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FORMULATION, DEVELOPMENT AND EVALUATION OF EMULGEL OF MOMETASONE FUROATE FOR EFFECTIVE TREATMENT OF TOPICAL DISEASE

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ABSTRACT

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. Emulgel have emerged as one of the most interesting topical delivery system as it has dual control release system i.e. gel and emulsion. One side the topical applications of the drug offers the potential advantages of delivering the drug directly to the site of action and secondly delivering the drug for extended period of time at the effected site. The aim of the present study was to develop an emulgel formulation of mometasone furoate using carbopol 941 as a gelling agent. In addition, light liquid paraffin as oil, Tween-20 and Span-20 as emulsifiers and propylene glycol as co-surfactant were selected for preparation of emulgel. The prepared emulgel were also evaluated for their physical properties, pH, drug content and rheological properties. Stability studies revealed no significant differences in formulation. Mometasone furoate emulgel formulation (F5) prepared by using carbapol 941 as gelling agent, emulsifying agent in its high level and liquid paraffin in its low level was the choice of formula, since it showed the highest drug release. So it can be concluded that topical emulgel enhanced permeation of mometasone furoate with avoidance of GIT adverse effect.

Keywords: Mometasone furoate, Emulgel, Psoriasis, *In-vitro* release test, Carbopol 941.

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 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]. When gels and emulsions are used in combined form the dosage forms are referred as EMULGELS [4]. Emulgels are also called as creamed gel, quassi emulsion, gelled emulsion [5]. In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase [6]. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent and pleasing appearance [7]. 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 [8]. 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 [9]. 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 [10]. 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 [11]. Emulgels 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.

MATERIALS AND METHODS

Materials

Mometasone furoate was obtained as a gift sample from Euphoria Healthcare Pvt. Ltd. Mumbai. Spans 20, Tween 20 were purchased from SD Fine Chemicals Mumbai, India. Carbopol 941 was purchased from CDH Laboratories New Delhi, India. Liquid paraffin, propylene glycol, methyl parabens and propyl parabens extra pure were purchased from Hi-Media laboratories Mumbai, India. All other chemicals used were of analytical grade and were used without any further chemical modification.

Method

Formulation development

Preparation of emulsion

The general method was employed for preparation of an emulsion was as follows: The oil phase was prepared by dissolving Span 20 in liquid paraffin in the different ration, while the aqueous phase was

prepared by dissolving Tween 20 in purified water.1gram of mometasone furoate was dissolved in 5ml of ethanol, while 0.15gm of methylparaben and 0.05gm of propylparaben were dissolved in 5 gm of propylene glycol and both were mixed with aqueous phase. Both the oily and aqueous phases were separately heated to 70-80°C. Then, the oil phase was added to the aqueous phase with continuous stirring at 500 rpm until cooled to room temperature [12].

Preparation of carbopol

Fifty (50) grams of the carbopol gel was prepared by dispersing 1 gram of carbopol powder in 50 ml purified water with aid of moderate speed stirrer (50 rpm), and then the pH was adjusted to 6.5-6.8 using 0.5 N of sodium hydroxide.

Formulation of Mometasone Furoate emulgel

Six formulations of mometasone furoate were prepared by dispersing the obtained emulsions with the gel in 1:1 ratio with gentle stirring until get homogenous emulgel. The composition of different formulation was given in Table 1.

Table 1 Composition of different formulation of emulgel (% w/w)

F. Code	Mometasone Furoate (mg)	Carbomer 941 (%)	Liquid Paraffin (%)	Span 20 (%)	Tween 20 (%)	Propylene Glycol (%)	Water (ml)
F1	100	0.5	5	2	5	5	100
F2	100	0.5	5	2	10	5	100
F3	100	1.0	10	4	5	5	100
F4	100	1.0	10	4	10	5	100
F5	100	1.5	5	2	5	5	100
F6	100	1.5	5	2	10	5	100

Evaluation of emulgel

Physical characteristic

The prepared emulgel formulations were inspected visually for their pH, colour, homogeneity, consistency, grittiness, texture and phase separation

Determination of pH

The pH of emulgel formulations was determined by digital pH meter. One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation for 30 min until constant reading obtained, and constant reading was noted. The measurement of pH of each formulation was done in triplicate and average values were calculated [13].

Washability

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

Extrudability study

The emulgel formulations were filled into collapsible metal tubes or aluminium collapsible tubes. The tubes were pressed to extrude the material and the extrudability of the formulation was checked [14].

Spreadability

Two glass slides of standard dimensions (6×2) were selected. The emulgel formulation whose spreadability had to be determined was placed over one of the slides. The second slide was placed over the slide in such a way that the formulation was sandwiched between them across a length of 6cms along the slide. 100 grams of weight was placed up on the upper slide so that the emulgel formulation between the two slides was traced uniformly to form a thin layer. The weight was removed and the excess of the emulgel formulation adhering to the slides was scrapped off. The lower slide was fixed on the board of the apparatus and one end of the upper slide was tied to a string to which 20 gram load could be applied with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6cms and separate away from lower slide under the direction of the weight was noted. The experiment was repeated and the average of 6 such determinations was calculated for each emulgel formulation [15, 16].

$$\textbf{Spreadability} = \frac{m.\ l}{t}$$

Where, S=Spreadability (gcm/sec), m = weight tied to the upper slide (20 grams),

l= length of glass slide (6cms), t = time taken is seconds.

Viscosity

The measurement of viscosity of the prepared emulgel was done using Brookfield digital Viscometer. The viscosity was measured using spindle no. 6 at 10 rpm and 25^0C. The sufficient quantity of gel was filled in appropriate wide mouth container. The emulgel was filled in the wide mouth container in such way that it should sufficiently allow to dip the spindle of the viscometer. Samples of the emulgel were allowed to settle over 30 min at the constant temperature (25 $\pm/1^0$C) before the measurements [17].

Drug content

1gm of the prepared gel was mixed with 100ml of ethanol. Aliquots of different concentrations were prepared by suitable dilutions after filtering the stock solution and the absorbance was measured at 248nm. Drug content was calculated by linear regression analysis of the calibration curve.

***In-vitro* drug release studies**

The *in-vitro* diffusion of drug from the different gel preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15 mm internal diameter and 100 mm height. The diffusion cell membrane was applied with 1 gram of the formulation and was tied securely to one end of the tube, the other end kept open to ambient conditions which acted as donor compartment. The cell was inverted and immersed slightly in 250 ml of beaker

containing neutralizing 7.4 pH phosphate buffer, freshly prepared as a receptor base and the system was maintained for 2 hrs at 37± 0.5^{o}C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of upto 12 hrs and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-Vis spectrophotometer at 248nm using neutralizing 7.4pH phosphate buffer as blank[18,19].

Drug release kinetics study

The results of in-vitro release profile obtained for all the formulations were plotted in kinetic models as follows,

1. Cumulative of drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining to be absorbed versus time (First order model)
3. Cumulative amount of drug release versus square root of time (Higuchi model)
4. Log cumulative drug released versus log time (Korsmeyer-Peppas model) [20].

RESULTS AND DISCUSSION

Emulgel formulations were white viscous creamy preparation with a smooth homogeneous texture and glossy appearance. Results have been discussed in Table 2. The results of extrudability and spreadability of all formulation were given in Table 3. From the result it was found that formulation F1-F6 has good washability ability, formulation F3, F5 has good extrudability and spreadability of all formulation was found to in range of 11.32 to 13.45. It was concluded that all the developed formulation showed acceptable spread ability, F5 formulation has more spread ability as compare to other formulation i.e. 13.45. The viscosity of the emulgel was obtained by using Brookfield digital Viscometer. The viscosity of the formulations increases as concentration of polymer increases and pH of prepared emulgel were measured by using pH meter (Orion Research, Inc., USA). The pH of the emulgel formulation was in the range of 6.52-6.82which considered acceptable to avoid the risk of skin irritation upon application to skin. % Drug content of all formulation was found to be in range of 97.85±0.32 to 99.85±0.41 Table 4. Release of drug from mometasone furoate emulgel was significantly slower, which confirmed that slight prolonged drug release rate. Incorporation of carbomer affected the release rate of the drug. By increasing the amount of carbomer, the release rate of the drug decreased, which could be related to the increased rigidity of the formulation, followed by its de-creased permeability for the drug. Optimized formulation F5 shows significantly improved in drug release rate as compare to marketed preparation. It was concluded that developed formulations deliver the drug for the treatment of skin disease Table 5 and Fig. 1. The kinetics of drug release from the optimized formulation (F5) was studied by mathematical modeling the drug release to zero order, first order kinetics Table 6 and Fig. 2, 3.

Table 2 Physical parameter of formulation batches

Formulation	Washability	Observation	Clogging	Homogeneity
F1	+++	white cream	Absent	Good
F2	+++	white cream	Absent	Good
F3	+++	white cream	Absent	Good
F4	+++	white cream	Absent	Good
F5	+++	white cream	Present	Good
F6	+++	white cream	Present	Good

Table 3 Extrudability and spreadability study

Formulation	Extrudability	Spreadability (gcm/sec)
F1	++	14.58
F2	++	13.25
F3	+++	12.25
F4	++	11.32
F5	+++	13.45
F6	++	11.74

Excellent: +++, Good: ++, Average: +, Poor: -

Table 4 Viscosity, pH and % drug content

Formulation	Viscosity (cps)	pH	% Drug content
F1	3255±23	6.71±0.02	98.74±0.25
F2	3445±15	6.59±0.01	97.85±0.32
F3	4565±21	6.52±0.03	98.85±0.14
F4	4325±18	6.74±0.04	99.05±0.62
F5	4625±16	6.82±0.03	99.85±0.41
F6	4521±17	6.81±0.02	98.15±0.22

* Average of three determinations

Table 6 *In vitro* drug release data for Different formulation F1-F6

S. No.	Time (min)	% Cumulative drug release						
		F1	F2	F3	F4	F5	F6	Marketed Formulation
0	0	0	0	0	0	0	0	0
1	15	43.32	38.45	35.45	34.45	21.45	20.25	35.65
2	30	62.25	65.56	52.23	51.23	36.65	32.24	49.98
3	60	72.32	73.32	69.98	65.58	45.58	41.14	65.58
4	90	85.56	84.45	78.85	75.65	65.58	60.23	99.14
5	120	98.85	97.85	98.12	98.45	88.89	81.14	-
6	240	98.92	99.12	98.85	99.45	99.45	92.23	-

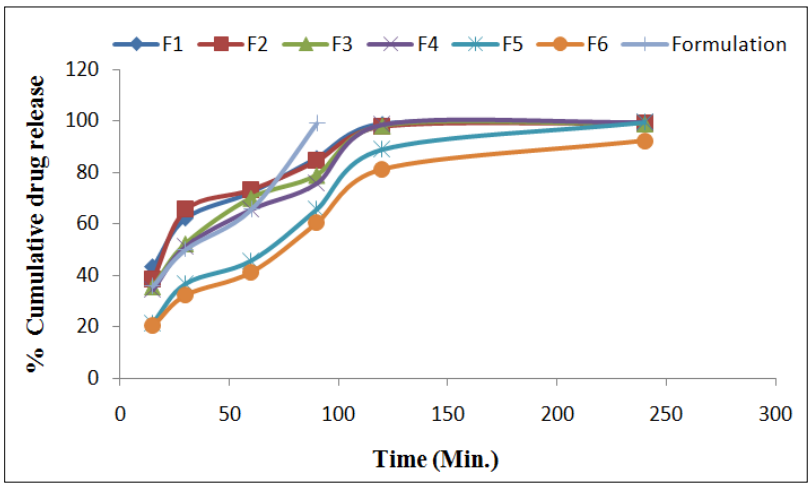

Fig. 1 Graph of % Cum. drug release of formulation F1-F6

Table 6 *In vitro* drug release data for optimized formulation F5

S. No.	Time (min)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release ± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	15	3.873	0.588	21.45	1.331	78.55	1.895
2	30	5.477	0.739	36.65	1.564	63.35	1.802
3	45	6.708	0.827	45.58	1.659	54.42	1.736
4	60	7.746	0.889	65.58	1.817	34.42	1.537
5	120	10.954	1.04	88.89	1.949	11.11	1.046
6	240	15.492	1.19	99.45	1.998	0.55	-0.260

* Average of three determinations

*

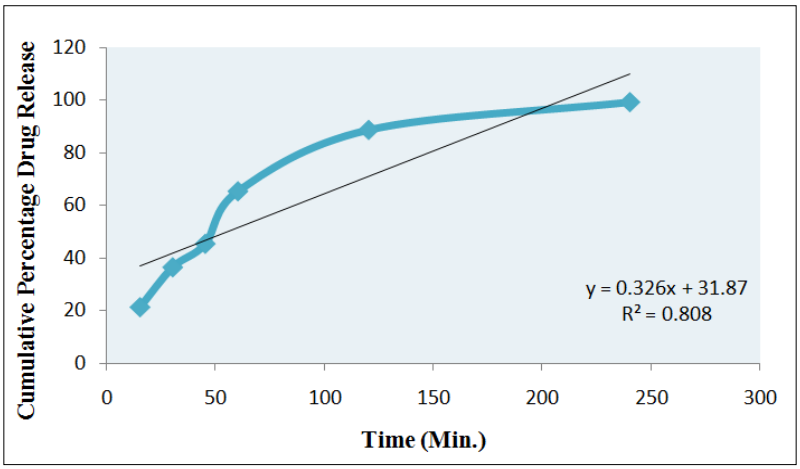

Fig. 2 Graph of zero order release kinetics of optimized formulation F5

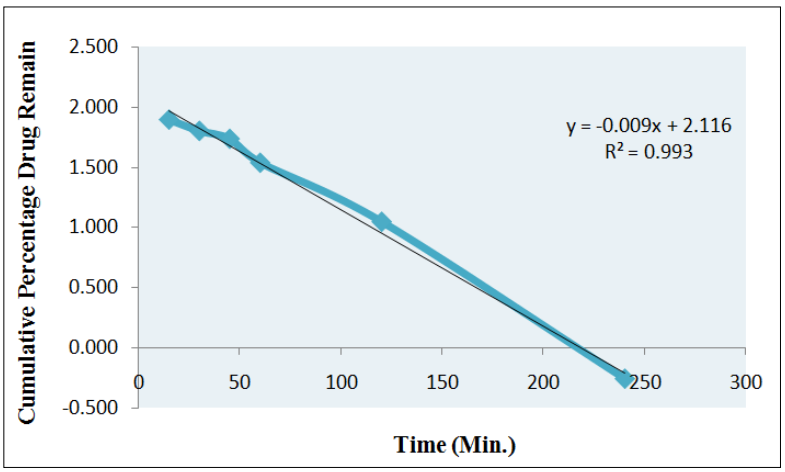

Fig. 3 Graph of first order release kinetics of optimized formulation F5

Conclusion

In the coming years, topical drug delivery will be used extensively to impart better patient compliance. Since emulgel is helpful in enhancing spreadability, adhesion, viscosity and extrusion, this novel drug delivery become popular. Moreover, they will become a solution for loading hydrophobic drugs in water soluble gel bases for the long term stability. In present investigation topical mometasone furoate emulgel was prepared by using carbopol 941 showed acceptable physical properties, pH, drug content, viscosity. In vitro releases of emulgel were also performed to determine drug release from emulgel and duration of drug release. From the in vitro studies, formulation F5 showed maximum release of 99.45% in 240 min. So mometasone furoate emulgel can be used for topical drug delivery for psoriasis.

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