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Formulation Development and Evaluation of Emulgel of Clindamycin Phosphate for Effective Treatment of Acne

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ABSTRACT

Emulgel have emerged as one of the most interesting topical delivery system as it has dual release control system i.e. gel and emulsion. The topical applications of the drug offers the potential advantages of delivering the drug directly to the site of action and delivering the drug for extended period of time at the effected site that mainly acts at the related regions. The major objective behind this formulation is enhancing the topical delivery of hydrophobic drug (clindamycin phosphate) by formulating clindamycin phosphate emulgel 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. Clindamycin phosphate is an antibiotic useful for the treatment of a number of infections. It is of the lincosamide class. Clindamycin phosphate is a semi synthetic lincosamide antibiotic that has largely replaced lincomycin due to an improved side effect profile. Clindamycin inhibits bacterial protein synthesis by binding to bacterial 50S ribosomal subunits. Topical clindamycin phosphate reduces free fatty acid concentrations on the skin and suppresses the growth of *Propionibacterium acnes* (Corynebacterium acnes), an anaerobe found in sebaceous glands and follicles. The prepared emulgel were evaluated for their physical appearance, pH determination, viscosity, spreadability, extrudability, *in vitro* drug release, anti acne activity and stability. All the prepared emulgel showed acceptable physical properties, homogeneity, consistency, spreadability, viscosity and pH value. The best formulation F4 showed better antiacne activity when compared with all formulation.

Keywords: Emulgel, Clindamycin phosphate, Extrudability, Spreadability, Antiacne activity

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INTRODUCTION

Acne vulgaris is a common dermatological disorder with prevalence reported to reach upto 85% of population across various regions[1]. It has a significant impact on the quality of life[2,3], psychosocial development as well as self-esteem of the patients[4]. It affects areas of the skin having the highest population of sebaceous follicles, most common being the face, the upper part of chest, and the back[5].Until recently follicular epidermal hyperproliferation with subsequent plugging of the follicles (comedones) was considered to be the earliest event in the development of acne and closed comedones were regarded as the precursors of inflammatory lesions[6,7].Current evidence has shown that inflammatory events can precede microcomedone formation and that the development of follicular duct plugs is also influenced, to some degree, by inflammation caused by *Propionibacterium acnes*[6, 8,9]. *P. acnes* are an anaerobic organism present in the sebaceous glands which contributes to the pathophysiology of acne in several ways. It stimulates inflammation by producing pro-inflammatory mediators through toll like receptor-2 (TLR-2) and activation of the innate immune system[8-10]. Antibiotic treatment against *P.acnes* is one of the essential elements for the treatment of acne vulgaris. Though systemic antibiotics have been used for several years to reduce the population of *P. acnes*, topical antibiotics are more acceptable because of their fewer side effects and interactions. Among the routinely prescribed topical antibiotics for acne vulgaris, clindamycin has retained better efficacy over a period of time[11]. Clindamycin also has anti-inflammatory properties which are likely to contribute to its anti-acne therapeutic effects in a significant manner[12]. Concentration of the drug in the pilosebaceous ducts affects the efficacy of topical antimicrobial agents. Moreover emergence of resistance also correlates with low and variable concentrations of the drug achieved in the pilo-sebaceous ducts[13,14]. Therefore, reliable drug delivery

systems providing better drug penetration can result in better efficacy and also help in the prevention of development of resistance. When gels and emulsions are used in combined form the dosage forms are referred as EMULGELS[6]. Emulgels are also called as creamed gel, quassi emulsion, gelled emulsion[7]. 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[8]. 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[9]. The aim of the present study was to statistically optimize emulgel for enhanced skin delivery of a model drug of anti-acne drug clindamycin phosphate, which was effective candidate for the treatment of acne [15-18].

MATERIALS AND METHODS

Materials

Clindamycin phosphate was kindly provided as a gift sample from Cure tech skin formulation Baddi, Himanchal Pradesh, India. 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. *Propionibacterium acne* was obtained from microbial culture collection, national centre for cell science, Pune, Maharashtra, India. All other chemicals used were of analytical grade and were used without any further chemical modification.

Method

Formulation development

Preparation of carbopol

Fifty grams of the carbopol gel was prepared by dispersing one 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.

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 given in table 1 while the aqueous phase was prepared by dissolving tween 20 in purified water as given in table 1. One grams of clindamycin was dissolved in 5 ml of ethanol, while 0.15 g of methylparaben and 0.05 g 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[19].

Formulation of clindamycin emulgel

Six formulas of clindamycin 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 Different formulas of clindamycin emulgel (%w/w)

Formulation	Clindamycin (mg)	Carbomer 941	Liquid paraffin	Span 20	Tween 20	Propylene glycol	Water
F1	500	0.5	5	2	5	5	100
F2	500	0.5	5	2	10	5	100
F3	500	1.0	10	4	5	5	100
F4	500	1.0	10	4	10	5	100
F5	500	1.5	5	2	5	5	100
F6	500	1.5	5	2	10	5	100

Determination of λ_{max} of clindamycin

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 10-50 µg/ml. 2 ml of standard solution mix with 1 ml methyl orange and extracted with 3 ml of chloroform. Pipette out the chloroform layer and take the absorbance against chloroform as blank. The spectrum of this solution was run in 400-800 nm range in U.V. spectrophotometer (Labindia-3000+). The spectrum peak point graph of absorbance of clindamycin phosphate versus wave length.

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[20].

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[21].

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 6 cms 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 6 cms 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[22,23].

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

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^{0}C. 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 ±/1^{0}C) before the measurements[24].

In-vitro drug release studies

The *in-vitro* diffusion of drug from the different emulgel preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15mm internal diameter and 100mm height. The diffusion cell membrane was applied with one 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 phthalate buffer, freshly prepared (pH 5.4) 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 up to 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 486 nm using neutralizing phthalate buffer as blank[25,26].

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)[27]

Antiacne activity studies

The prepared emulgel formulations were tested against *propionibacterium acne* strain using well diffusion method. Clindamycin used as standard drug. There were 3 concentration used which are 30, 20 and 10 µg/ml for antibiogram studies. The plates were incubated at 37^{o}C for 24 hr. and then examined for clear zones of inhibition around the wells with particular concentration of drug.

RESULTS AND DISCUSSION

λ_{max} of clindamycin was found to be 486 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 10-50µg/ml Fig.1. 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 washability, 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, F4 has good Extrudability and Spreadability of all formulation was found to in range of 12.25to14.56. 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 6.9 to7.05 which considered acceptable to avoid the risk of skin irritation upon application to skin table 4. Release of drug from clindamycin 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 decreased permeability for the drug. Optimized formulation F4 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 acne vulgaris table 5 and Fig 2. The kinetics of drug release from the optimized formulation (F4) was studied by mathematical modeling the drug release to zero order, first order kinetics Table 6 and Fig.3, 4. The antiacne activity of clindamycin emulgel (F4) was studied Table 7. The zone of inhibition was measure for antiacne activity of drug. The same activity was observed as compared to standard drug.

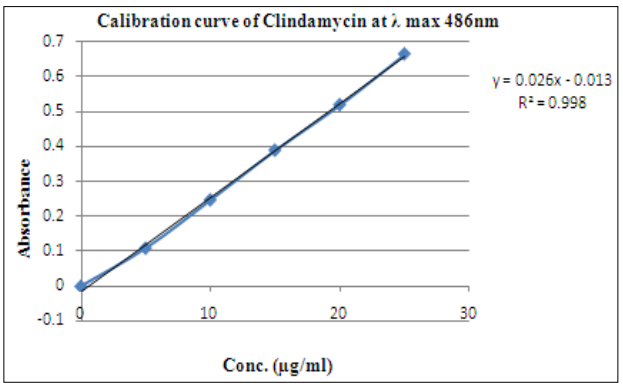

Fig.1 Calibration curve of clindamycin phosphate in phosphate buffer pH 7.4 at 486nm

Table 2 Physical parameter of formulation batches

Formulation	Colour	Homogeneity	Consistency	Phase separation
F1	White	Excellent	Excellent	None
F2	White	Excellent	Excellent	None
F3	White	Excellent	Excellent	None
F4	White	Excellent	Excellent	None
F5	White	Excellent	Excellent	None
F6	White	Excellent	Excellent	None

Table 3 Result of washability extrudability and spreadability study

Formulation	Washability	Extrudability	Spreadability (gcm/sec)
F1	+++	++	12.25
F2	+++	++	13.36
F3	+++	+++	14.56
F4	+++	+++	13.23
F5	+++	++	14.56
F6	+++	++	14.56

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

Table 4 Viscosity and pH

Formulation	Viscosity (cps)	pH
F1	3280	7.05
F2	3345	7.02
F3	3280	6.95
F4	3250	6.98
F5	3352	7.05
F6	3365	7.00

Table 5 % Cum. drug release of formulation F1-F6

		% Cum. drug release						
S. No.	**Time (min)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**Marketed**
1	0	0	0	0	0	0	0	0
2	15	15.65	22.15	20.23	25.65	22.45	20.23	42.23
3	30	26.65	32.25	33.12	36.65	38.89	35.65	65.56
4	45	37.89	45.65	46.65	49.98	48.85	42.23	79.98
5	60	46.65	52.25	53.32	57.89	53.32	50.32	94.46
6	120	63.32	70.23	69.98	88.98	69.98	65.56	-
7	240	76.65	74.56	76.65	98.89	82.23	75.56	-

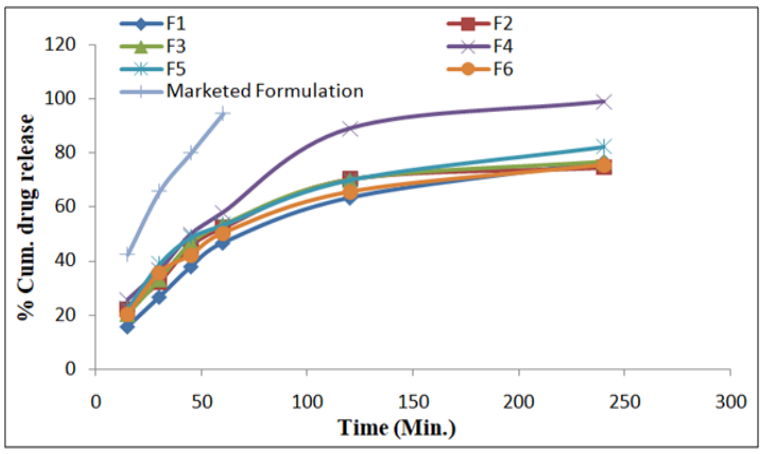

Fig. 2 Graph of % Cum. drug release of formulation F1-F6

Table 6 *In Vitro* drug release data for optimized formulation F4

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
15	3.873	0.588	25.65	1.409	74.35	1.871
30	5.477	0.739	36.65	1.564	63.35	1.802
45	6.708	0.827	49.98	1.699	50.02	1.699
60	7.746	0.889	57.89	1.763	42.11	1.624
120	10.954	1.040	88.98	1.949	11.02	1.042
240	15.492	1.190	98.89	1.995	1.11	0.045

* Average of three determinations

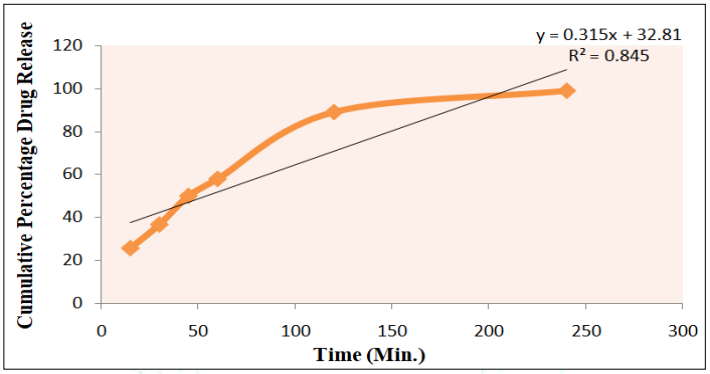

Fig. 3 Graph of Zero order release kinetics of optimized formulation F4

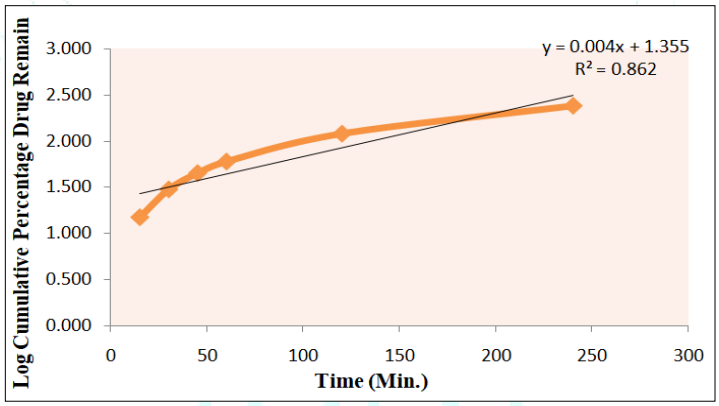

Fig. 4 Graph of First order release kinetics of optimized formulation F4

Table 7 Antiacne activity of optimized emulgel F4

S. No.	Name of drug	Microbes	Zone of inhibition		
			10 µg/ml	20 µg/ml	30 µg/ml
1.	Clindamycin	*propionibacterium acne*	26.5±0.1	29.5±0.2	33.5±0.2
2	F4	*propionibacterium acne*	27.5±0.2	30.2±0.2	34.8±0.2

CONCLUSION

From the above results we can conclude that the clindamycin phosphate emulgel formulations prepared with carbopol-941, light liquid paraffin, tween-20, span-20 and propylene glycol showed acceptable physical properties, drug release and anti acne activity, which remained unchanged upon storage for 3 months. However, the carbopol-941based emulgel in its low concentration with the formulation code F4 proved to be the formula of choice, since it showed the highest drug release and anti acne activity when compared to the marketed clindamycin gel. So, clindamycin phosphate emulgel can be used as anti acne medication for topical drug delivery.

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