Original Article

Development and characterization of clobetasol propionate loaded nanoemulgel for management of psoriasis

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ABSTRACT

The aim of the present study is to formulate clobetasol propionate loaded nanoemulgel for the treatment of plaque psoriasis. Homogenization method is used for the formulation of nanoemulgel and prepared formulation was characterized on the basis of size, entrapment efficiency, polydispersity index, viscosity, spreadability, zeta potential, % *in vitro* release, *in vitro* skin permeation, and retention studies. The optimized formulation of nanoemulgel (F2) has shown the significant sustained release of clobetasol propionate.

Keywords: Nanoemulgel, nanoemulsion, permeation, retention, sebaceous gland

INTRODUCTION

Psoriasis

Psoriasis vulgaris is an autoimmune disease caused by inappropriate activation of the cellular immune system. Psoriasis is a psychosocially, and at times medically, debilitating disorder that affects 1–3% of the population worldwide.[1] It basically involves excessive growth and deviant differentiation of keratinocytes.[2] There is an increase in proliferation of epidermis with dilation of dermal capillaries, infiltration of inflammatory cells in skin layers (dermis, and epidermis), and localized infiltration into skin layers. It leads to localized skin deregulation that plays a major role in the development of scaly erythematous plaques.[2] Other symptoms are swelling of the skin, pain, itching, and skin flaking.[3]

Clobetasol propionate is classed as a very potent topical corticosteroid. Topical steroids are used in addition to moisturizers for treating inflammatory skin conditions such as eczema and dermatitis. Due to its anti-inflammatory, antipruritic, and immune-modulating properties, clobetasol propionate is used to treat psoriasis.[4] Clobetasol propionate appears to induce phospholipase A2 inhibitory proteins, thereby controlling the release of the inflammatory precursor arachidonic acid from membrane phospholipids by phospholipase A2.[5]

For topical formulations, use of conventional excipients could serve the purpose only to a limited extent of absorption, penetration, and retention through psoriatic barrier cells.[6] With the discovery of newer chemicals such as squalene biocompatible and biodegradable materials such as phospholipids and novel drug delivery technologies such as deformable liposomes, solid lipid nanoparticles, liposomes, nanostructured lipid carriers, microemulsions, and nanoemulsions have the possibility to improve the efficiency and safety of the topical products to a great extent and also improve the absorption, penetration, and retention in skin.

The aim of this study is to develop a nanoemulgel composed of clobetasol propionate loaded nanoemulsions and to evaluate its potential in the plaque psoriatic. The nanoemulgel was prepared by dispersing the clobetasol propionate loaded nanoemulsions in carbopol gel base.[7,8] We also had used squalene in our formulation which is a sebum derived lipid and shows its affinity toward sebaceous glands and because of which drug shows depot effect in it and retention of drug in the skin was increased.[9]

MATERIALS AND METHODS

Materials

Clobetasol propionate was procured as free gift sample from Helios Pharmaceuticals Pvt. Ltd. Squalene was purchased from

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Sigma-Aldrich, Mumbai. Acetonitrile was purchased from CDH Analytical reagents. Acetone, chloroform, hydrocortisone, and methanol were purchased from SDFCL (Mumbai, India). Methanol, L-tyrosine, and 1-Octyl sulfonic acid were purchased from Loba Chemie. Hydrogenated soy phosphotidycholine was purchased from Avanti.

Methods

Preparation of nanoemulgel

Homogenization method is used for the formulation of nanoemulgel. There are three steps involved in the formulation of nanoemulgel which is given below;

1. Preparation of nanoemulsion
2. Preparation of hydrogel
3. Finally, nanoemulgel will be produced by the incorporation of nanoemulsion into a gel with continuous stirring.[10]

Method of preparation of nanoemulsion

The aqueous and lipid phases of nanoemulsions were fabricated separately. The aqueous phase consisted of double-distilled water and PF68 (3.2%, w/v). The lipid phase consisted of different ratio of squalene and soybean phosphatidylcholine. Both phases were separately heated at 85°C for 15 min. The aqueous phase was then added to lipid phase and mixed under homogenization at 12,000 rpm for 20 min. Subsequently, a probe-type sonicator set at a power of 25 W was employed to treat the mixture for 15 min. A 10-ml volume was prepared for each batch.[9a,b]

Preparation of gel

Gel was chosen as a vehicle for incorporation of nanoemulsion for skin delivery. Carbopol 940 (0.25 g) was dispersed in distilled water (100 ml) by stirring at 800 rpm for 60 min.[11] The mixture was neutralized by dropwise addition of triethanolamine. Mixing was continued until a transparent gel appeared, while the amount of the base was adjusted to achieve a gel with pH 5.5.

Incorporation of nanoemulsion into carbopol 940 solution

Carbopol 940 (0.4% w/v) was dispersed in distilled water by stirring at 800 rpm for 60 min. The mixture was neutralized by dropwise addition of triethanolamine. Colloidal suspension was added to the mixture with continuous mixing till a transparent gel appeared; the pH 5.5 of the gel was adjusted with the help of base (triethanolamine) and the final gel was kept overnight for swelling.

Characterization of nanoemulsions

Particle size

The mean particle size of the prepared nanoemulsion was obtained using particle size analyzer. The particle size analyzer (Beckman Coulter counter) is a new series generation instrument that uses photon correlation spectroscopy, which determines particle size by measuring the rate of fluctuation in the laser light intensity scattered by particles as they diffuse through a fluid, for size analysis measurements.

Characterization of gel formulation

Physical examination

The prepared gel formulations were inspected visually for their color, homogeneity, and consistency.

pH

pH is a measure of the concentration of hydrogen ions in a solution. Numerically, it is the negative logarithm of that concentration expressed in moles per litre (M). The pH values of the prepared gels were measured by a pH (Pico) meter (Lab India instruments Pvt. Ltd.).

Viscosity

Viscosity measurements were carried out at room temperature (25–27°C) using a Brookfield Rheometer. The spindle (R3-C75-1) was employed for each treatment, while formulations were measured over shear rates ranging from 10 to 100/s.[12]

Drug content

100 g the gel was dissolved in 10 ml of dichloromethane. Then, on 20 ml methanol was added to it to precipitate the polymer. The solution obtained was filtered and volume was made to 100 ml. The solution obtained was diluted suitably with methanolic phosphate buffered saline (PBS) and peak height was measured by high-performance liquid chromatography (HPLC) method at 215 nm.[13]

Spreadability

It was determined by wooden block and glass slide apparatus. Weights about 20 g were added to the pan and the time was noted for upper slide (movable) to separate completely from the fixed slides.[14]

Spreadability was then calculated using the formula;

$S = M.L/T$

Where,

S = Spreadability

M = Weight tide to the upper slide

L = Length of the glass slide

T = Time taken to separate the slide completely from each other.

In vitro drug release study

In vitro release study of marketed gel, and nanoemulgel was carried out using dialysis bag method.[15] In this method, 1 ml formulation was added to donor compartment after centrifugation and resuspension. Receptor compartment was taken into 100 ml of phosphate buffer saline pH 5.5 in a conical flask. This flask was taken in incubator shaker and speed of shaker was maintained at 60 rpm at 37°C. At specific time intervals, samples (2 ml) were withdrawn and filtered. Same volume (2 ml) was replaced after each sampling. The drug content in the sample was determined by HPLC method being developed at 215 nm.

Physical storage stability studies

The stability of vesicles to retain the drug (i.e., drug retentive behavior) was assessed by keeping the nanoemulsions at two different temperature conditions, i.e., 5±1°C (Refrigerator; RF), and 25±2°C (Room temperature; RT) for a period of 6 months as per the ICH guidelines. The optimized formulations were kept in sealed vials (20 ml capacity). The samples were withdrawn periodically and analyzed for entrapment efficiency, polydispersity index (PDI), and particle size.

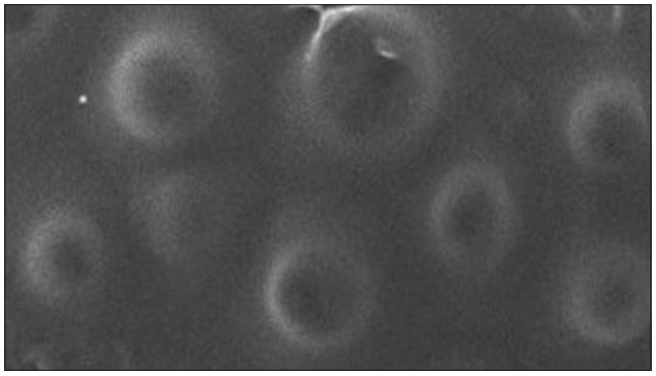

Figure 1: Scanning electron microscopic image of clobetasol propionate loaded nanoemulsion

RESULTS

Preparation and characterization of clobetasol propionate loaded nanoemulsion

Optimization of the blank-and drug-loaded nanoemulsion

Nanoemulsion was optimized using different surfactant concentration, lipid ratio, homogenization speed, and sonication time for both blank- and drug-loaded [Table 1]. This study has demonstrated that the optimized blank nanoemulsion formulation has a particle size of 212.1 ± 11.1 nm and PDI 0.162 ± 0.03 nm. The optimized drug (as clobetasol propionate) is a potent drug (dose 0.5 mg through transdermal route), we have selected its concentration on the bases of studies reported by Gordon and Feldman[16,17] loaded formulation have a particle size and PDI of 240.5 ± 9.2 and 0.282 ± 0.03, respectively.

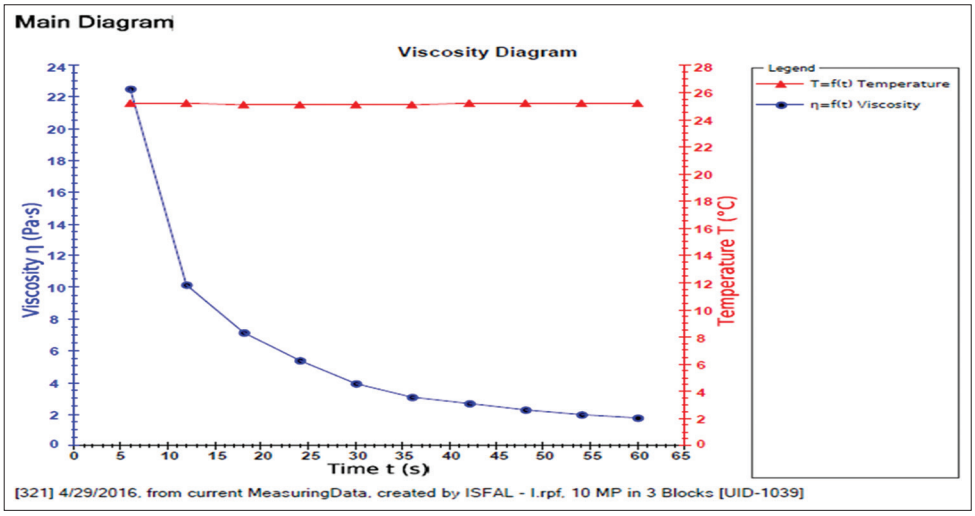

Figure 2: Rheology study of clobetasol propionate loaded nanoemulgel (F3)

Table 1: The particle size determination of blank and drug (clobetasol propionate) loaded nanoemulsion (*n*=3)

Formulation code	Drug conc.	Surfactant conc. (PF68)	Lipid ratio (Squalene: Soybean phosphatidylcholine)	Particle size (nm)	Polydispersity index
F1	-	3.5%	4:1	212.1±11.1	0.162±0.03
F2	0.05%	3.5%	4:1	240.5±9.2	0.282±0.03

Table 2: Characterization of clobetasol propionate loaded nanoemulgel on the basis of carbopol concentration (*n*=3)

S. No.	Carbopol 940 (w/v)	pH	Spreadability (gm.cm/sec)	% Drug content
F3	0.25%	5.51±0.91	21.12±0.15	88.61±0.39
F4	0.3%	5.10±0.28	19.91±0.12	88.12±0.31
F5	0.35%	5.30±0.91	18.41±0.31	88.27±0.42
F6	0.4%	5.51±0.71	16.34±0.71	89.19±0.21
F7	0.45%	5.78±0.07	15.24±0.88	89.24±0.11
F8	0.5%	6.41±0.21	14.29±0.23	90.02±0.23

Table 3: The physical stability studies of optimized nanoemulgel formulation (F3) under different temperatures

Storage conditions	Particle size (nm)		Polydispersity index	
	Initial	After 6 months	Initial	After 6 months
4°C±2°C	140.5±9.2	219.8±8.2	0.282±0.03	0.140±0.02
25°C±2°C	140.5±9.2	232.1±9.1	0.282±0.03	0.169±0.04

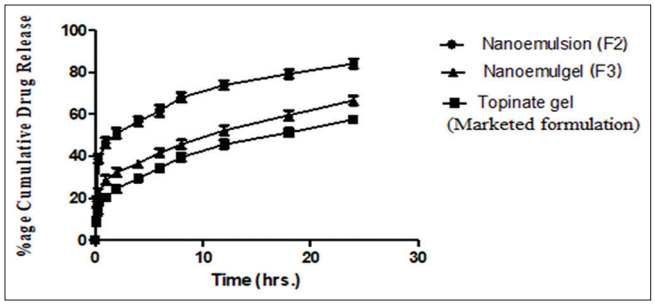

Figure 3: Percentage *in vitro* release of clobetasol propionate in 10% methanolic phosphate buffered saline phosphate buffered saline (pH 5.5). Values expressed as mean ± SD (n = 3)

Centrifugation test

This test was performed to ensure the stability of the emulsion whether it is monophasic or not. In this, the optimized formulation was first diluted with 200 ml of water and then centrifuged at 7500 rpm for 10 min. There was no sign of phase separation in the optimized emulsion.

Morphology

Shape and surface morphology of optimized formulation (F2).

SEM was performed to study vesicle morphology that revealed that nanoemulsion was spherical in shape Figure 1.

Optimization and characterization of gel

Nanoemulgel was prepared in different batches using a different concentration of carbopol 940 w/v with formulation codes and optimized for the various parameters such as pH, spreadability, % of carbopol, and % drug content [Table 2], nanoemulgel prepared using carbopol 940 was 0.25%w/v and was optimized formulation. Carbopol gel 0.25% shows good rheological properties, swelling index, and spreadability. A prepared gel containing nanoemulsion was a transparent gel with a smooth and homogeneous appearance.

Rheology

Clobetasol propionate loaded nanoemulgel (F3) exhibited rheological behavior at 37°C as depicted in Figure 2. Gel follows Newtonian flow at below 37°C while at below 37°C gel shows pseudoplastic behavior. Studies suggested that viscosity decreases with increase in shear rate.

The percentage in vitro release graph of clobetasol propionate in 10% methanolic PBS (pH 5.5)

The rate of drug release across the dialysis membrane was slower for nanoemulgel than the nanoemulsion and was least for the marketed gel (dominate). The drug release from nanoemulsion in PBS (pH 5.5) was approximately 84.24 ± 1.35% after 24 h. The nanoemulgel formulations showed the release of 66.83 ± 2.05% while marketed gel showed the release of 57.67 ± 1.63% after 24 h. The *in vitro* release profile of different formulations is shown in Figure 3 the % cumulative release profile. The release profiles of clobetasol propionate from nanoemulgel showed biphasic release processes, where initial burst release of the surface-adsorbed drug was observed, followed by slow diffusion from the lipid nanoemulsion. At the initial 4 h, the little higher drug release of nanoemulgel was observed. Afterward, lipid nanoemulsion diffusion in gels played an important role in the release profiles and drug release rate slowed down.

Physical stability studies

Grittiness was not found in the formulation (F3) and there is no change in the spreadability of the formulation.

Nanoemulsion was stable in terms of aggregation and fusion. There was a slight change in the size of the formulations [Table 3]. The results of the stability studies suggest that formulating nanoemulsion in carbopol gel under refrigerated conditions minimizes the stability problems of the nanoemulsion.

CONCLUSIONS

Clobetasol propionate was successfully formulated in nanoemulgel. Stability studies suggest that the stability of the nanosystems was maximum at the lower temperature range. Nanoemulsion shows better *in vitro* release than nanoemulgel and marketed formulation. From above studies, we can conclude that clobetasol propionate loaded nanoemulgel formulation can effectively use for the treatment of plaque psoriasis.

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DISCLOSURE STATEMENT

The authors have declared no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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