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Original Research Article

Formulation, development and characterization of topical organogel of mometasone furoate for the treatment of skin disease

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ABSTRACT

Background: Topical glucocorticoid formulations are widely used for effective treatment and control of a variety of dermatoses. Mometasone furoate is a medium potency, synthetic, non-fluorinated topical corticosteroid, indicated for the relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses including psoriasis. The percutaneous absorption increases risk associated with systemic absorption of topically applied formulation. Controlled release of the drug to the skin could reduce the side effects while reducing percutaneous absorption. Organogels are semi-solid materials, in which an organic phase is immobilized by a three-dimensional network composed of self-organized system, forming the aqueous phase.

Aims & Objectives: The present study deals with the preparation and evaluation of a pluronic lecithin organogel gel containing mometasone furoate for transdermal delivery. Blank pluronic lecithin organogel were prepared using ricinoleic acid as the oil phase.

Materials and Methods: Formulation, Development and Characterization of Topical Organogel of Mometasone Furoate was carried out and evaluated for the treatment of Skin Disease. The absorption maxima of mometasone furoate were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer (Labindia UV 3000+) using concentration range of 5-25μg/ml mometasone furoate in 7.4 phosphate buffers. The IR spectrum of sample drug and drug with excipients shows the peak values which are characteristics of the drug.

Results: The formulated gel formulation was evaluated with parameter appearance, consistency, drug content pH, viscosity, spreadability, in-vitro release test, washability, extrudability study and stability studies. FT-IR studies revealed no interaction between the drug and excipients. Selected organogels (F3) showed a drug content of 99.45±0.14% and drug release of 99.12 % in10 hrs.

Conclusion: The results suggest that the developed organogels formulation containing mometasone furoate can be of actual value for improving the clinical effectiveness in the treatment of psoriasis.

1. Introduction

Psoriasis is a chronic inflammatory skin disease characterized by skin thickening, scaling and epidermal alterations including inflammatory infiltrate in the epidermal and dermal region.[1] The disease involves series of linked cellular changes in the skin involving hyperplasia of epidermal keratinocytes, vascular hyperplasia, ectasia and infiltration of T-lymphocytes, neutrophils and other types of leucocytes in affected skin.[2] For the management of psoriasis, topical therapy is most commonly used in majority of patients. However, challenges associated with

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psoriatic skin such as skin rigidization, absence of normal moisturising factors like water and imbalance of skin lipids poses stiff challenge in designing an effective topical delivery system.[3] Organogels are semi-solid systems, in which an organic liquid phase is immobilized by a three-dimensional network composed of self-assembled, intertwined gelator fibres.[4] There are two main types of organogels namely fluid-filled organogels and solid-fibre based organogels. They are thermo-reversible and can accommodate both hydrophilic and hydrophobic compounds within the gel structure.[5,6] Despite their liquid composition, these systems demonstrate the appearance and rheological behavior of solids.[7] The thermo-reversible property of the organogels has generated much interest for the potential use of the organogels as novel drug delivery system.[8] Recently, pluronic-lecithin organogels (PLOs) have gained popularity as transdermal and topical drug delivery systems owing to their biphasic composition and versatility; PLO can enhance solubility of poorly soluble drugs and enhance penetrability of hydrophilic drugs.[9] Compared with other topical vehicles like creams, tinctures, lotions and emulsions, the organogels have several advantages such as ease of preparation, thermodynamic stability and enhanced topical performance along with biocompatibility makes the organogel a vehicle of choice for topical drug delivery, which not only gives localized effect, but also systemic effect through percutaneous absorption.[10] Mometasone furoate, a prodrug of free mometasone, is a non-fluorinated synthetic corticosteroid which is mainly used topically to reduce skin inflammation in psoriasis and eczema. It has anti-inflammatory, antipruritic and anti hyperproliferative activity.[11] Mometasone furoate penetrates the stratum corneum and binds to glucocorticoid receptors in viable epidermis and dermis and blocks the production of cytokines such as IL-1, IL-6 and TNF-alpha.[12] Several problems have been reported with the conventional drug delivery of mometasone furoate such as low drug uptake due to barrier function of the stratum corneum, swelling of hair follicles, skin burning and may lead to skin atrophy if used for long period.[13] The systemic absorption of drug through topical route may lead to severe side effects such as reversible suppression of hypothalamic-pituitary-adrenal (HPA) axis, Cushing's syndrome, hyperglycaemia and glycosuria.[14] Organogel are potential carriers for improving the drug retention at the target site and to reduce the risks of both local and systemic side effects associated with topical corticosteroids.

2. Materials and Methods

2.1. Materials

Mometasone furoate was obtained as a gift sample from Euphoria Healthcare Pvt. Ltd. Mumbai. Soya lecithin, ricinoleic acid and poloxamer were purchased from Himedia Laboratory, Mumbai. Ethanol, chloroform, sodium chloride di potassium hydrogen orthophosphate, disodium hydrogen phosphate purchased from CDH chemical Pvt. Ltd. New Delhi. Dialysis membrane of Mol Wt cutoff 1200 was purchased from Himedia Laboratory, Mumbai. Demineralized and double distilled water was prepared freshly and used whenever required. All other reagents and chemicals used were of analytical grade.

2.2. Determination of λ max of mometasone furoate

Accurately weighed 10 mg of drug was dissolved in 10 ml of 7.4 pH buffer solution in 10 ml of volumetric flask. The resulted solution 1000μg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with 7.4 pH buffer solution. Prepare suitable dilution to make it to a concentration range of 5-25μg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+). A graph of concentration Vs absorbance was plotted.

2.3. FTIR spectroscopy

Infrared spectrum of any compound gives information about the groups present in that particular compound. IR spectrum of mometasone furoate was recorded using Perkin Elmer Instrument spectrum one (model) using KBr pellets. Various peaks in IR spectra were interpreted for different groups and were matched with reference IR spectra.

2.4. Preparation of the pluronic organogel

The oil phase was prepared by mixing lecithin and ricinoleic acid in a 1:0.5 and 1:1 ratio of 50:50 (w/w) mixture of lecithin in ricinoleic acid.[15] The mixture was allowed to stand overnight to allow standing overnight to allow for the complete dissolution of lecithin in the ricinoleic acid. Polaxamer solution (20%w/v) was prepared using the cold method. The poloxamer solution was stored under refrigerated conditions at 4^{o}C overnight in order to enhance the dissolution of the polymer. PLO gel was prepared by mixing 1 part of oil phase (Mixture of lecithin and ricinolic acid) with four parts aqueous phase (20% w/v poloxamer solution) using a vortex mixture. Six pluronic organogel formulae were presented in Table 1.

2.5. Evaluation of mometasone furoate loaded organogel[16–19]

2.5.1. Physical characteristic

The physical characteristic was checked for gel formulations (homogeneity and texture).

2.5.2. Washability

Formulations were applied on the skin and then ease and extent of washing with water were checked manually.

Table 1: Formulation of mometasone furoate loaded organogel

Ingredient	F1	F2	F3	F4	F5	F6
Mometasone furoate (%)	1	1	1	1	1	1
Soya lecithin (%)	0.25	0.5	0.75	0.25	0.5	0.75
Ricinoleic acid (%)	0.5	0.5	0.5	1	1	1
Poloxamer (%)	10	20	30	10	20	30
Water (ml)	50	50	50	50	50	50

2.5.3. Extrudability study

Extrudability was based upon the quantity of the gel extruded from collapsible tube on application of certain load. More the quantity of gel extruded shows better extrudability. It was determine by applying the weight on gel filled collapsible tube and recorded the weight on which gel was extruded from tube.

2.5.4. Measurement of viscosity

Viscosity measurements of prepared organogel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm; viscosity.

2.5.5. PH measurements

pH of selected optimized formulations was determined with the help of digital pH meter. Before each measurement of pH, pH meter should be calibrated with the help of buffer solution of pH 4, pH 7 and pH 9.2. After calibration, the electrode was dipped into the vesicles as long as covered by the vesicles. Then pH of selected formulation was measured and readings shown on display were noted.

2.5.6. Drug Content

Accurately weighed equivalent to 100 mg of organogel was taken in beaker and added 20 ml of methanol. This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 1.0 ml of filtered solution was taken in 10 ml capacity of volumetric flask and volume was made upto 10 ml with methanol. This solution was analyzed using UV-Spectroscope at λ_{max} 242nm.

2.5.7. Spreadability

Spreadability of formulation is necessary to provide sufficient dose available to absorb from skin to get good therapeutic response. An apparatus in which a slide fixed on wooded block and upper slide has movable and one end of movable slide tied with weight pan. To determine spreadability, placing 2-5gm of gel between two slide and gradually weight was increased by adding it on the weight pan and time required by the top plate to cover a distance of 6cm upon adding 20gm of weight was noted. Good spreadability show lesser time to spread.

Spreadability (gcm/sec) = weight tied to the upper slide× length of glass slide/ time taken is seconds.

2.5.8. In vitro drug diffusion study

The In-vitro diffusion study is carried by using franz diffusion cell. Egg membrane is taken as semi permeable membrane for diffusion. The Franz diffusion cell has receptor compartment with an effective volume approximately 60 ml and effective surface area of permeation 3.14sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A two cm^2 size patch taken and weighed then placed on one side of membrane facing donor compartment. The receptor medium is phosphate buffer pH 7.4. The receptor compartment is surrounded by water jacket so as to maintain the temperature at 32 ± 0.5°C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell. During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each sampling. The samples withdrawn are analyzed spectrophotometrically at wavelength of drug 242nm.

2.5.9. Release kinetics

In order to elucidate mode and mechanism of drug release, the invitro data was transformed and interpreted at graphical interface constructed using various kinetic models. The zero order release Eq. (1) describes the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of transdermal systems, matrix tablets with low soluble drugs, coated forms, osmotic systems etc., where the drug release is independent of concentration.

$$Qt = Qo + Kot \quad (1)$$

Where, Qt is the amount of drug released in time t, Qo is the initial amount of the drug in the solution and Ko is the zero order release constant

The first order Eq. (2) describes the release from the system where release is concentration dependent e.g. pharmaceutical dosage forms containing water soluble drugs in porous matrices.

$$\log Qt = \log Qo + K1\,t\,/2.303 \quad (2)$$

Where Qt is the amount of drug released in time t, Q is the initial amount of drug in the solution and K1 is the first order release constant.

Higuchi described the release of drug from insoluble matrix as a square root of time as given in Eq. (3)

$$Qt = KH\sqrt{t}\ (3)$$

Where, Qt is the amount of drug released in time t, KH is Higuchi's dissolution constant[20].

The following plots were made: cumulative % drug release vs. time (zero order kinetic models); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (Higuchi model). The curves plotted may have different slopes, and hence it becomes difficult to exactly pin-point which curve follows perfect zero order release kinetics. Therefore, to confirm the kinetics of drug release, data were also analyzed using Korsemeyer's equation (4).

$$Qt/Q\infty = kKP.tn \quad (4)$$

Where Q_t / Q_∞ is the fraction of drug released at time t, k_{KP} a constant compromising the structural and geometric characteristics of the device and n is the release exponent.[21]

3. Result and Discussion

The absorption maxima of mometasone furoate were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer (Labindia UV 3000+) using concentration range of 5-25μg/ml mometasone furoate in 7.4phosphate buffers Figure 1. The IR spectrum of sample drug and drug with excipients shows the peak values which are characteristics of the drug and the graph were shown in Figures 2 and 3. Mometasone furoate showed a linear relationship with correlation coefficient of 0.999 in the concentration range of 5-25μg/ml in phosphate buffer pH 7.4. Melting point of drug was found 218-220°C while it was 215-228°C reported in standard monograph. All the data of preformulation study were found similar as given in standard monograph which confirmed that the drug was authenticated and pure in form and it could be used for formulation development of mometasone furoate loaded organogels. It was observed that the freshly prepared formulations were off white. The clogging was found absent in all formulations and having good homogeneity and smooth texture was found in all formulations. Results of evaluation of organogels formulation (F1-F6) of optimized formulation (F3) were given in Table 2. All the formulations exhibited good washability and left no traces over the skin on washing with water due to non-greasy properties. The all the prepared organogel formulation were found average extrudability and good washability. Spreadability, pH, viscosity, percentage assay of the formulations F1-F6 were studied and found to be in the range. The formulation F3 showed the good spreadability, pH, viscosity, percentage assay among all formulation. Results of In-vitro drug release from optimized formulation (F3) are given in Table 3 was found 99.12% after10 hrs. The in vitro drug release data of the formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi and Korsmeyer's -pappas models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of formulation was maximum i.e 0.977 hence indicating drug release from formulations was found to follow Korsmeyer's -pappas model of drug release kinetics Table 4 and Figures 4, 7, 6 and 5.

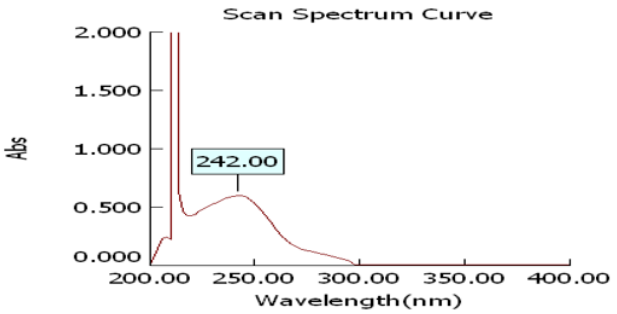

Fig. 1: Standard calibration curve of mometasone furoate

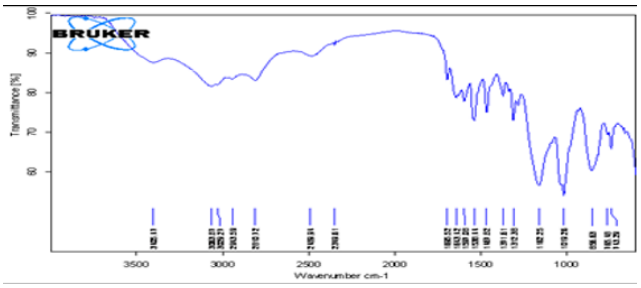

Fig. 2: FT-IR spectrum of pure drug (mometasone furoate)

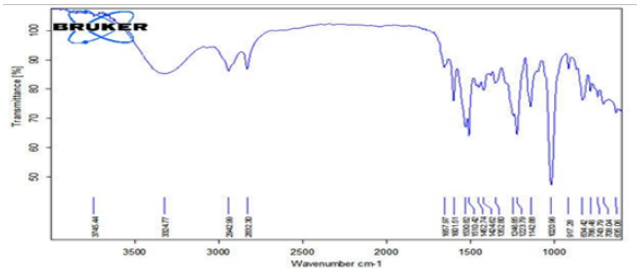

Fig. 3: FT-IR spectrumof pure drug and excipients

4. Conclusion

In the present study, the mometasone furoate loaded pluronic lecithin organogel was successfully prepared by using ricinoleic acid as the oil phase. The topical delivery of mometasone furoate to the skin by means of organogel could possibly minimize the side effects. The results suggested that the developed organogel formulations have the desired stability and show sustained release with a significant reduction in psoriatic lesions. Therefore, it can be concluded that organogel based formulation could be used as potential drug delivery approach for treating psoriasis.

Table 2: Results of evaluation of organogels formulation

F. Code	Washability	Extrudability (gm)	Spreadability (gcm/sec)	pH*	Viscosity* (cps)	% assay
F1	Good	145±2	11.65±0.15	6.9±0.1	2560±25	98.85±0.25
F2	Good	149±3	12.32±0.25	6.8±0.2	2675±45	98.78±0.32
F3	Good	152±2	12.54±0.21	6.9±0.1	2785±23	99.45±0.14
F4	Good	142±4	11.65±0.15	7.1±0.2	2489±21	98.98±0.26
F5	Good	145±3	11.85±0.26	7.2±0.1	2540±15	99.01±0.32
F6	Good	148±5	12.52±0.34	6.8±0.2	2630±23	99.86±0.17

*Average of three determinations (n=3)

Table 3: *In Vitro* drug release data for F3

Time (H)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
0.5	0.707	-0.301	22.32	1.349	77.68	1.890
1	1.000	0.000	36.65	1.564	63.35	1.802
2	1.414	0.301	48.85	1.689	51.15	1.709
4	2.000	0.602	58.98	1.771	41.02	1.613
6	2.449	0.778	68.87	1.838	31.13	1.493
8	2.828	0.903	82.25	1.915	17.75	1.249
10	3.162	1.000	99.12	1.996	0.88	-0.056

* Average of three determinationsII

Table 4: Regression analysis data of organogels formulation

Batch	Zero Order	First Order	Higuchi's Model	Korsmeyers Peppas Equation
	R2			
F3	0.965	0.746	0.976	0.977

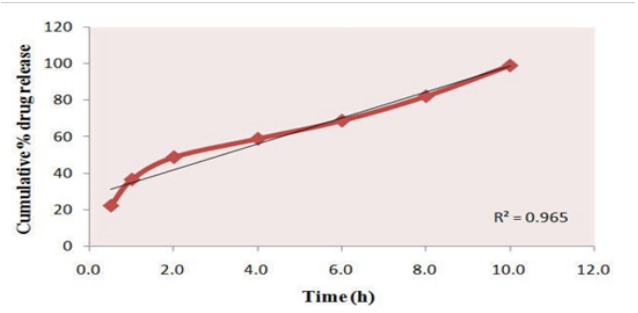

Fig. 4: Cumulative % drug released Vs Time

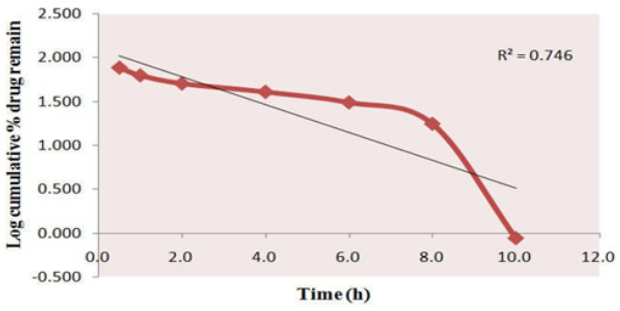

Fig. 5: Log cumulative % drug remaining Vs Time

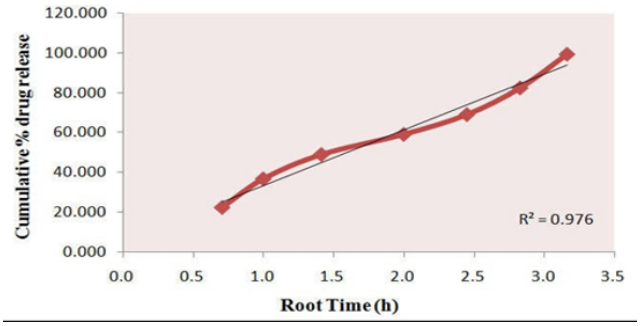

Fig. 6: Cumulative % drug released Vs Square root of Time

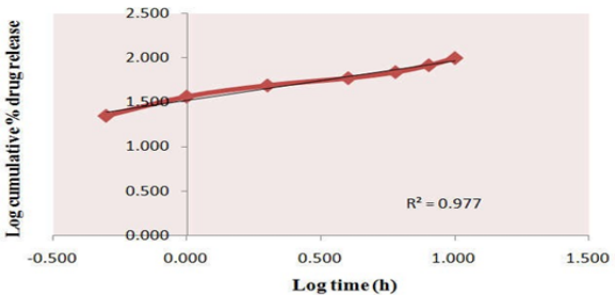

Fig. 7: Log cumulative % drug released Vs log Time

5. Source of Funding

None.

6. Conflict of Interest

None.

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