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Research Article

DEVELOPMENT OF NOVEL MICROEMULSION BASED TOPICAL FORMULATION OF CLOBETASOL PROPIONATE AND SALICYLIC ACID FOR THE TREATMENT OF PSORIASIS

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ABSTRACT

Clobetasol propionate a glucocorticoid receptor agonist is an effective anti-inflammatory, immunomodulatory and antiproliferative agent. Salicylic acid a lipophilic monohydroxybenzoic acid exhibits potent keratolytic action. The objective of this work was the development of a novel formulation containing Clobetasol propionate and Salicylic acid for improved anti-psoriatic activity. Clobetasol propionate, a BCS Class II moiety with poor permeation across the skin was formulated as a microemulsion along with incorporation of Salicylic acid in a gel base and evaluated. Microemulsion was prepared using water titration method containing oil, surfactant, co-surfactant and water. Optimized formulation was subjected to in-vitro and ex-vivo skin diffusion studies for drug release. Surface study of optimized formulation was done by scanning Electron Microscopy. In vivo anti-psoriatic activity was performed using Imiquimod Induced Psoriasis-like skin as a model. Ex-vivo drug diffusion exhibited 20.05% and 10.36% respectively for Clobetasol propionate and Salicylic acid as against a diffusion of 32.68% and 18.40% for marketed product, studied for a period of nine hours. Skin retention after 24hrs was 36.25% and 25.6% of Clobetasol propionate and Salicylic acid indicating that the developed formulation can provide sustained release. Encouraging antipsoriatic activity was obtained for the developed formulation

Keywords: Microemulsion, Psoriasis, Clobetasol propionate, Salicylic acid

INTRODUCTION

Psoriasis is a common, chronic, non-contagious, auto-immune disorder that primarily affects the skin of about 2-3% of population world-wide[1]. It is characterized by scaly, red and itchy plaques on entire scalp, forehead, behind ears or neck, chest, arms, elbows, armpits, under the breasts, around the genitals, knees, legs, toenails and fingernails[2]. It is more common in people between the age group of 15 and 35, according to National Psoriasis Foundation and

Clobetasol propionate (CP) is a highly potent glucocorticoid receptor agonist, exerts its action by inhibition of phospholipase A2 which leads to the inhibition of synthesis of arachidonic acid and controls the biosynthesis of prostaglandins and leukotrienes[3]. However, the clinical use of CP has some practical disadvantages. The main limitation lies in the barrier function of the skin, which is considered one of the most impermeable epithelia of the human body to exogenous substances.The main challenge for a topical formulation in Psoriasis treatment is to provide sufficient drug penetration into the skin, without inducing any significant irreversible alteration to the skin barrier function[4].

Salicylic acid (SA) exhibits keratolytic action that helps in psoriasis to soften and remove the hyper keratinized scales formed due to the accumulation of the dead cells on the skin which act as a major barrier for drug delivery across the skin. Moreover, Salicylic acid also has anti-inflammatory activity via suppressing the activity of cyclooxygenase (COX), an enzyme that is responsible for the production of pro-inflammatory mediators such as the prostaglandins. Microemulsions can provide benefits like low skin irritation, enhanced drug solubility, good thermodynamic stability and excellent permeation ability when compared with conventional formulations[5].

MATERIALS AND METHODS

Clobetasol propionate was received as a gift sample from Sumit laboratories (Vapi, India). Salicylic acid was purchased from Loba chemie (Mumbai, India).Isopropyl Myristate, oleic acid, ethanol and Propylene glycol were purchased from S.D. Fine chemicals (Mumbai, India).PEG 400, PEG 600, Tween 20, Tween 40, Tween 60 and Tween 80 were purchased from Mohini Organics (Mumbai, India). Caprylo caproyl macrogol-6 glycerides (Labrasol) and diethyleneglycol monoethyl ether (Transcutol P) Capyrol PGMC and Labrafac Lipophile WL 1349 were received as gift samples from Gattefosse (Mumbai, India). Carbopol Ultrez 10NF was received as a gift sample from Lubrizol (Mumbai, India).Diplomax ointment (Leeford, India) and Imiquimod 5% cream (Glenmark, India). All other chemicals used were of analytical grade.

The following preliminary studies were carried out.

SATURATION SOLUBILITY STUDIES

Saturation solubility studies were carried out to determine solubility of Clobetasol propionate in in various oils, surfactants and co-surfactants .

Equilibrium solubility of drug was determined by Shake flask method using Orbital shaker.

Excess amount of Clobetasol propionate i.e. 100 mg was added in 2 ml of oil, surfactant and co-surfactant in 5 ml stoppered vials and briefly vortexed. The vials were then placed in orbital shaker for 24 hours followed by centrifugation at 6000 rpm for 30 minutes. The concentration of Clobetasol propionate in filtrate was determined by UV spectrophotometer (UV 1800, Shimadzu) at λmax 235nm. The excipients which Clobetasol propionate showed maximum solubility were selected[7].

Screening of Oils for Microemulsion formation

The saturation solubility of Clobetasol propionate in various oils such as Oleic acid, Capryol PGMC,IPM (Isopropyl Myristate) , Labrafac lipophilic WL 1349,Oleic acid + Labrafac lipophilic WL 1349 (1:1) were determined.

Screening of Surfactants for Microemulsion formation

For selecting surfactant with good solubilizing capacity for Clobetasol propionate, the saturation solubility of Clobetasol propionate in various surfactants like Labrasol®, Tween®20,Tween®40,Tween®60,Tween®80 as determined.

Screening of Co-surfactants for Microemulsion formation

The property of modifying the elasticity of interfacial tension depends largely on the chain length of co-surfactants and also on its concentration. The saturation solubility of Clobetasol propionate in various co-surfactants like Transcutol® P, PEG-400, PEG-600, Propylene Glycol (PG) were determined.

Emulsification ability of Surfactants and Co-surfactants

Different surfactants were screened for its emulsification ability 300 mg of surfactant was mixed with 300 mg of the selected oil phase. The mixture was gently heated at 45–60^{0}C for homogenizing the components. 50 mg of this mix was accurately weighed and diluted with double distilled water to 50 ml to yield fine emulsion. The ease of formation of emulsion was monitored by noting the number of volumetric flask inversions required to give uniform emulsion. The resulting emulsions were observed visually for relative turbidity. The emulsions were allowed to stand for 2hr and percent transmittance was assessed at 638.2 nm by UV-spectrophotometer. Similarly, emulsification ability of co-surfactant was evaluated.

Pseudo Ternary Phase diagrams

Pseudo ternary phase diagram were constructed to observe the oil in water micro emulsion[6]. Briefly, mixtures of (Oleic acid) and (Labrasol+ Transcutol-P) were prepared as the oil phase and Smix (surfactant and co-surfactant). The concentration of surfactant to co-surfactant (Smix) was varied from 1:1 to 2:1. The mixtures were mixed with the oil phase to give ratios of 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80, and 10:90. By applying the aqueous phase titration, distilled water was titrated drop by drop to the oil and Smix mixture stirred using a magnetic stirrer at ambient temperature. After each addition, the mixture was observed for appearance. The end point of the titration was the point where the solution turns turbid or cloudy. And the quantity of water (aqueous phase) required to make the mixture turbid was noted. The percentage of each incorporated components were then calculated and the same procedure was followed for the other Smix ratios to plot the pseudo ternary phase diagram. The pseudo ternary phase diagram was constructed using chemix school 3.6 software. The clear and stable microemulsion zones were identified. Selected formulations were subjected to various physical stability tests[7].

CHARACTERIZATION OF OPTIMISED MICROEMULSION CONTAINING CP.

PHYSICAL STABILITY STUDIES

To overcome the problem of metastable formulations, physical stability tests were performed[6]. Selected formulations were subjected to the following:

- Heating-Cooling Cycles: Six cycles between refrigerator temperature (40c) and 450c with storage at each temperature for not less than 48h were conducted, and the formulations were examined for stability at these temperatures.
- Centrifugation studies: Formulations were centrifuged at 10,000 rpm for 30 mins, and examined for phase separation.
- Freeze-thaw Cycles: The formulations were subjected to Freeze-thaw Cycles between -40c and room temperature for not less than 48 hours at each temperature and examined for any phase separation.

PERCENT TRANSMITTANCE

Percent transmittances of each batch were checked by UV at 638.2 nm using doubled distilled water as blank.

GLOBULE SIZE AND POLYDISPERSIBILITY INDEX

The average droplet size of microemulsion was determined by photon correlation spectroscopy instrument (Malvern Zetasizer, UK). Light scattering was monitored at 25°C at the scattering angle of 90°C. The sample of optimized microemulsion was subjected to droplet size analysis.

ZETA POTENTIAL

Zeta potential identifies the charge on the droplets. Zeta potential of the optimized microemulsion was determined using Zetasizer (Malvern Instrument) to analyze the fluctuations in light scattering due to Brownian motion. Light scattering was monitored at 25°C at 90°C angle.

SURFACE MORPHOLOGY

Scanning Electron Microscopy analysis (SEM) is done to study morphology of microemulsion.

IN-VITRO DIFFUSION STUDIES

Franz diffusion cell with an effective diffusion area of 2 cm^2 was used for performing the in-vitro diffusion studies. Dialysis membrane having a molecular weight cut of 10,000 Dalton was used. Microemulsion based gel containing Clobetasol propionate and Salicylic acid was placed on the membrane and the release profiles were estimated. Diffusion medium (Phosphate buffer 5.5: ethanol 1:1) was used. Analysis was done by UV spectrophotometer. Percent cumulative release of drug was then plotted as a function of time.

EX –VIVO DIFFUSION STUDIES

Franz diffusion cell with an effective diffusion area of 2 cm^2 was used for the experiment. Pig ear skin was placed between the donor and receptor compartment of Franz diffusion cell with the stratum corneum facing the donor compartment. Microemulsion based gel containing Clobetasol propionate and Salicylic acid was placed on the skin and release profiles were determined by UV spectrophotometer[8].

IN-VIVO ANTI-PSORIATIC STUDIES

The protocol to carry out in-vivo anti-psoriatic activity was approved by the Institutional Animal Ethics Committee Registration number: CPCSEA/IAEC/P-30/2017 (Mumbai, India). The committee's guidelines were followed for the studies. The anti-psoriatic and sustaining action of the optimized formulation was evaluated by the Imiquimod Induced Psoriasis-like Skin as a model.

Female C57BL/6 mice seven to eleven weeks old were used as a model for inducing psoriasis. The mice were shaven on dorsal skin using Veet cream as a depilatory agent, excess cream was removed from the skin. The 5% Imiquimod cream (Glenmark) was used as a psoriasis inducing agent.

The mice were divided in four groups Normal Control group, Disease Control group, Treatment group and Standard group. The normal control group was used to compare with psoriasis induced groups the intensity of the skin inflammation, redness, and lesions. The Imiquimod cream was applied to all the groups except normal control group. The Imiquimod cream with dose 62.5 mg was topically applied on the dorsal skin of mice every day for 7-8 consecutive days.

After induction of psoriasis the mice were sacrificed for penetration measurement of drugs through Psoriasis skin. The mice were sacrificed by spinal dislocation method. The penetration evaluation was done using Franz diffusion apparatus. Skin was excised from Female C57BL/6 mice of seven to eleven weeks old procured from ACTREC, (Kharghar). The skin was immediately mounted on the Franz diffusion cell or frozen at -20°C for a maximum period of 4 weeks. The Optimized formulation and marketed cream was applied on psoriasis induced skin in donor compartment and placebo gel was applied to the control group. Sink conditions were maintained in the receptor compartment. All samples were evaluated by UV Spectrophotometry.

SKIN RETENTION STUDIES

Porcine skin was cut into small pieces and placed in 10 ml of phosphate buffer pH 5.5: ethanol (1:1). It was placed in water shaker bath for 30 minutes followed by sonication for 30 minutes and centrifugation at 5000 rpm for 15 minutes. The aliquots were used to determine the amount of drugs present in skin barrier.

TREATMENT OF MICE USING OPTIMIZED GEL FORMULA ON PSORIASIS INDUCED MICE

Female C57BL/6 mice of seven to eleven weeks old were used for inducing psoriasis. 5% Imiquimod cream with dose 62.5 mg was topically applied on the dorsal part of mice every day for 7-8 consecutive days. After induction of psoriasis the treatment was given by topically applying optimized gel formulation to the dorsal skin of mice every day for 1 week. The evaluation was done visually like intensity of lesion, inflammation, red patches.

RESULTS AND DISCUSSION

CRITERIA FOR EXCIPIENT SELECTION

The excipients selected were pharmaceutically acceptable, non-irritating, and non-sensitizing to the skin and categorized as GRAS (generally regarded as safe). Higher solubility of the drug in the oil phase is important, as it would help the drug to remain in the solubilized form in a microemulsion. Surfactant and co-surfactant were used in the microemulsion to reduce the o/w interfacial tension[9].

SATURATION SOLUBILITY STUDIES

Saturation solubility of Clobetasol propionate was carried out in various oils, surfactants and co-surfactants.
The solubility of Clobetasol propionate in various oils is depicted in Table1.1.
Amongst all the oils evaluated for equilibrium solubility, the solubility of Clobetasol propionate was found to be highest in Oleic acid (24.22mg/ml). Hence, oleic acid was considered as oil for further formulation and development.
The solubility of Clobetasol propionate in various surfactants and co-surfactants were depicted in Table1.2.
Solubility of Clobetasol propionate was found to be highest in Tween 80 (90.60mg/ml). Tween 80 showed gel formation during microemulsion formation. Hence, Labrasol (83.49mg/ml) was considered as surfactant and amongst all the co-surfactants evaluated for equilibrium solubility, the solubility was highest in Transcutol-P (39.71mg/ml). Hence, Transcutol-P was considered as co-surfactant for further formulation and development.

Emulsification ability of Surfactants and Co-surfactants

The emulsification ability of various surfactants and co-surfactants based on their transmittance studies is depicted in Table 1.3.
Tween 80 when combined with oils and water showed % Transmittance of only 66.73% due to its gelling property it was not selected. Labrasol showed % transmittance of 50.43% and Transcutol-P 92.07%. Therefore, based on saturation solubility and % transmittance data. Labrasol and Transcutol-P were selected as surfactant co-surfactant respectively.

Construction of Pseudo Ternary Phase diagram

The Ternary phase diagram depicted in figure 1 showed that the Microemulsion region decreased with the increasing ratio of Smix Surfactant and Co-surfactant from 1:1 to 2:1.Labrasol and Transcutol-P in 2:1 ratio found to accommodate maximum area of microemulsion in the phase diagram. The Microemulsion formed using 2:1 ratio of Smix was comparatively less viscous and clear than that obtained from 1:1 ratio of Smix. Hence, 2:1 ratio of Smix was considered for formulation development.

Optimization of Clobetasol propionate loaded Microemulsion

From the pseudo ternary phase diagram, four different points from the microemulsion region representing different concentration oil, Smix and water. The different percent compositions of oil, Smix and water in selected points are depicted in Table 1.4.

PHYSICAL STABILITY STUDIES

Microemulsions are considered to be thermodynamically stable systems with no phase separation, creaming, or cracking. Selected formulations from phase diagram were subjected to different stress stability testing like heating cooling cycle, centrifugation, and freeze–thaw cycle as in Table 1.5.

The optimized microemulsion did not show any change with respect to its physicochemical characteristics during stress studies. Hence, this indicates that the optimized microemulsion has good physical stability.

PERCENT TRANSMITTANCE

The observations of % Transmittance depict clarity of the microemulsions prepared for optimization and details are tabulated in Table 1.6.
The Percent Transmittance was found to be highest in Microemulsion Batch D i.e. 97.78% containing 5% oil, 45%Smix and 50water %.

GLOBULE SIZE AND POLYDISPERSIBILITY INDEX

The optimized microemulsion exhibited globule size as Z average diameter was found to be 247.8 and polydispersity index of 0.213 indicating homogeneity in size distribution. The result is shown in figure 2.

ZETA POTENTIAL

Zeta potential of optimized microemulsion was found to be -32.9 as shown in the figure 3 indicating negative charge on the droplet surface which prevents aggregation of droplets

SURFACE MORPHOLOGY

The drug is present in a completely dissolved state in the microemulsion. Figure 4 concludes that particles are globular with globule size in the nanometer scale.

IN-VITRO DIFFUSION STUDIES

Percentage of Clobetasol propionate and Salicylic acid diffused from the microemulsion based gel was 42.89% and 70.02% respectively and from the marketed ointment was 69.17% and 78.72% respectively at the end of 9 hours, as shown in figure 5.

EX –VIVO DIFFUSION STUDIES

Percentage of Clobetasol propionate and Salicylic acid diffused from the microemulsion based gel was 20.05% was 10.36% respectively and from the marketed ointment was 32.68% and 18.40% respectively at the end of 9 hours as shown in figure6.

IN-VIVO STUDIES

Imiquimod cream was applied to all the groups except normal control group. The Imiquimod cream with dose of 62.5 mg was topically applied on the dorsal part of mice every day for 7-8 consecutive days. The induction of psoriasis was indicated in Figure 8 and normal shaved skin for comparison was showed in Figure7.
The percentage of Clobetasol propionate and Salicylic acid diffused from the microemulsion based gel was 12.36% was 4.22% respectively and from the marketed ointment was 25.36% and Salicylic acid was 10.36% respectively at the end of 9 hours.

SKIN RETENTION STUDIES

Skin retention studies were carried out for the determination of amount of drug that remains in skin barrier. The % retention was determined using a developed Absorbance correction method as mentioned in Table 1.7.
From the above results it was observed that the retention of Clobetasol propionate was 36.25% against the marketed ointment which was 29.6%. Similarly, the retention of Salicylic acid was 25.6% against the marketed ointment which was 15.8%. Hence, concluded that the developed microemulsion based gel was more effective than conventional formulation.

TREATMENT OF MICE USING OPTIMIZED GEL FORMULA ON PSORIASIS INDUCED MICE

After induction of psoriasis, treatment was given by topically applying optimized gel formulation to the dorsal skin of mice every day for 1 week. The evaluation was done visually to check intensity of lesion, inflammation and red patches. Images of psoriasis induced mice and after treatment are shown in Figure 9 and 10.
After 1 week of application of optimized microemulsion based gel formulation it was observed that the erythema and scaling disappeared.

Table 1.1: Solubility studies of Clobetasol propionate in Oils

Sr. No.	Oil	Solubility (mg/ml)
1.	IPM	2.5
2.	Capryol PGMC	5.476
3.	Labrafac lipophilic WL 1349	7.45
4.	Oleic acid	24.22
5.	Oleic acid + Labrafac (1:1)	12.50

Table 1.2: Solubility studies of Clobetasol propionate in surfactants and co-surfactants

Surfactant	Solubility (mg/ml)	Co-surfactant	Solubility (mg/ml)
Tween 20	77.87	PEG-400	37.72
Tween 40	78.63	Transcutol-P	39.71
Tween 60	76.75	PEG-600	35.18
Tween 80	90.60	Propylene Glycol	20
Labrasol	83.49	-	-

Table 1.3: Emulsification ability of Surfactants and Co-surfactants

Sr. No.	Surfactant/Co-surfactants	% Transmittance
1	Labrasol	50.43%
2	Tween 80	66.73%
3.	Transcutol P	92.07%
4.	PEG-400	55.90%
5.	PEG-600	65.291

Table 1.4: Percent Composition of Clobetasol propionate loaded microemulsion formulated for Optimization along with formulation codes

Batch Code	Oil % (Oleic acid)	Smix (2:1) % (Labrasol+Transcutol P)	Water %
Batch A	5	60	35
Batch B	5	55	40
Batch C	5	50	45
Batch D	5	45	50

Table 1.5: Physical stability studies of drug loaded formulations

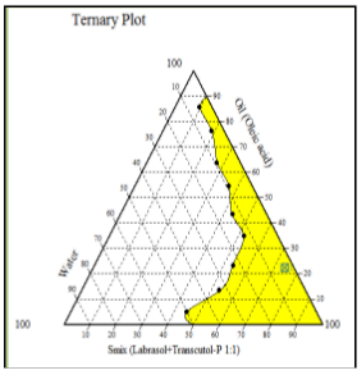
Bach Code	Heating Cooling cycles	Freeze thaw cycles	Centrifugation studies
Batch A	Passed	Passed	No phase separation
Batch B	Passed	Passed	No phase separation
Batch C	Passed	Passed	No phase separation
Batch D	Passed	Passed	No phase separation

Table 1.6: Percent Transmittance studies of Clobetasol propionate loaded Microemulsion

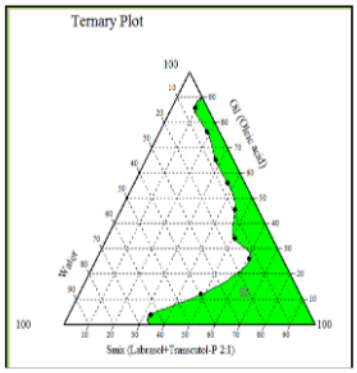
Sr. No.	Microemulsion	Percent Transmittance
1.	Batch A	95.00%
2.	Batch B	95.70%
3.	Batch C	95.57%
4.	Batch D	97.78%

Table 1.7: Skin retention studies

%Skin Retention (After 9 hours)			
Microemulsion Based gel		Marketed Ointment	
Clobetasol propionate	Salicylic acid	Clobetasol propionate	Salicylic acid
36.25	25.6	29.6	15.8



Ternary Plot 1:1 Smix



Ternary Plot 2:1 Smix

Figure 1: Pseudo Ternary Phase diagram of Smix ratio 1:1 and 2:1

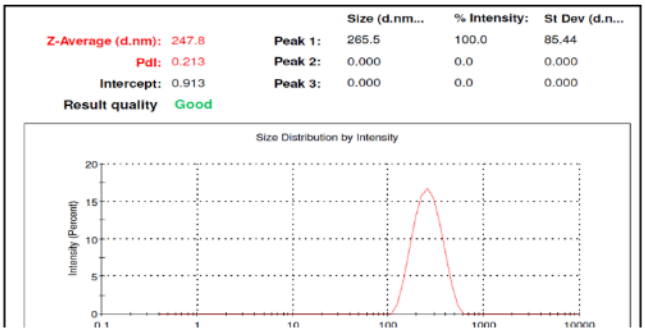


Figure 2: Globule size and Polydispersity index of optimized Clobetasol propionate loaded Microemulsion

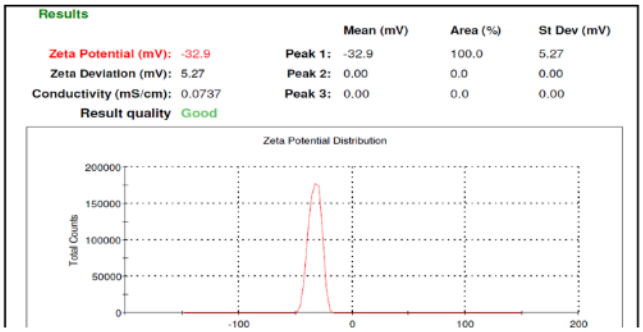


Figure 3: Zeta potential of optimized Clobeatsol propionate loaded Microemulsion

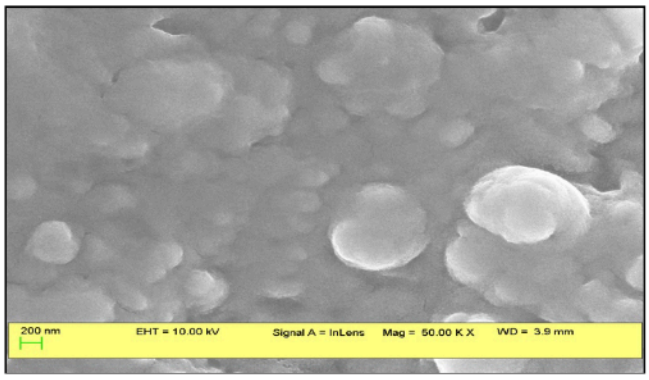


Figure 4: Scanning Electronic Microscopy of the optimized Clobetasol propionate loaded Microemulsion

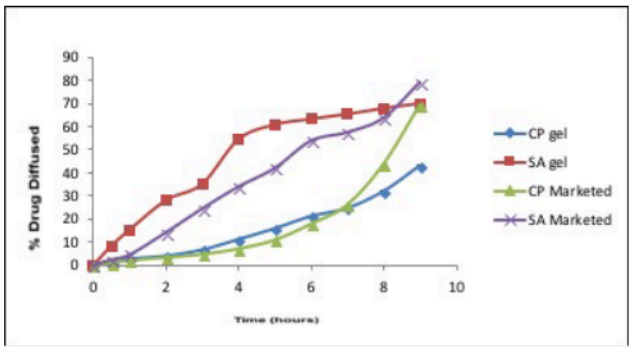


Figure 5: In-vitro diffusion of microemulsion based gel and marketed Ointment

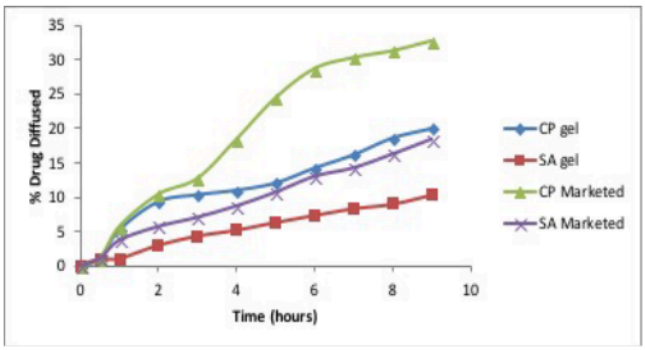


Figure 6: Ex-vivo diffusion of microemulsion based gel and marketed Ointment



Figure 7: Mice without symptoms of Psoriasis



Figure 8: Mice with symptoms of Psoriasis

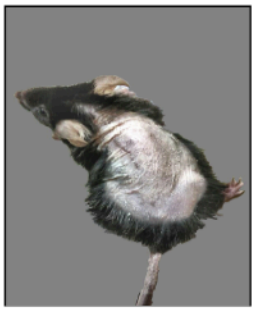


Figure 9: Psoriasis induced in mice

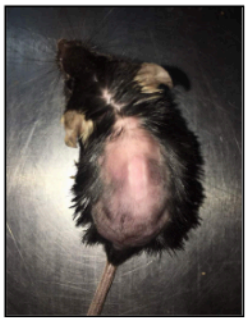


Figure 10: After treatment with Microemulsion based Gel

CONCLUSION

The present study shows that microemulsion containing 5% oil (Oleic acid), 45% Smix (Labrasol+Transcutol P) and 50% water formed a stable and clear microemulsion. Drug diffusion study of Clobetasole propionate loaded micro emulsion exhibited improved permeation as compared to conventional products. The optimized formulation exhibited better skin retention in comparison with conventional formulation and in-vivo anti psoriasis activity studies prove that the developed microemulgel formulation can be a promising product in the treatment of Psoriasis.

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