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FORMULATION AND EVALUATION OF SOLID LIPID NANOPARTICLE GEL FOR TOPICAL DELIVERY OF CLOBETASOL PROPIONATE TO ENHANCE ITS PERMEATION USING SILK SERICIN AS PERMEATION ENHANCER

Ashok A. Hajare [*1], Pallavi D. Velapure [1], Prashant N. Rathod [1], Kiran S. Patil [2] and Swapnil S. Chopade [3]

Department of Pharmaceutics [1], Bharati Vidyapeeth College of Pharmacy, Kolhapur - 416008, Maharashtra, India.
Department of Pharmaceutical Quality Assurance [2], Department of Pharmaceutics [3], Tatyasaheb Kore College of Pharmacy, Warananagar, Panhala, Kolhapur - 416113, Maharashtra, India.

Keywords:

Solid lipid nanoparticles, Clobetasol propionate, Silk sericin, Solvent injection method

Correspondence to Author:
Dr. Ashok A. Hajare

Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Kolhapur - 416008, Maharashtra, India.

E-mail: ashok.hajare@bharatividyapeeth.edu

ABSTRACT: The objective of this present work was to develop Solid Lipid Nanoparticle (SLN) gel for topical delivery of clobetasol propionate to enhance its permeation using silk sericin as a permeation enhancer. The proposed Clobetasol propionate gel loaded with solid lipid nanoparticle was prepared by solvent injection method. The effects of different strengths of lipid on the particle size, zeta potential, drug entrapment and release, and drug excipient interactions and the thermal behavior were evaluated. The final gel formulations were obtained by adding carbopol as a gelling agent and sericin a natural silk protein as a permeation enhancer and tested by an *in-vitro* gelling test. Prepared gel was evaluated for viscosity, pH, and *in-vitro* permeation properties. This study showed that the combination of carbopol with silk sericin produced the most promising gel formulation for topical application in the treatment of psoriasis. In this study, it was demonstrated that silk sericin-based gel, blended with solid lipid nanoparticle, could be produced with a cost-effective and industrially scalable technique. The outcome represents the starting point for the development of potential topical formulations suitable for the treatment of psoriasis.

INTRODUCTION: Psoriasis is one of the common skin disorders caused by many environmental factors such as trauma, drugs, infection, alcohol, smoking, and stress [1]. Disease recognized today as Psoriasis Vulgaris, or plaque psoriasis is the most common form of the condition. Psoriasis affects the scalp, elbows, knees and lumbar region of the back, where high epidermal turnover observed.

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Chronic erythematous plaques covered with silvery scales are the classical features of this disorder. There are various modes of treatments like topical, ultraviolet light (phototherapy) and systemic for psoriasis [2]. Topical therapies are the backbone of the management of psoriasis and it is most commonly used. They are safe and well-tolerated by the patients. Patient adherence may be the largest barrier to treatment success with topical therapies [3].

Clobetasol propionate (CP) is BCS class II corticosteroid with anti-inflammatory, antipyretic, and vasoconstrictive properties [4]. It is the most potent of currently available topical steroids as predicted by the vasoconstrictor assay. The clinical use of CP has a limitation that its poor permeability through the skin reduces its therapeutic

effectiveness at the target site [5]. It acts by inhibition of phospholipase A2, which leads to the inhibition of synthesis of arachidonic acid and controls the biosynthesis of prostaglandins and leukotrienes. CP available in various dosage forms such as ointment, cream, lotion, and foam are in use for the treatment of mild to moderate psoriasis [6]. The major challenge for topical formulations used to treat psoriasis is to provide a sufficient drug penetration into the skin without inducing any significant irreversible alteration to the skin barrier function [7-27]. Clinically, CP has some practical disadvantages such as poor permeability through the skin which reduces its therapeutic effectiveness at the target site.

Novel Nano-drug Delivery systems are of considerable interest nowadays as these allow for drugs or bioactive small molecules to be introduced at specific target sites [8]. A solid lipid nanoparticle (SLN) is the most promising technique appealing to major attention as novel colloidal drug carriers for topical use [9]. SLN has significant advantages such as powerful permeation ability, and high drug-loading capacity for topical delivery when compared with the other carriers such as liposomes and nanoemulsion [10-11]. Topical vehicles like chemical enhancers and solvents system that modifies drug permeation through the skin attracting the researcher. Since, chemical enhancers are irritant they may be harmful, especially in the chronic application.

Sericin is a protein which is coated on the surface of fibroin fiber when *Bombyx mori* silkworm spins cocoon for protective and adhesive effects [12]. Sericin could be extracted by boiling cocoon in an alkaline solution or through high temperature and high-pressure extraction process [13]. Sericin is a macromolecular globular protein, composed of 18 kinds of amino acids is characterized by the presence of 32 percent of serine [14]. Most of them possess strong side polar groups, making sericin water-soluble [6]. Because of its good hydrophilicity, reaction activity, biocompatibility and biodegradability, sericin has been applied widely in biomedical materials such as cell culture scaffolds, drug carriers, and tissue engineering scaffolds along with it is antioxidant and anticoagulant properties it shows good wound healing activity. Sericin is a silk protein and has different biological functions such as oxidation resistance, antibacterial and antimicrobial activity and protection against solar ultraviolet radiation (UV), easy absorption and moisture release [15-19]. Sericin based SLN gel could be a useful attempt for the enhanced absorption of CP through the topical route. The present work was aimed at the preparation of CP loaded SLN for powerful permeation ability and high drug-loading capacity and develop them to CP loaded SLN topical gel with help of sericin. The objective behind the proposed work was to enhance drug uptake through the skin and provide prolonged and improved therapeutic efficiency along with a reduction in the toxicity.

MATERIALS AND METHODS: Clobetasol propionate was received as a gift sample from Unison Pharmaceuticals, Baddi, India. Carbopol 934 was provided by Gripphon laboratories. Glycerol monostearate was purchased from West Coast Laboratories Mumbai. Soya lecithin was purchased from Mylochem Mumbai and Tween 80 from Loba Chemicals Pvt. Ltd. The dialysis membrane was purchased from Himedia Laboratories Pvt. Ltd., Mumbai. Silk cocoons were gift sample from Sericulture Institute, Pune, India. All the other reagents and solvents were of analytical reagent grade.

Extraction and Purification of Silk Sericin: Dried *Bombyx mori* silk cocoons were cut into small pieces. Those pieces are treated with boiling aqueous solution of 0.5% sodium carbonate for 20 min with continuous stirring. The whole mass of small pieces was repeatedly washed with distilled water to remove the glue-like sericin [20].

Preparation of Drug Loaded SLN: The CP loaded SLN were prepared by using the solvent injection method [21-22]. The lipid phase was prepared by melting GMS and lipophilic surfactant soya lecithin together, respectively. The drug was dissolved in ethanol and added into the melted lipid phase. This solution was taken in a glass syringe and was injected rapidly into the aqueous phase containing Tween 80 (having the same temperature as that of lipid phase) and sonicated for 3 min by using sonicator. The formed dispersion was stirred under mechanical stirrer for 30 min at 400 rpm, to get nanoparticulate dispersion. The composition of different batches is shown in **Table 1**.

TABLE 1: COMPOSITION OF SLN FORMULATION

Formulation codes	Drug (mg)	GMS (mg)	Soya lecithin (mg)	Ethanol (mL)	Tween 80 (mg)	Distilled water (mL)
F1	10	100	50	2	400	20
F2	10	100	100	2	400	20
F3	10	200	100	2	400	20
F4	10	200	200	2	400	20
F5	10	400	200	2	400	20
F6	10	200	400	2	400	20
F7	10	400	400	2	400	20

Characterization of CP Loaded SLN:

Particle Size Analysis: Particle size of prepared SLN was determined by using Malvern Zetasizer, (Nano ZS). The dispersion was diluted appropriately 20 times with double distilled water before running the sample in the instrument, to ensure that the light scattering signal, as indicated by particle count per second, which was within instruments sensitivity range [25].

Zeta Potential: Measurement of zeta potential is a requirement to know the stability of SLN dispersion. Zeta potential of prepared SLN dispersion was measured by Zetasizer [25].

Entrapment Efficiency: The entrapment efficiency, which corresponds to the percentage of drug encapsulated within and adsorbed on to the nanoparticle, was determined by measuring the concentration of free CP in the dispersion medium. A volume of 2 mL of each drug-loaded formulation was centrifuged at 5300 rpm for 30 min to separate the lipid and aqueous phase. The supernatant was then diluted with ethanol and analyzed by a UV VIS spectrophotometer at 239 nm using Model 1371, Electronics India. The entrapment efficacy of nanoparticle was calculated as follows: [25]

Entrapment efficiency (%) = (Initial amount of drug – amount of free drug) / (Initial amount of drug) × 100

Drug Content: An amount of SLN equivalent to 0.05% of CP was dissolved in 100 mL of ethanol in a volumetric flask. SLN solution was kept for 24 h under constant stirring to obtain complete solubility of drug. The solutions were then filtered, diluted suitably and analyzed spectrophotometrically at 239 nm using ethanol as a reference solvent.

FTIR Study: FTIR is an important tool to analyse the purity of the drug and excipient. FTIR spectrum shows the fundamental peaks corresponding to the chemical nature of the drug and excipient. FTIR spectrums were obtained for CP and all excipients alone and in combination. The spectrums were analyzed to determine any possible interaction among drug and excipients under investigation [25.]

PXRD Analysis: X-ray diffraction yields the atomic structure of materials based on the elastic scattering of X-rays from the electron clouds of the individual atoms in the system. PXRD patterns of SLN powder were recorded at room temperature on X-ray diffract meter (Philips Analytical XRD, PW 3710) with CuKα radiation (1.54 Å), at 40 kV, 40 mA passing through a nickel filter. PXRD study reveals information about the crystallographic structure, chemical composition and physical properties of materials. Freeze-dried product of optimized formulation was subjected to PXRD study by using X-ray diffract meter. For this, the samples of pure drug, physical mixture and freeze-dried product of CP loaded SLN formulation were irradiated with monochromatized CuKα radiation and analyzed between 10° to 70° (2θ).

DSC Study: Thermal behavior of SLN was analyzed by DSC on a Shimadzu differential scanning calorimeter (TA Instruments, model SDT 2960, USA) equipped with intracooler and refrigerated cooling system. Thermo grams of drug and excipients alone, in combination as a physical mixture and optimized freeze-dried product, were obtained using DSC equipped with an intracooler. Platinum crucible used with alpha alumina powder as a reference to calibrate the DSC temperature and enthalpy scale. The powder samples were hermetically kept in the aluminum pan and heated at a constant rate of 10 °C per min, over a temperature range of 35 °C to 250 °C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 150 mL/min [25].

***In-vitro* Drug Release:** *In-vitro* drug release studies were carried out using a dialysis bag

method with a molecular weight cut off of 14000 Da. The *in- vitro* drug release study was conducted within 24 h after the preparation of drug-loaded SLN. The SLN equivalent to 0.05% of the drug was transferred to the dialysis bag membrane and the tube was introduced in the beaker containing phosphate buffer (7.4) solution. The medium was stirred on mechanical stirrer at 100 rpm with 37 °C. At predetermined time intervals, 5 mL dissolution medium was withdrawn and replaced with the same amount of fresh medium. The amount of CP released from SLN was measured by using UV spectroscopy.

Formulation of SLN Loaded Gel: Carbopol l934 was soaked in distilled water under mechanical stirring. This dispersion was kept overnight for complete hydration of the polymer. SLN formulation F2 (quantity equivalent to 0.05% w/w of CP) was added with stirring to ensure uniform mixing of the drug in dispersion. Lyophilized Sericin, 1% was added in dispersion with continuous stirring. After complete dispersion triethanolamine was slowly added to form a fine gel.

TABLE 2: COMPOSITION OF GEL FORMULATION

Composition	F1	F2	F3
Carbopol	0.5%	1%	1.5%
SLN	≅ 0.05% CP	≅ 0.05% CP	≅ 0.05% CP
Sericin	1%	1%	1%
Triethanolamine	q.s.	q.s.	q.s.
Distilled water	q.s.	q.s.	q.s.

Evaluation of Gel:

Physical Appearance and Homogeneity: Physical appearance and homogeneity of the gel were observed visually. Clarity is one of the most important characteristics. The formulations were examined for visual appearance and clarity by visual observation against a white and black background to check the presence of any particulate matter.

Viscosity: Viscosity of instilled formulation is an important factor in determining the residence time of drug on the skin. The rheological studies of the formulations were carried out with a Brookfield viscometer (RVDV II+ Pro model) using a sample adaptor with spindle number (SC4-21), and angular velocity was increased gradually from 0.5 to 100 rpm. Then, the hierarchy of angular velocity was reversed (100 to 10 rpm). The average of two readings was used to calculate the viscosity. The pH of the formulations was raised from 5.0 to 7.4 by adding a 0.5 N sodium hydroxide solution, and simultaneously the temperature was increased from 25 °C to 37 °C. The viscosity of samples was recorded before and after jellifying [24].

pH: pH is one of the most important factors involved in the formulation process. Two areas of critical importance are the effects of pH on solubility and stability. The preparation should be non-irritating to the skin. The pH of the prepared SLN gel after the addition of all the ingredients was measured using a digital pH meter.

Drug Content Uniformity: To ensure that all the formulations contain the same amount of active drug, drug content analysis of prepared gel was carried out using a spectrophotometric method. The vials containing the preparation were shaken for 2-3 min and 1 ml of preparation was transferred to 100 ml volumetric flask and volume were made up with phosphate buffer pH 7.4. An aliquot of the sample was withdrawn and further diluted to 10 mL with the same phosphate buffer. The concentration of CP was determined at 239 nm by using a UV-Visible spectrophotometer.

***In-vitro* Drug Release Studies:** The sericin based SLN loaded gel, plain CP loaded gel and marketed cream formulation (MOMATE®) were studied for their diffusion through dialysis membrane LA-395 (Mol. Wt. cut off 14,000 Da, Hi-media) using Phosphate buffer (pH 7.4) as release media. The membrane was soaked in dist. water and kept overnight. A fixed quantity of formulations, *i.e.*, SLN loaded gel, Silk sericin based SLN gel and marketed cream (each containing 0.05% w/w of CP) was placed in different bags of dialysis membrane. The media was continuously stirred on mechanical stirrer at a speed of 100 rpm. The temperature was maintained at 37 °C. The dissolution was carried out for 24 h. At predetermined time intervals of 1 h, the sample was withdrawn and replaced with the same volume of release media. The percent cumulative drug released or diffused at different time intervals analyzed by using UV spectrophotometer at 239 nm [24].

RESULTS AND DISCUSSION:

Characterization of SLN:

Particle Size: Analysis of the result shows that the particle size range was 190 nm to 559.11 nm. The smallest particle size 190 nm was obtained for the formulation that contained 200 mg lipid (F2). The largest particle size was seen in formulation F6 wherein it was 559.11 nm at 600 mg lipid.

The amount of lipid used was found to be directly proportional to the particle size. The surfactant concentration played an important role in maintaining particle size within the nano size. In addition to the quantity of lipid used particle size also depends on surfactant concentration which when optimum, submicron particle size was achieved with a low particle size distribution **Table 3**.

Zeta Potential: Measurement of zeta potential gives an indication of particle charge and in turn the stability of the dispersion. In general zeta potential should be high; dispersion having this value lower than -30 mV and higher than +30 mV is usually considered best for the dispersion to be stable. Within this range, particle aggregation is less likely to occur for charged particles due to electronic repulsion. Zeta potential for different formulations is given below in **Table 3**.

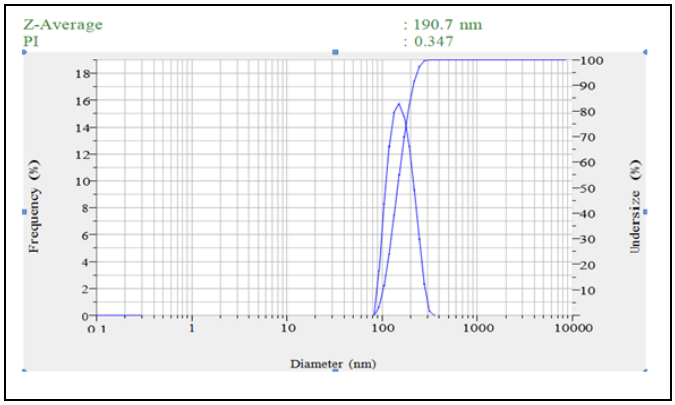

FIG. 1: PARTICLE SIZE OF OPTIMIZED SLN FORMULATION

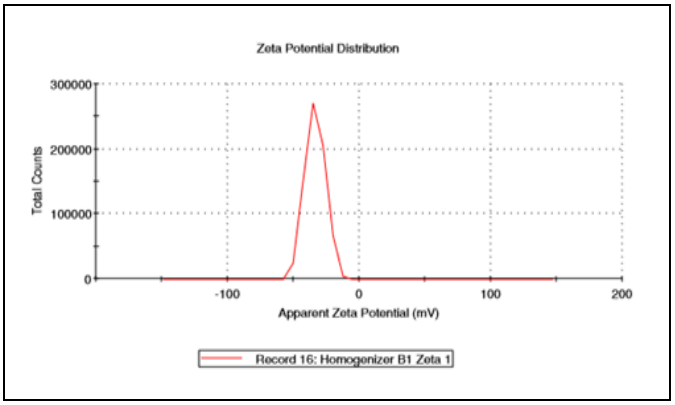

FIG. 2: ZETA POTENTIAL OF OPTIMIZED SLN FORMULATION

Entrapment Efficiency: Entrapment efficiency of prepared SLN by other production methods than homogenizer was low. Entrapment efficiency using both hot and cold pressure homogenizer can possible above 90%. The entrapment efficiency of formulations under investigation was in the range of 54-85%. Formulation F2 showed the highest EE 85.13 ± 1.38% whereas, formulation F1 showed lowest entrapment efficiency 36.85 ± 0.67. The Entrapment efficiency of formulations containing the highest level of lipid and surfactant was more than the formulations containing a low level of lipid and drug. This finding of EE not only depends on the concentration of the surfactant used.

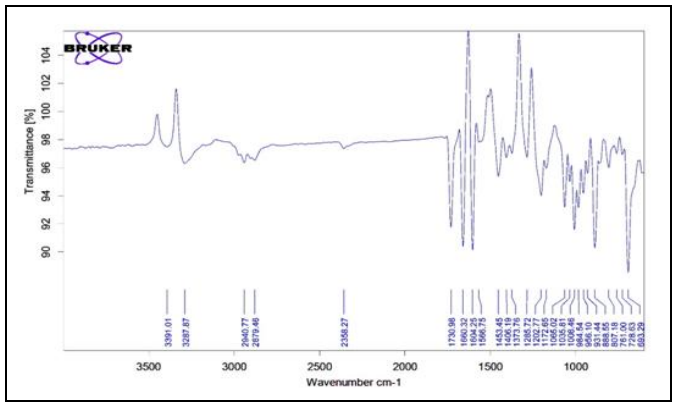

FIG. 3: FT-IR SPECTRUM OF CP

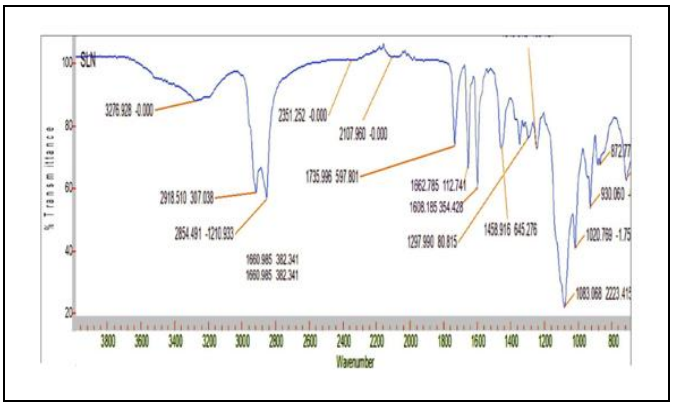

FIG. 4: FTIR SPECTRA OF SLN FORMULATION

Drug Content: The drug content of the freeze-dried SLN formulations was determined by UV spectroscopic method at 239 nm. The drug content of the optimized formulation of SLN was found to be 91.18%.

Low loss of diluents and lipids in the mixture of optimized formulations during freeze-drying. Percent drug content of different formulations shows **Table 3**.

FTIR Spectra: The FTIR spectra of pure CP, physical mixture and CP SLN are shown in **Fig. 5**. The FTIR analysis exhibited no distinct physical or chemical interaction of the drug with either the lipids or surfactant.

The characteristic peaks of CP were observed in the SLN formulation indicating little interaction while a few peaks were found to be missing which might be an indication of proper entrapment of the drug within the lipid matrix.

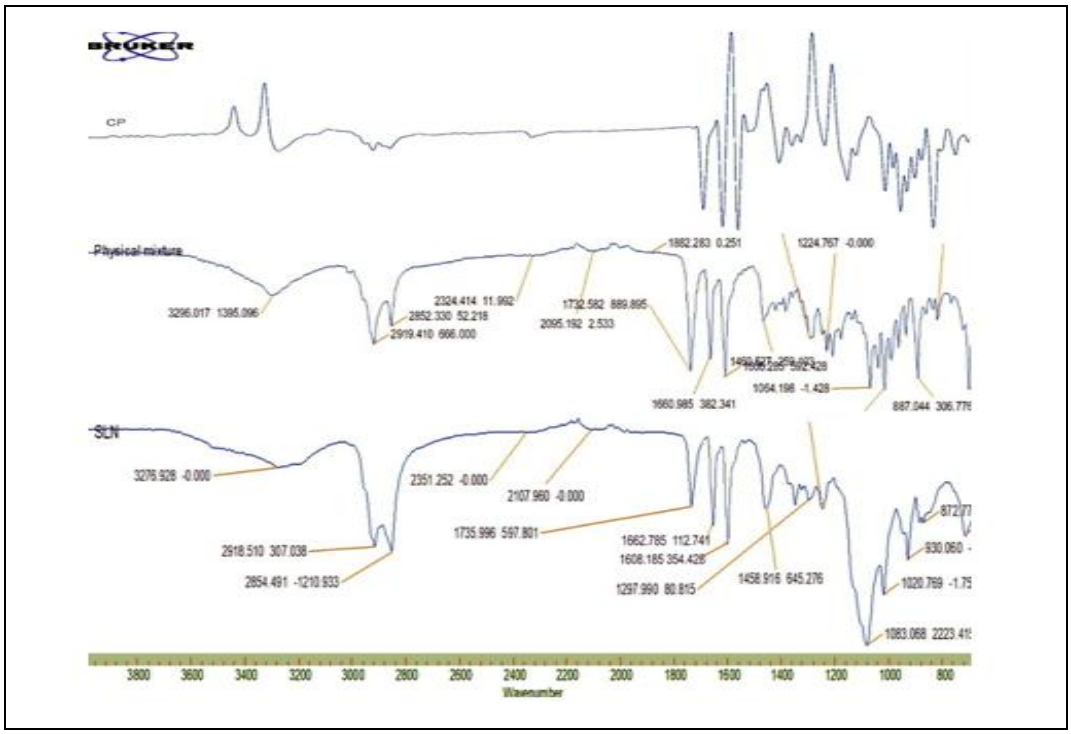

FIG. 5: OVERLAIN FTIR SPECTRA OF (A) CP (B) PHYSICAL MIXTURE (C) SLN FORMULATION

PXRD: Drug shows a sharp peak in diffract gram but in SLN formulation does not shows characteristics peak. GMS shows characteristics peak in the physical mixture, but it does not appear in SLN formulation. So it indicates the crystallinity of lipid was reduced in SLN formulation. The relative reduction in the diffraction intensities in the CP SLN thus can be predicted due to the change in the orientation of crystals or reduction in the quality of crystals of CP and this change in diffraction pattern support conversion of crystalline drug to amorphous form and contributes in the enhancement of the solubility of the drug. The PXRD of pure CP, physical mixture and CP SLN is shown in **Fig. 6**, **Fig. 7** and **Fig. 8**.

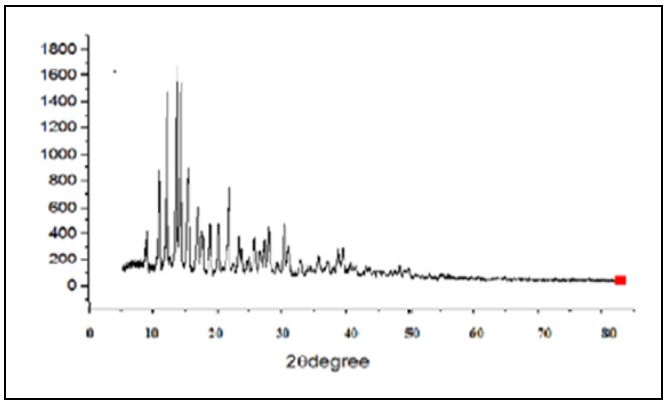

FIG. 6: PXRD DIFFRACTOGRAM OF CP

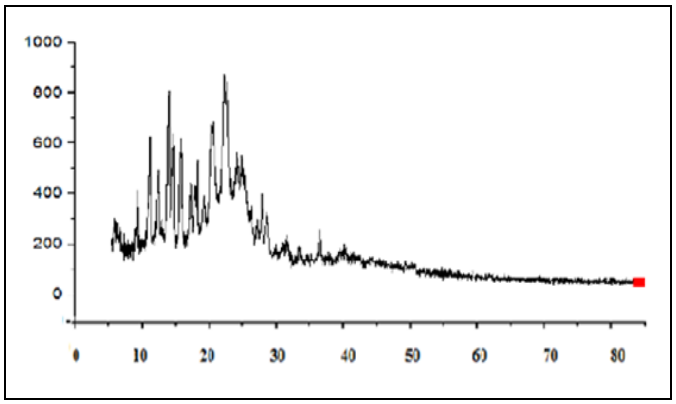

FIG. 7: PXRD SPECTRUM OF PHYSICAL MIXTURE

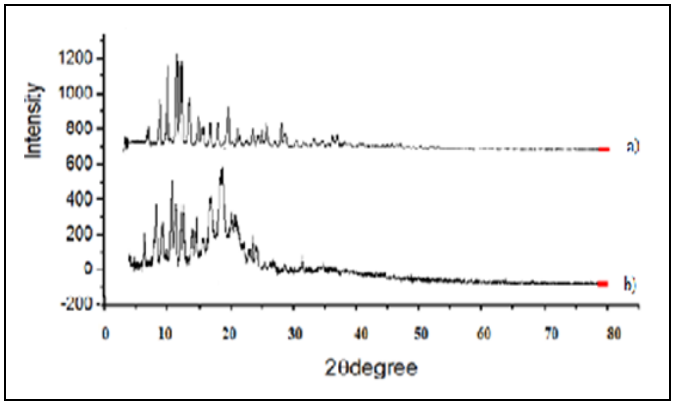

FIG. 8: OVERLAIN DIFFRACTOGRAM OF (A) CP (B) PHYSICAL MIXTURE

DSC: Thermogram of CP, physical mixture, and SLN formulation are shown in **Fig. 7**. The thermogram of pure CP shows a sharp endothermic peak starting at 201.81 °C with a melting point of 205.92 °C, indicating crystalline nature. In the thermogram of a physical mixture, the endothermic peak of CP was retained but with a reduction in peak height. The endothermic peak of lipid was also retained between 50-60 °C in SLN formulation. The thermogram of CP in SLN formulation starting at 160 °C with a melting point of 165.60 °C. Shifting of endothermic peak of CP with a decrease in intensity indicating the conversion of crystalline CP to the amorphous form which confirmed the complete dissolution of the drug in the molten lipid matrix.

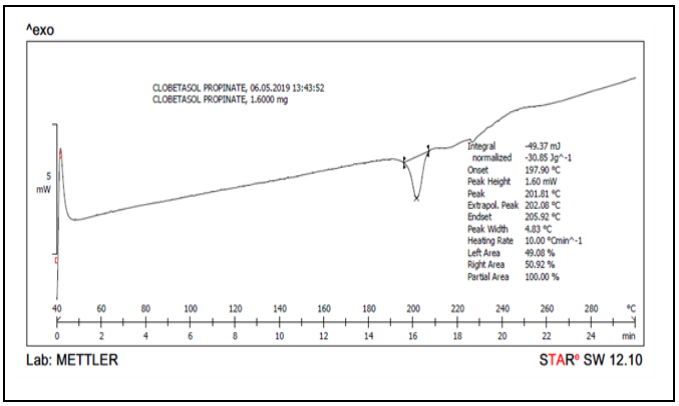

FIG. 9: DSC THERMOGRAM OF CP

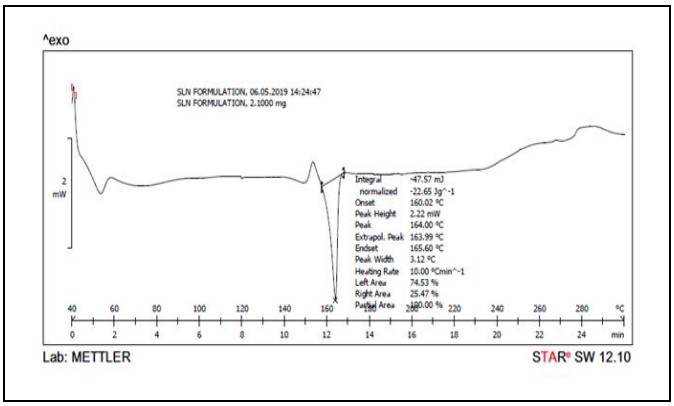

FIG. 10: DSC THERMOGRAM OF SLN

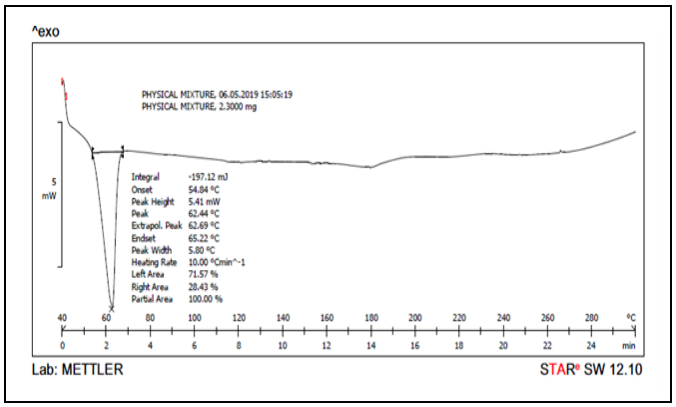

FIG. 11: DSC THERMOGRAM OF PHYSICAL MIXTURE

***In-vitro* Drug Release Study:** *In-vitro* release studies were carried out using the dialysis bag method with molecular weight cut off 14000 Da. Dialysis membranes retained SLN's and pass CP molecules, which were released over time into the dissolution medium. **Table 3** shows the percentage release of the CP from various batches. Significant variations in the release rate were observed in prepared SLN batches. Results reveal initial burst release in the first 4 h for all SLN formulations,

where nearly 40% of drug release was observed which may be due to drug absorbed at the surface of nanoparticles or precipitated in a lipid matrix. Drug release in the later stage was continuous and slow indicating that the drug release rate was following diffusion from a rigid matrix structure. SLN formulation F2 showed the most sustained release from all other batches.

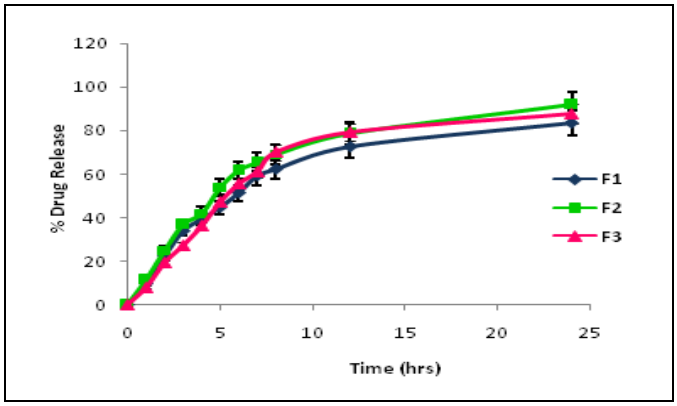

FIG. 12: *IN-VITRO* DRUG RELEASE STUDY

Evaluation of SLN Loaded Gel: Table 4 shows the characterization of different batches of gel. Formulated gel appeared to be white and translucent and displayed homogeneity in texture. The pH of the gel was observed to be 5.3 ± 0.6 which is compatible with the pH of the skin. Total drug content was noted as 91%. The viscosity of CP solid lipid nanoparticles loaded topical gel was found to be 5.5 cps.

***In-vitro* Drug Diffusion Study:** The comparative study of *in-vitro* drug diffusion of SLN loaded gel, silk sericin based SLN gel, marketed cream. The ideal topical formulation should show a release or diffusion for a sufficiently long period, so as to avoid frequent application with better patient compliance. The marketed cream showed release up to 65% at 24 h. SLN loaded gel showed release up to 81% slower diffusion of the drug through a dialysis membrane and followed a sustained release profile but sericin based SLN loaded gel shows enhance permeation of CP through dialysis membrane shows drug release up to 91% at 24 h with controlled release of a drug.

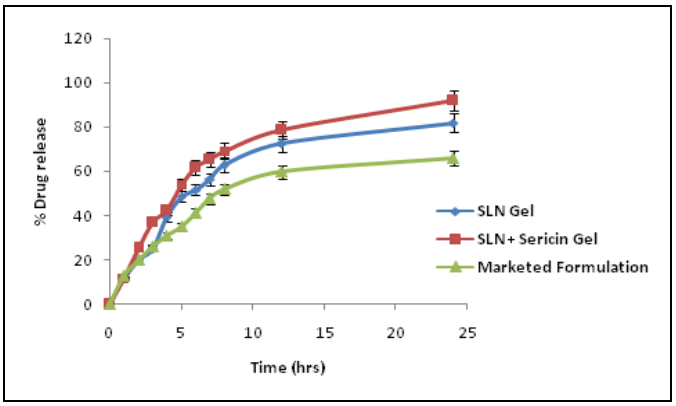

FIG. 13: *IN-VITRO* DRUG DIFFUSION STUDY

Physical Characterization of CP Loaded SLN: The comparison of physical properties of the CP loaded SLN is shown in **Table 3**. Drug uniformity results were found to be good among different batches of CP loaded SLN, and the percentage of drug content was more than 91%. The results also showed an acceptable and homogenous distribution of the drug in the formulations.

TABLE 3: CHARACTERISTICS OF CP LOADED SLN

Formulation code	Particle size (nm)	Zeta potential	Entrapment efficiency (%)	Drug content (%)	Drug release (%)
F1	198.23	-17.54	36.55 ± 0.67	89.27	80.98 ± 0.74
F2	190.07	-31.00	62.42 ± 0.06	91.89	81.09 ± 0.18
F3	278.54	-25.95	59.29 ± 0.88	77.62	79.58 ± 2.93
F4	203.40	-11.33	41.11 ± 0.39	82.34	86.66 ± 1.57
F5	756.00	-32.49	55.59 ± 0.76	69.11	76.59 ± 1.90
F6	545.11	-28.31	64.98 ± 0.01	87.55	72.43 ± 0.26
F7	503.25	-24.01	68.88 ± 0.01	89.55	75.41 ± 0.24

Physical Characterization of Sericin Based CP Loaded SLN Gel: The physical properties of the Sericin based CP loaded SLN gelin **Table 4**. Drug uniformity results were found to be good among different batches of Sericin based CP loaded SLN gel.

TABLE 4: CHARACTERISTICS OF SERICIN BASED CP LOADED SLN GEL

Evaluation Test	G1	G2	G3
pH	5.1 ± 0.2	5.3 ± 0.6	5.01 ± 0.7
Viscosity	5.8 cps	5.5 cps	5.3 cps
Homogeneity	+++	+++	++
Drug Content	89.67 ± 0.11	91.30 ± 0.76	84.90 ± 0.61

CONCLUSION: The present research work could be demonstrated that the successful preparation of CP incorporated SLNs by the solvent injection method. The formulated SLNs were subjected to several characteristic evaluations. Evaluation parameters revealed that the percentage of lipid and surfactant have significant effects on the particle size, drug content, entrapment efficiency and *in-vitro* release of CP from the SLN formulation. SLN formulation F2 was the most effective formulation with optimum particle size, high entrapment efficiency and improved release profile.

The *in-vitro* permeation study indicated revealed sustained permeation of CP from the SLN gel and maintained drug concentration over a prolonged period of time. The permeation parameters indicated the enhancement of CP permeation from sericin based SLN gel as compared to conventional gel. The results depict that the topical application of the CP SLN gel system is an effective and safe alternative to the conventional gel for the possible management of psoriasis.

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CONFLICTS OF INTEREST: We declare that we have no conflicts of interest.

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