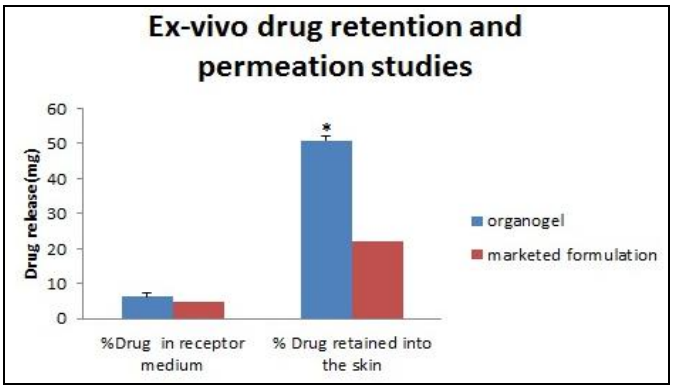


FIG. 3: EX-VIVO PERMEATION STUDY OF PLO AND MARKETED PREPARATION ACROSS FULL THICKNESS RODENT SKIN. THE COLUMNS AND THE ERROR BARS REPRESENT MEANS±SD FOR *N* = 3 EXPERIMENTS. *(P < 0.05) SIGNIFICANT DIFFERENCE IN COMPARISON TO HALOBETASOL PROPIONATE MARKETED FORMULATION.

Skin irritancy potential of the developed formulation was evaluated in wistar rats after 2 weeks of continuous application. The organogel exhibited less irritancy than the marketed formulation. White patchy appearance was observed in PLO group as well as marketed cream group (**Fig. 4**). The validity of the study was confirmed by the erythema and edema observed in positive control group. Histopathology was done on treated tissue after the completion of irritation studies and absence of dermal infiltration of inflammatory cells was observed. No visible change in skin morphology and no visible irritation signs were observed after the application of PLO and marketed formulation (**Fig. 5**). The white patchy appearance in both treated group is due to the blanching effect of corticosteroids [29]. Lecithin is a well reported biocompatible surfactant and the present studies were hypothesized to exploit the biocompatible properties of lecithin in management of allergic and sensitive skin in AD [30].

Presence of surfactant and penetration enhancer in the marketed formulations raise a concern for dermal irritation or toxicity, but sub-acute dermal toxicity study did not demonstrate any signs of irritation or toxicity with developed product [31]. Thus, the developed formulation may be considered to be safe for use as topical drug delivery vehicle.

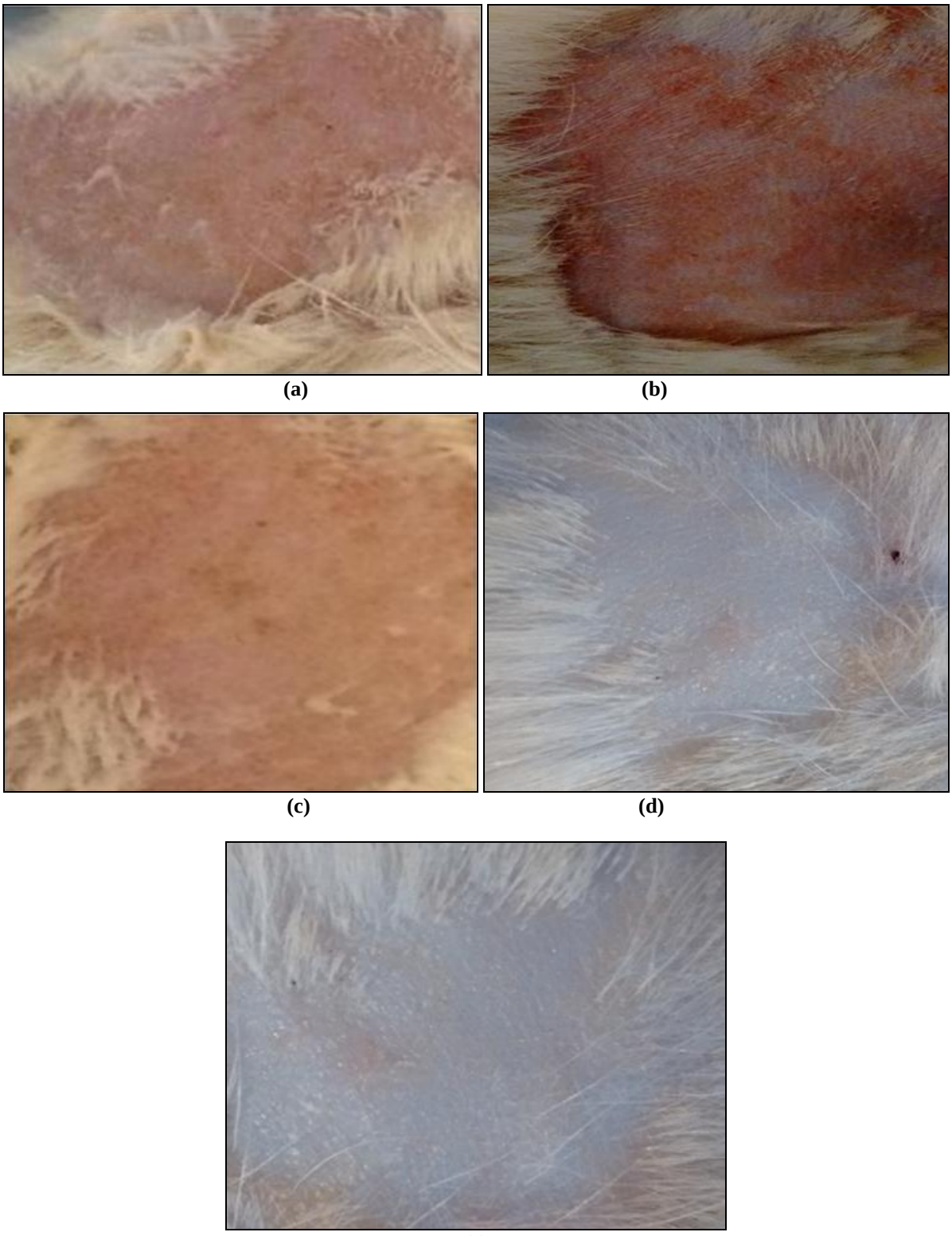
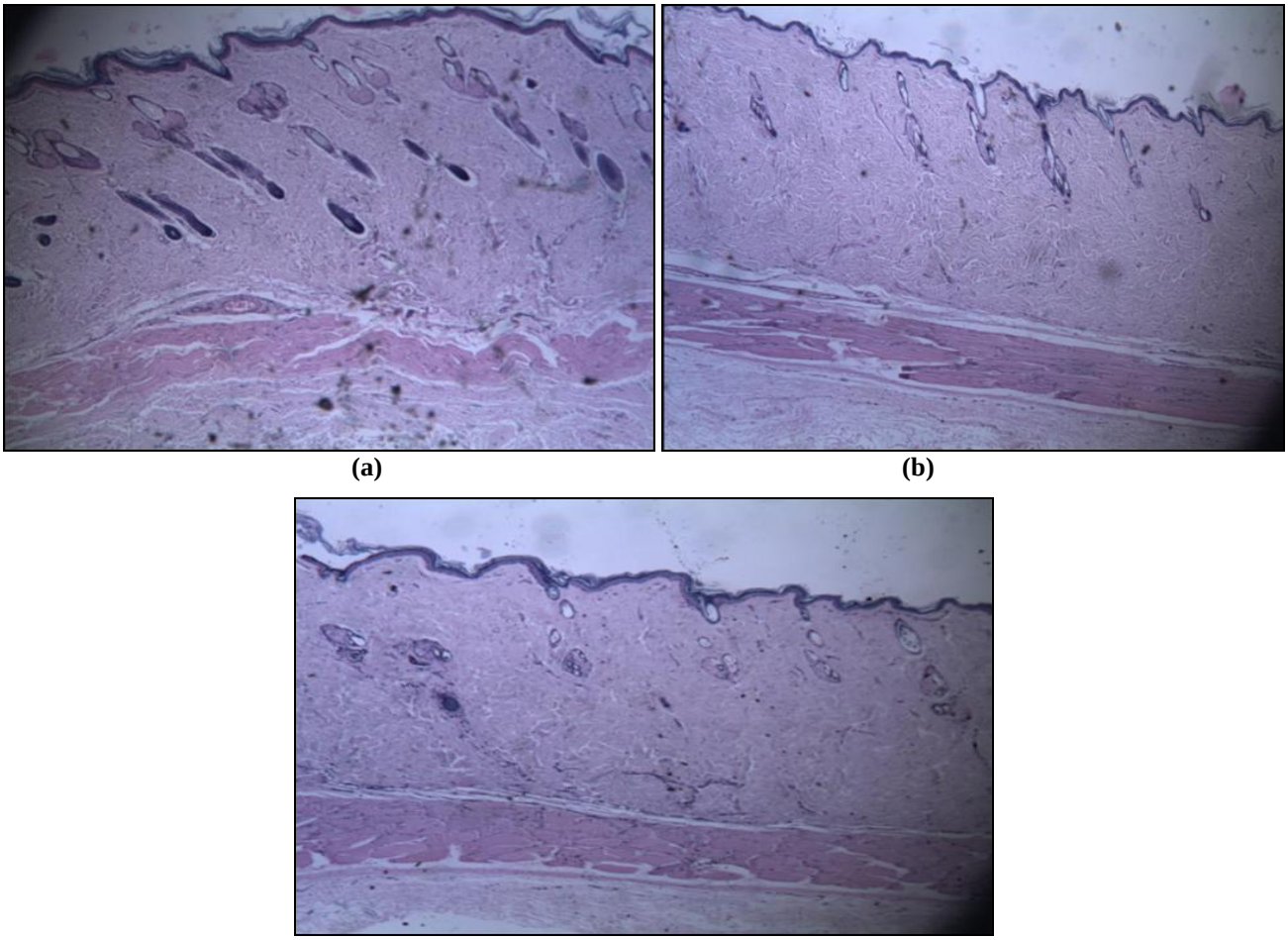


FIG. 4: SKIN IRRITATION STUDIES SHOWED (A) NORMAL SKIN BEFORE ANY TREATMENT AND AFTER TREATMENT WITH (B) 0.88% FORMALIN SOLUTION (C) SALINE SOLUTION (D) HP PLO (E) MARKETED FORMULATION

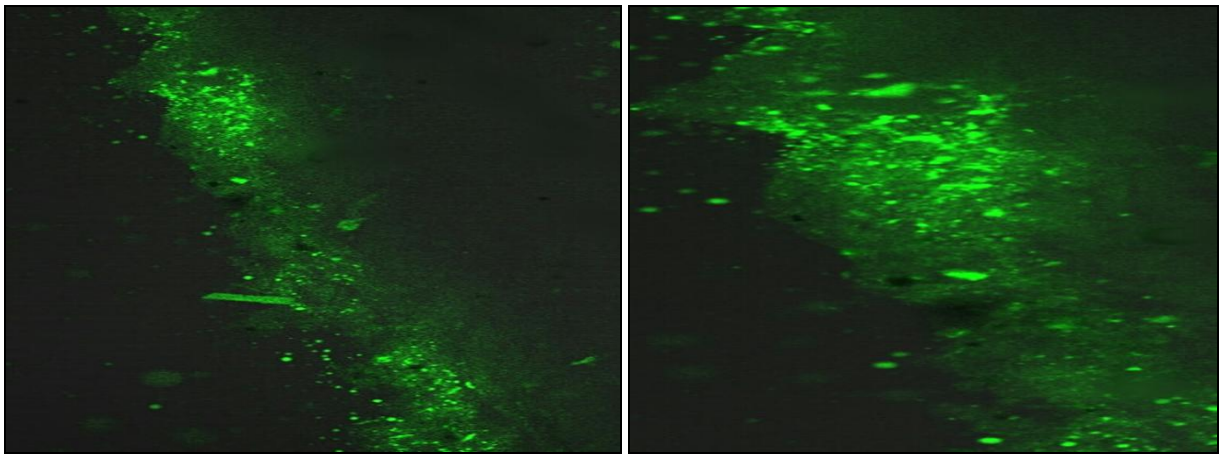


(a) (b)

(c)

FIG. 5: HISTOLOGY OF RAT SKIN (a) AFTER TREATMENT WITH 0.8% FORMALINE SOLUTION (b) AFTER TREATMENT WITH ORGANOGEL (b) AFTER TREATMENT WITH MARKETED FORMULATION

Comparative assessment of skin penetration profiles of different formulation was done by confocal laser scanning microscopy. Confocal laser scanning microscopy showed high fluorescence intensity in PLO treated skin as compared with the marketed cream treated skin. Fluorescent marker loaded PLO showed higher and deeper skin penetration as compared to marketed formulation (**Fig. 6**). Thus, evidencing that the skin penetration of organogel was superior to marketed formulation and the studies qualitatively confirmed the higher dermal deposition of marker with the organogels.



(a) (b)

FIG. 6: PENETRATION OF 6-COUMARIN INTO RAT ABDOMINAL SKIN FROM (a) MARKETED FORMULATION (b) OPTIMIZED ORGANOGEL FORMULATION

CONCLUSION: HP can be successfully formulated as a PLO which showed enhanced permeation and skin retention. The developed formulation is an alternative to conventional halobetasol propionate cream by virtue of its ability to enhance dermal localization of HP. This presents a possibility of dose reduction of drug. Further, the developed formulation exhibited non irritancy and excellent biocompatibility which is often a drawback of synthetic surfactant based commercial preparations. It is expected that this formulation will not aggravate AD, alleviate xerosis and maximize the therapeutic efficacy of the ultra potent corticosteroid. This could translate to better management of dermatological pathologies like AD which become severe, resistant and relapse with time.

CONFLICT OF INTEREST: There is no conflict of interest to declare.

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