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SOLID LIPID NANOPARTICAL IN CORPORATED CREAM OF CLOBETASOL-17-PROPIONATE: DEVELOPMENT AND *IN-VITRO* EVALUATION

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Keywords:

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ABSTRACT: The clinical efficacy of glucocorticoids is dependent on its potency and on its ability to be absorbed in to the skin and therefore, reach its site of action. Colloidal drug carriers such as solid lipid nanoparticles could target glucocorticoids to the epidermis, where the anti-inflammatory action takes place. Topical corticosteroids have long been the chronic stage in the treatment of steroid responsive dermatitis. Creams containing Clobetasol-17-propionate (CP) as active ingredients are categorized as super potent class I topical dermatological corticosteroids. For the drug molecule to reach the cutaneous microcirculation, enhance, the systemic circulation, have to transverse both the lipophilic stratum cornium and much more viable epidermis. Various formulations of solid lipid nanoparticles were formulated using various ingridients *viz.* Compritol 888 ATO, lutrol F68, tween 80 *etc*. the cream formulations were evaluated as there pH, drug content, viscosity, spreadability, extrudability and percent drug release. *In-vitro* diffusion study using cellophane membrane as well as rat skin mounted in Franz diffusion cell. CP was analyzed spectrophotometrically at 240 nm.

INTRODUCTION: Topical corticosteroids have significantly enhanced the treatment of patients with dermatoses such as psoriasis and eczema [1, 13]. In particular, group I high potency corticosteroids such as Clobetasol-17-propionate have proved safe and effective for limited course treatment of inflammatory and pruritic manifestation of moderate to severe corticosteroid responsive dermatoses [2]. Colloidal drug carriers such as solid lipid nanoparticles could target glucocorticoids to the epidermis, where the anti-inflammatory action takes place [3, 14]. Topical delivery includes external topical that are spread, sprayed, or otherwise dispersed on to cutaneous tissues to cover the affected area.

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Since, topical drug delivery system reduces the gastrointestinal problems associated with oral route, it has been recognized as an alternative route to oral delivery. The topical drug delivery has the additional advantage as such systems allow the terminate of medications whenever desired [4].

Moreover topical drug delivery system offer large surface area for drug application as compare to that of buccal or nasal cavity.

MATERIAL AND METHODS: Clobetasol-17-propionate was a gift sample from Macleods Pharmaceutical Pvt. Ltd., Mumbai (Maharashtra), cetomacrogol 1000 purchased from S. D. Fine Chem. Ltd., Mumbai, cetosteryl alcohol, white soft paraffin, light liquid paraffin purchased from RFCL limited, New Delhi, propylene glycol, methyl paraben, propyl paraben from Merck and Co. Inc, USA, thymol from SAS Chemical Co., Mumbai, Compritol 888 ATO from Gettefosse, lutrol F68 purchased from BASF. All the chemicals used in the present study were of analytical grade.

Formulation of Clobetasol-17-propionate SLN Cream: [5] In order to prepare solid lipid nanoparticles (SLN) of CP, various ingridients *viz.* compritol 888, lutrol F68, tween 80 *etc*. were selected.

Development of SLN'S of CP: Purified water was heated at 85ºC and this temperature was maintained throughout the process. To this accurately weighed quantity of lutrol F68 and tween 80 was added and stirred until to get a clear solution (Mixture 1). Compritol 888 ATO was weighed accurately and melted in a separate vessel. To this Clobetasol-17-propionate was added and stirred to get a clear solution (Mixture 2).

TABLE 1: FORMULA OF SLN'S OF CP

S. no.	Ingredients	Concentration (g)
1	Clobetasol 17-propionate	0.44
2	Compritol 888	10.00
3	Lutrol F68	20.00
4	Tween 80	4.00
5	Purified water	365.56

Finally, the Mixture 2 was added to Mixture 1 under ultra-turrax stirrer at 13,000 rpm for at least 15 min. The temperature was maintained 85 ºC throughout the process. After homogenization of the abow dispersion, it was kept aside and allowed to cool down at room temperature. Formulas are given in **Table 1**.

Development of Cream of CP: [5] Purified water was taken in a stainless steel vessel and heated up to 65 ºC. To this heated water, weighed quantity of methyl paraben and propyl paraben were added. Chlorocresol and monobasic sodium phosphate were then added to it. 65 ºC was maintained throughout this process. 200 g SLN'S of CP was weighed accurately and heated to 65 ºC, was added to the mixture and labeled as Mixture A. In the another vessel the weighed quantity of cetosteryl alcohol, white soft paraffin, cetomacrogol 1000 and light liquid paraffin were melted according to their increasing melting points while maintaining the temperature 65 ºC. This mixture was then added to Mixture A under ultra-turrax at 45,000 rpm for at least 30 min. Finally, the mixture was stirred using mechanical stirrer and allowed to cool at room temperature, filled in to collapsible tubes and labelled properly. Compositions of different cream formulations are given in **Table 2**.

TABLE 2: COMPOSITION OF VARIOUS CLOETASOL-17-PROPIONATE SLN'S CREAMS

Ingredients (g)	F14	F15	F16	F17	F18	F19	F20	F21
Cetomacrogol 1000	12.00	16.00	10.00	14.00	16.00	16.00	12.00	14.00
Cetosteryl alcohol	38.00	36.80	36.00	36.8	36.8	36.8	35.8	37.8
Methyl paraben	1.00	0.80	0.80	0.80	0.80	0.80	0.80	0.80
Propyl paraben	0.01	0.08	0.06	0.08	0.08	0.07	0.08	0.08
Chlorocresol	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36
Light liquid paraffin	29.80	30.80	30.80	30.80	29.80	31.80	30.80	30.80
Monobasic sodium phosphate	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27
White soft paraffin	39.20	39.20	39.20	39.20	39.20	38.20	39.20	38.20
Purified water	79.36	75.69	82.51	77.69	76.69	75.68	80.69	77.69
SLN preparation	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0

Evaluation of Cream: The formulated creams were inspected visually for colour, presence of any grittiness and feel. To evaluate the feel, the formulation was put in between the index finger and thumb and grittiness/smoothness was observed manually. The pH of formulated cream was determined using pH meter. 1 g of cream was stirred in distilled water to get a uniform dispersion. Volume was made up to 100 ml. For drug content analysis each formulation (1g) was taken in a 100 ml volumetric flask, diluted with Ethanol and shaken to dissolve the drug in it. The solution was filtered through Whatman filter paper no. 42. The content of the drug was estimated spectrophotometrically by using standard curve plotted at λ_{max} 240 nm [6, 7].

The apparatus used for extrudability was suitably fabricated in the laboratory. It consists of a wooden block inclined at an angle of 45º fitted with a thin metal strip at one end. While another end was free. The formulations were filled in the collapsible pressed under the influence of varying weight. The extrudability of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm ribbon of cream in 10 sec. The extrudability of the formulation was determined using the grading system.

An apparatus suggested by Multimer *et al*., (1956) was fabricated in the laboratory and used for the determination of spreadability of cream formulations. The apparatus consists of a wooden block, with a fixed glass slide and movable glass slide with one end tied to weight pan rolled on the pulley, which was in horizontal level with fixed slide. An excess of cream sample 2.5 g was placed between on the ground slide and sandwiched by another glass slides having the same dimensions as that of the fixed ground slide and provided with a hook. A 1000 g weight was placed on slides for 5 min to compress the sample to a uniform thickness and excess of the cream scrapped off from the sides. Weight (60 g) was added to the pan. The time (seconds) required by top slide to cover a distance of 5 cm was noted. It was calculated using

$$S = ml / t$$

Where, S - Spreadability in g.cm / sec, m - Weight tied to upper slide, l - Length of glass slide, t - Time in sec.

Length of glass slide was 11.3 cm and weight tied to upper slide was (60g) throughout the experiment. Viscosity of the formulated cream was determined using Brookfield DV II + PRO viscometer. In a clean and dry 250 ml beaker, take the test sample. Determine the viscosity of the test sample as per standard operating procedure of viscometer by using spindle no. 3 and 4. Viscosity of the sample find out at spindle speed of 0.3, 0.5, 0.6, 1.0, 1.5 and 2.0 rpm for ascending and descending order respectively. Dial reading calculated for the reading of viscosity, shear rate and shear stress [8].

***In-vitro* Diffusion Studies:** [9] To test the pattern of release of drug from various cream formulations, *in-vitro* diffusion studies were carried out. The developed formulations were subjected to *in-vitro* diffusion studies using Franz diffusion cell. The receptor compartment was filled with a mixture of ethanol and freshly prepared phosphate buffer saline pH 7.4 taken in the ratio of 3:7 respectively. The diffusion cell was covered with a cellophane membrane. The temperature of the mixture was maintained at 37 ± 1 ºC and receptor solution was stirred with a magnetic stirrer at 600 rpm throughout the experiment. Care was taken that no air bubbles should be trapped under the membrane. Aliquots (2 m) were withdrawn at regular interval of 1 h for a period of 8 h, and replaced with equal volume of freshly prepared ethanol and phosphate buffer saline pH 7.4 mixture equilibrated at 37 ± 1 ºC. All the samples were suitably diluted with diffusion medium and analyzed spectro-photo-metrically at 240 nm for Clobetasol 17-propionate content. The percent drug release was calculated for each time interval.

Stability Studies: [8, 15] The final formulation was also subjected to the 25 ºC ± 2 ºC at 60 ± 5% RH, 40 ºC ± 2 ºC at 75 ± 5% RH condition of temperature and relative humidity during stability studies. Formulation was evaluated for various parameters after one month. The parameters of the creams studied *i.e.* drug content, *in-vitro* diffusion study, viscosity and pH.

***In-vivo* Study:** [10, 11, 12] The optimized cream formulation was evaluated for skin irritation studies using 10 mice (Grouped in 2 each group having 5 mice). The experimental protocol entitled "Solid lipid nanopartical in corporated cream of Clobetasol-17- Propionate: development and *in-vitro* evaluation" was approved by the Institutional Animal Ethics Committee, Loar Shiva College of Pharmacy, Sirsa vide Approval Number LSCP/IAEC/2010. The hair of the dorsal portion was removed applying a hair removal cream and the skin was washed properly one day prior to use. The area shaved marked by marker for cream application. The application sites were examined for dermal reaction in accordance with draize scoring criteria. The erythema score were given from 0-4 depending upon the degree of erythema as 0- No erythema, 1- Slight erythema (Barely perceptible light pink), 2-Moderte erythema (Dark pink), 3- Moderate to severe erythema (Light red), 4- Severe erythema (Extreme redness)

RESULTS AND DISCUSSION: Topical corticosteroids have significantly enhanced the treatment of patients with dermatoses such as psoriasis and eczema. In particular, group I high potency corticosteroids such as clobetasol-17-propionate have proved safe and effective for limited course treatment of inflammatory and pruritic manifestation of moderate to severe corticosteroid responsive dermatoses. Penetration enhancement technology is a challenging development that would increase the number of

drugs available for topical and transdermal administration. **Table 3** depicts the pH, drug content and viscosity values of all the eight (F14-F21) cream formulations of CP. As is evident from **Table 3** pH values of all formulations was found to be in the range of 5.11 to 6.40, which is close agreement with the desired pH range (5.4-6.4) of such formulations**,** hence rendering them more acceptable to the human skin. The drug content was found in the range of 93.52 to 100.34%. This is again in consonance with reported values of drug content for a CP cream [17]. Also the values of viscosity for all CP cream formulation were in the desirable range. All the CP cream formulations were evaluated in terms of spreadability and extrudability. All the formulations have shown acceptable spreadability, however, most of the formulations have exhibited poor (+) or good (++) extrudability. Formulation F15 exhibited excellent (+++) extrudability.

TABLE 3: pH, PERCENT DRUG CONTENT, VISCOSITY, SPREADABILITY AND EXTRUDABILITY OF FORMULATION F14-F21

Formulation	pH ± S.D.(n=3)	% Drug content	Viscosity (KcP)	Spreadability ± SD (n=3)	Extrudability
F14	5.81±0.020	98.96	12.51	27.03±0.23	++
F15	5.98±0.023	99.65	14.41	24.52±0.44	+++
F16	5.30±0.020	98.27	13.53	19.93±0.09	+
F17	5.29±0.015	99.31	16.74	21.47±0.14	++
F18	5.74±0.037	97.93	15.32	24.53±0.27	++
F19	5.48±0.020	98.62	11.23	23.65±0.75	++
F20	6.16±0.036	97.58	13.13	21.59±0.57	++
F21	6.25±0.030	100.34	14.52	23.65±0.26	++

Poor (+), Good (++), Excellent (+++),

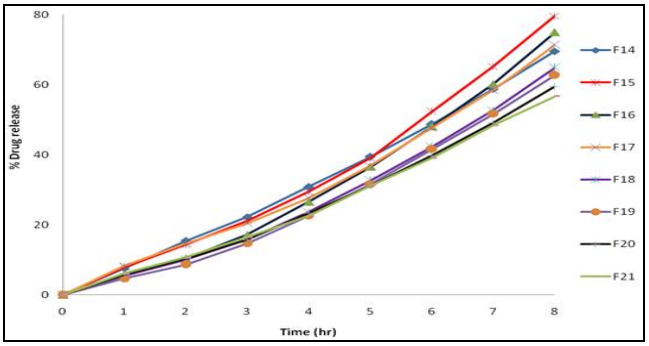

FIG. 1: DRUG RELEASE PROFILE OF FORMULATION F14 TO F21

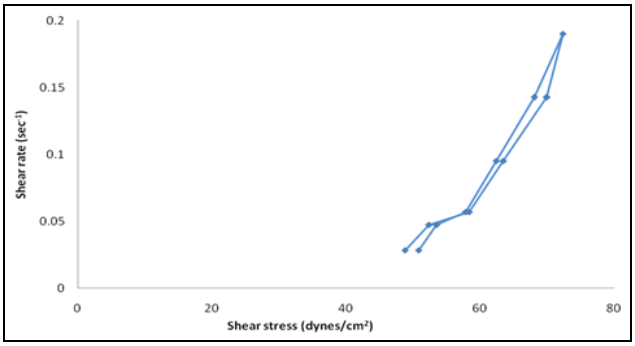

FIG. 2: RHEOGRAM OF FORMULATION F15

TABLE 4: RHEOLOGICAL BEHAVIOUR OF FORMULATION F15

	RPM	Shear rate (sec^{-1})	Shear stress ($dynes/cm^2$)		RPM	Shear rate (sec^{-1})	Shear stress ($dynes/cm^2$)
Ascending	0.3	0.0285	50.863	Descending	1.5	0.1427	69.986
	0.5	0.0475	53.543		1.0	0.0951	63.485
	0.6	0.057	57.899		0.6	0.057	58.427
	1.0	0.0951	62.429		0.5	0.0475	52.427

TABLE 5: STABILITY STUDIES OF FORMULATION F7 AND F15

Parameters	Storage condition F15	
	25° C/60 % RH	40° C/75 %RH
Drug content (%)	99.61	99.58
% Drug release	74.03	73.96
Viscosity (KcP)	14.41	14.43
pH	5.97	5.98

Fig. 1 shows their corresponding release profiles. Among the formulations developed, formulation F15 showed better release. Rheological behavior of the semisolid is essential to achieve spreading, adherence on the skin, removal from containers and release of the drug from the bases. The data for the rheogram of formulations F15 is shown in **Table 4** and the rheograms for F15 is shown in **Fig. 2**.

TABLE 6: SHOWS SKIN IRRITATION TEST FOR FORMULATIONS F15 AND PLACEBO

Mice tail marking	Group I		Group II	
	Test	Draize score	Control	Draize score
I	F15	0	PL	0
II	F15	0	PL	0
III	F15	0	PL	0
IIII	F15	0	PL	0
IIIII	F15	0	PL	0

Formulation exhibited plastic behavior with thixotropy indicating the high quality of developed formulation F15. The developed cream formulations were subjected to stability study as per ICH guidelines for the period of one month. The stability evaluation data were mentioned in **Table 5**. The studied formulations was found to be stable and do not show any loss of drug content, change in % drug release, viscosity and pH. *In-vivo* skin irritation study shows no irritation on mice.

CONCLUSION: From the current investigation it can be concluded that Topical cream formulation of Clobetasol-17-propinate (CP) can successfully be prepared using solid lipid nanoparticles (SLNs) of CP. Formulation parameters *viz.* penetration enhancers greatly affect the topical cream formulations of CP. The order of penetration enhancement effect shown by various penetration enhancers used in the current studies are as follows oleic acid > isopropyl myristate > polysorbate 80 > thymol. The developed formulation using SLN's of CP (F15) showed excellent extrudability and spreadability in addition to desirable pH, drug content, consistency, *etc*. The selected formulation F15 exhibited better drug release performance vis-à-vis marketed cream formulation of CP (LOBATE®, Mapromax life sciences Pvt. Ltd). The formulation F15 was observed to be smooth and free from any irritant effect when studied on mice. Formulation F15 showed plastic behaviors with thixotropy and drug release was governed by Pappas kosrmear modal. The stability studies carried out on selected CP cream formulation F15 showed no alteration in drug content, pH, viscosity, *etc*., hence were stable for the studied period.

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CONFLICT OF INTEREST: Nil

REFERENCES:

1. Wozel G: Psoriasis treatment in different location: scalp, nail and intertriginous areas. Clinics in Dermatology 2008; 26: 448-459.
2. Windersberg S, Leopold CS and Guy RH: Bioavalability and bioequivalence of topical glucocorticoids Euro Jou of Pharmaceutics and Biopharmaceutics 2008; 68(3): 453-66.
3. Senyigit T, Sonvico F, Barbieri S, Ozer O, Santi P and Colombo P: Lecithin/chitosan nanoparticles of Clobetasol-17-propionate capable of accumulation in pig skin. J Control Release 2010; 142: 368-373.
4. Soni M, Kumar S and Gupta GD: Transdermal drug delivery: A novel approach to skin permeation. J Pharm Res 2009; 2(8): 1184-1190.
5. Mader K and Mehnert W: Solid lipid nanoparticles-concept, procedures and physicochemical aspects. CRC press, London 2005: 1-22.
6. Aejaz A, Azmail K, Sanaullah S and Mohsin A: Studies on Aceclofenac solid dispersion in corporated gels: development, characterization and *in-vitro* evaluation. Int J Pharmacy and Pharma Sci 2010; 2(1): 111-115.
7. Senyigit T, Padula C, Ozer O and Santi P: Different approaches for improving skin accumulation of topical corticosteroids. Int J Pharm 2009; 380: 155-160.
8. Chakole CM, Shende MA and Khadatkar SN: Formulation and evaluation of novel combined Halobetasol propionate and fusidic acid ointment Int. J. Chem. Tech. Res 2009; 1(1): 103-116.
9. Tsai JC: Content and transdermal delivery of Clobetasol 17-propionate from commercial cream and ointments. J Food Drug Analysis 2002; 10(1): 7-12.
10. Bharkatiya M: Designing and characterization of drug free patches for transdermal application. Int J Pharm Sci and Drug Res 2010; 2 (1): 35-39.
11. Laithy HM: Novel transdermal delivery of Timolol malete using sugar esters: Preclinical and clinical studies. Eur J Pharm Biopharm 2009; 72: 239-245.
12. Tanwar YS, Chauhan CS and Sharma A: Development and evaluation of Carvedilol transdermal patch. Acta Pharm, 2007; 57: 151-159.
13. Overgaard HS, Kezic S, Jakasa I, Engebretsen KA, Abibach H and Thyssen JP: Skin absorption through atopic dermatitis skin: a systematic review, British J of Dermatology 2017; 177: 84-106.
14. Almeida LN and Araujo TG: Solid lipid nanoparticles: The efficiency carrier for topical delivery of hydrophilic drugs, W J of Pharma and Pharm Sciences 2017; 6(9): 177-184.
15. Yamamoto Y, Fukami T, Onuki Y, Metori K, Suzuki T and Koide T: Comparision of pharmaceutical properties among Clobetasol propionate cream formulation: considerations from near infrared spectra, Vibrational spectroscopy. 2017; 93: 17-22.
16. Weidinger S and Novak N: Atopic dermatitis. Lancet 2016; 387: 1109-1122.
17. Andersen RM, Thyssen JP and Maibach HI: Qualitative *vs.* quantitative atopic dermatitis criteria in historical and present perspectives. J Eur Acad Dermatol Venereol 2016; 30: 604-618.

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