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PREPARATION AND OPTIMIZATION OF CLOTRIMAZOLE ANTI-DANDRUFF EMULGEL

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ABSTRACT

Dandruff is a common embarrassing disorder that affects about 5% of the global population. Several antifungal agents are available in the market in different topical preparations. One such antifungal agent is Clotrimazole. Also emulgels are evolving as a promising drug delivery system. The purpose of the present investigation was to prepare an anti-dandruff emulgel of clotrimazole using gelling agents like Carbopol 940, Lutrol F127 and HPMC K4M in various concentrations. Mentha Oil was used as a permeation enhancer. All the formulations were evaluated for physical appearance, pH, spreadability, viscosity, drug content, invitro release, antifungal activity and skin irritation studies. Out of all the formulations, F3 showed the highest drug release and drug content and the best antifungal activity along with good spreadability and extrudability. So it can be concluded that the formulation F3 containing gelling agent Lutrol F127 possesses the best anti-dandruff activity of all the formulations.

KEYWORDS : *Dandruff, Clotrimazole, emulgel, Carbopol, Lutrol F127, HPMC K4M.*

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INTRODUCTION

Dandruff is a common embarrassing disorder that affects about 5% of the global population[1]. It is an abnormal condition that is associated with visualisation of distinctive flakes on the hair, scalp or clothes that are usually associated with itching[2-3]. It does not exhibit apparent inflammation and is confined to the scalp[2] . *Pityrodporium ovale* is strongly suspected to play a role in the manifestation of dandruff[4-5]. The visible symptoms of dandruff i.e. superficial flaking and redness, are manifestations of abnormal epidermal structure and function. However, the underlying stratum corneum irregularities occur throughout the scalp suggesting the actual flakes are the end result of a cycle of skin distress that may or may not be visible to the unaided eye[6].

Several antifungal agents are available in the market in different topical preparations as anti-dandruff agents e.g. zinc pyrithione, salicylic acid, imidazole derivatives, glycolic acid, steroids, and sulphur and coal tar derivatives. One of these antifungal agents is clotrimazole[7]. Clotrimazole is 1-[(2-chlorophenyl) diphenylmethyl]-1H-imidazole. It has a broad spectrum antifungal activity[8,9]. It is the first choice drug for topical treatment of tinea pedis, tinea cruris, and tinea corporis, candidiases due to candida albicans. It is also effective for the topical treatment of vulvovaginal and oropharyngeal candidiasis [9-11].

A wide variety of pharmaceutical and cosmetic preparations are available for skin care and topical dermatological diseases. They range from solid to semisolid preparations. In semisolid preparations, the use of emulgels has expanded rapidly for insoluble and hydrophobic drugs[12]. Emulgels are basically oil in water or water in oil emulsions containing a suitable gelling agent. These are widely used now a days because they possess the properties of both emulsions and gels and thus have high patient compatiblity[13,14]. Thus, these are widely used drug delivery system to deliver various insoluble and hydrophobic drugs[15-17].

In the present investigation, anti-dandruff emulgel formulations were prepared using Carbopol 940, Lutrol F127 and HPMC K4M as gelling agents in varying concentration. Mentha Oil was used as a permeation enhancer. The influence of varying concentration of gelling agents on drug content, in vitro drug release and anti fungal activity was investigated.

MATERIALS

Clotrimazole was a gift sample from Macleods Pharmaceutical Ltd. Carbopol 940 was procured from S.D. Fine Chemicals, Mumbai. Lutrol F127 was a gift sample from BASF India Ltd. HPMC K4M was a gift sample from Macleods Pharmaceutical Ltd. *Pityrodpodium ovale* strain was obtained from MTCC & Gene Bank. All other chemicals and reagents used in the study were of analytical grade.

METHODS

Preparation of Emulgel:

Different formulations were prepared using varying concentration of gelling agent. The method only differed in process of making gel in various formulations. The method of preparation of emulsion was same in all the formulations. In formulations F1 and F2, the gel base was prepared by soaking Carbopol 940 in water for 24 hours. In formulations F3 and F4, the gel base was prepared by dispersing Lutrol F127 in heated distilled water (75°C) and the dispersion was cooled and left overnight. In formulations F5 and F6, the gel base was prepared by dispersing HPMC K4M in heated distilled water (75°C) and the dispersion was cooled and left overnight. The pH of all the formulations was adjusted to 5.5 to 6.5 using tri ethanol amine (TEA).

The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin. The aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl and propyl paraben were dissolved in propylene glycol and mixed with aqueous phase. Clotrimazole was dissolved in ethanol and mixed with aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. Mentha oil was then added to the formulation with continuous stirring.

The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the Emulgel[18,19].The composition of different formulations has been discussed in Table 1.

Table 1: Composition of different formulation batches in % w/w

INGREDIENTS	F1	F2	F3	F4	F5	F6
Clotrimazole	4	4	4	4	4	4
Carbopol 940	1.0	1.2	-	-	-	-
Lutrol F127	-	-	15	20		-
HPMC K4M	-	-	-	-	1.0	1.2
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s
Liquid paraffin	7.5	7.5	7.5	7.5	7.5	7.5
Tween 20	0.5	0.5	0.5	0.5	0.5	0.5
Span 20	1	1	1	1	1	1
Propylene glycol	5	5	5	5	5	5
Ethanol	2.5	2.5	2.5	2.5	2.5	2.5
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03
Propyl paraben	0.01	0.01	0.01	0.01	0.01	0.01
Mentha oil	4.0	4.0	4.0	4.0	4.0	4.0
Purified water	q.s	q.s	q.s	q.s	q.s	q.s

Characterization of emulgel

Physical appearance

The prepared Emulgel formulations were evaluated visually for their colour, consistency, homogeneity, extrudability and grittiness[20].

Measurement of pH

The pH of Emulgel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml of distilled water and checked for pH. The measurement of pH of each formulation was done in triplicate and the average values were calculated[21].

Spreadability

An ideal emulgel formulation is characterized by properties good spreadability. It denotes the extent of area to which the gel readily spreads on application to skin or affected area. Good spreadability also ensures good therapeutic efficacy of a formulation. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from emulgel and placed in between the slides under the direction of certain load. Lesser the time taken for the two slides to separate, better is the spreadability. It is calculated by using the formula[20].

$$S = \frac{M * L}{T}$$

Where

M = wt. tied to upper slide

L = length of glass slides

T = time taken to separate the slides

Rheological Study

The viscosity of the formulated batches was determined using a Brookfield Viscometer (Brookfield DV-E viscometer) with spindle 07. The formulation whose viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min. at the assay temperature (25±1ºC) before the measurement was taken. Spindle was lowered perpendicular in to the centre of Emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 50 rpm for 10 minutes. The viscosity reading was noted down. The average of three readings were taken in 10 minutes was noted as the viscosity of Emulgel[22].

Drug content determination

1 gm of Emulgel formulation was weighed and it was dissolved in 100 ml of Methanol. The volumetric flask was kept for 2 hours and shaken well in a orbital shaker to mix it properly. The solution was passed through the whatmann filter paper and filtered. The absorbance was measured

spectrophotometrically at 261 nm after appropriate dilution against corresponding Emulgel concentration as blank and the drug content was determined[23, 24].

In vitro release study

Franz diffusion cell (20 ml cell volume) was used for invitro drug release studies. Emulgel (200 mg) was evenly applied onto the surface of cellophane membrane. The cellophane membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 5.5) solution to solubilise the drug and then it was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time interval and replaced with fresh PBS. Correction factor was considered in calculations. Samples were analyzed for drug content by UV visible spectrophotometer at 261 nm after appropriate dilutions. The cumulative amount of drug released across the cellophane membrane was determined as a function of time[25].

Antifungal activity

The hair gel formulations were subjected to antifungal activity by adopting disc diffusion method. The test strain used was *Pityrodpodium Ovale* in Sabouraud's dextrose agar media[7].

Skin irritation test (Patch test)

A set of 8 rats were used in the study. The emulgel was applied on the properly shaven skin of rat. Any undesirable skin changes, i.e. change in color of the skin, change in skin morphology were checked for a period of 24 hours[26].

Stability study

Stability study was performed on all formulations. The preparations were packed in collapsible aluminium tubes (5 g) and subjected to stability studies at 25°C/ 60 % RH & 30°C/65 % RH, for a period of 3 months. Samples were withdrawn at interval of 45-days and were evaluated for physical appearance, rheological properties, and drug content[27].

RESULTS

Physical Appearance

Emulgel formulations were white, viscous , non gritty , creamy preparations with a homogeneous texture and glossy appearance. Results have been discussed in Table 2.

Measurement of pH

The pH of all the formulations were in the range of 6.1 to 6.4 which is normal range with that of the scalp pH. The data is shown in table 3.

Spreadability test

Spreadability was carried out on all formulations. Spreadability data indicates that all the formulations were easily spreadable by small amounts of shear. Spreadability of the Emulgel decreases with the increase in the concentration of the polymer. The spreadability coefficient was found to be highest for formulations containing Carbopol 940 as the gelling agent i.e. F1 and F2 respectively. Results for the spreadability coefficient are shown in Fig 1.

Rheological Study

The viscosity study was carried out on all the formulations. It was found out that the viscosity of the emulgel formulation increases with the increase in polymer concentration. The viscosity was found to be the highest for formulations containing Lutrol F127 as the gelling agent i.e. F3 and F4. Results for the rheological study is shown in Fig 2.

Drug content determination

The result for the drug content determination for all the formulations is shown in table 4 and Fig. 3.

In vitro release study

The cumulative percent release data of all the formulations is shown in table 5 and Fig. 4. The invitro release of all the formulations is in the following order : F3> F1> F4> F2> F5> F6 where the amount of drug released after 2 hours is 67.63%, 65.87%, 64.58, 61.39%, 54.64% and 50.89% respectively. Thus it can be observed that as the concentration of the polymer increases the amount of drug diffused decreases.

Antifungal activity

The zone of inhibition for all the formulations is shown in table 6. The zones of inhibition of all the formulations are in the following order : F3> F4> F1> F2> F5> F6.

Skin irritation test (Patch test)

The rats were observed for a period of 24 hours and no erythema or inflammation was observed. Thus all the formulations passed the patch test.

Stability study

Stability studies of all the formulations were performed as per ICH guideline. It was observed that all the emulgel formulations showed no major alteration in pH, extrudability, appearance and drug content.

Table 2: Physical characteristics of Clotrimazole Emulgel formulations

Sr. No	Formulation	Colour	Consistency*	Homogeneity*	Extrudability*	Grittiness
1	F1	White	++	Good	++	-
2	F2	White	++	Good	++	-
3	F3	White	+++	Excellent	+++	-
4	F4	White	+++	Excellent	+++	-
5	F5	White	++	Fair	++	-
6	F6	White	++	Fair	++	-

*Each reading is average of 3 determinations Excellent+++ Good++ Fair++

Table 3: pH of different formulations

Sr. No	Formulations	pH*
1	F1	6.34
2	F2	6.29
3	F3	6.38
4	F4	6.36
5	F5	6.19
6	F6	6.15

*Each reading is average of 3 determinations

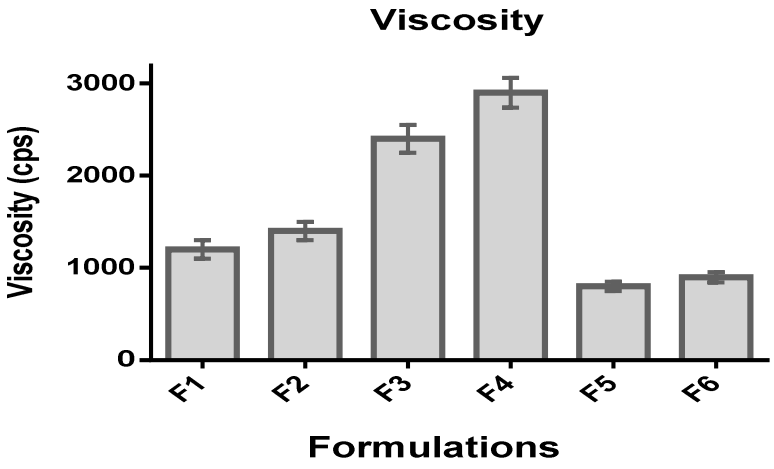

Fig.1: Spreadability coefficient of all formulations.

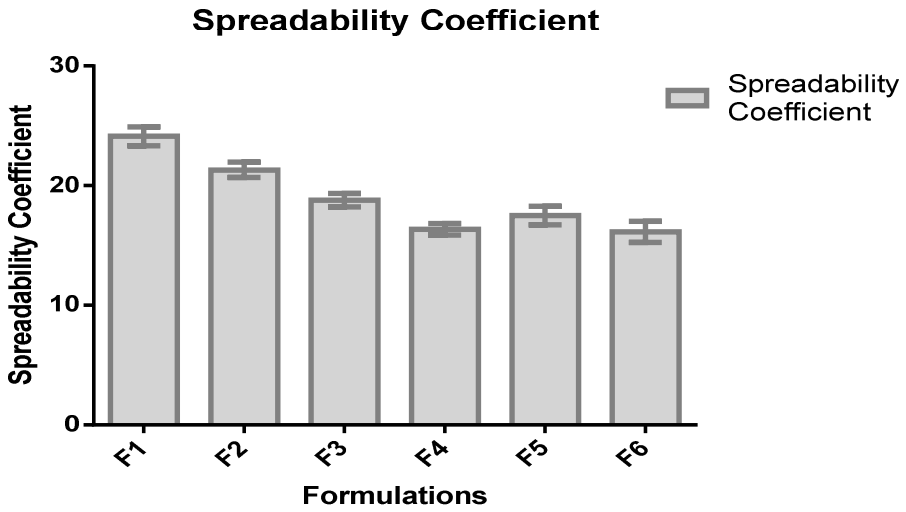

Fig.2: Rheological study of all the formulations

Table 4: Drug Content of formulations

Sr. No	Formulations	Drug Content*
1	F1	95.92 ± 1.04
2	F2	95.47 ± 0.89
3	F3	97.75 ± 1.13
4	F4	98.73 ± 1.43
5	F5	94.33 ± 1.02
6	F6	95.47 ± 0.87

*Each reading is average of 3 determinations

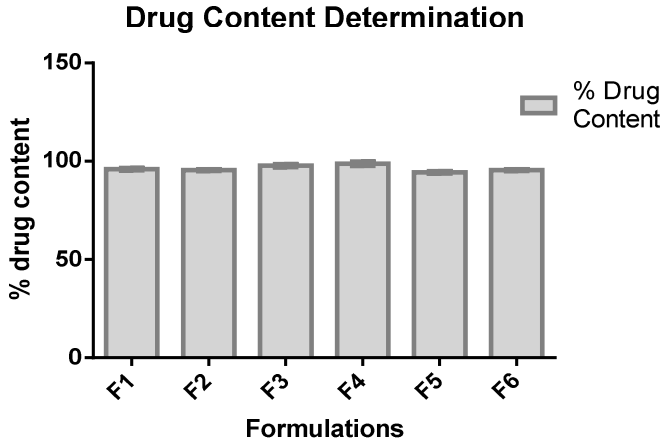

Fig.3: Percent Drug Content of formulations

Table 5: In vitro release profile of all the formulations

Time	F1	F2	F3	F4	F5	F6

0	0	0	0	0	0	0
5	14.5 ± 0.13	2.78 ± 0.26	3.33 ± 0.12	1.11 ± 0.15	1.66 ± 0.6	1.11 ± 0.5
10	20.64 ± 0.26	13.75 ± 0.58	16.5 ± 0.36	3.83 ± 0.26	4.91 ± 2.9	3.83 ± 1.6
30	46.87 ± 1.6	45.42 ± 1.66	48.61 ± 068	45.36 ± 0.5	23.63 ± 6.9	22.02 ± 5.6
45	54.38 ± 3.8	53.25 ± 2.38	58.64 ± 0.89	55.5 ± 1.9	35.47 ± 3.5	33.88 ± 3.8
60	58.60 ± 5.1	56.11 ± 5.9	62.5 ± 3.9	57.66 ± 2.7	45.38 ± 2.9	42.69 ± 5.1
90	61.59 ± 3.4	58.16 ± 2.1	66.16 ± 5.2	60.86 ± 2.6	49.30 ± 3.2	46.66 ± 2.9
120	65.878 ± 3.1	61.389 ± 2.0	67.639 ± 2.6	64.583 ± 3.9	54.639 ± 3.9	50.889 ± 3.6

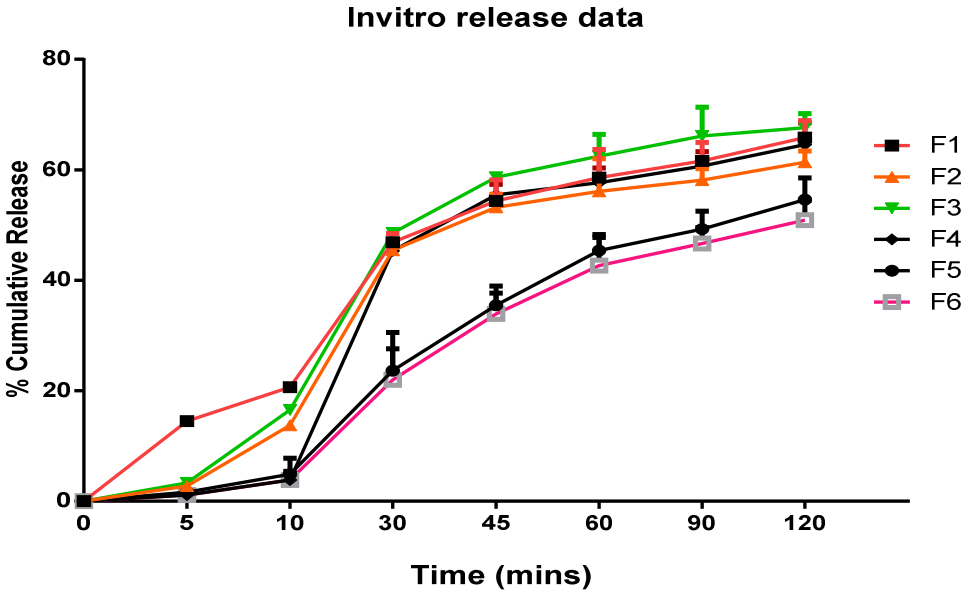

Fig.4: Invitro release data of all the formulations

Table 6: Zone of inhibition (mm) of all the formulations.

Formulations	Zone of inhibition (mm)
F1	26
F2	25
F3	30
F4	27
F5	22
F6	21

DISCUSSION

Thus from the above data we can conclude that all the emulgel formulations prepared using varying concentration of Carbopol 940, Lutrol F127 and HPMC K4M as gelling agents showed acceptable physical properties, pH, spreadability, viscosity,

drug content, drug release and antifungal activity. All the formulations were found to be stable over a period of 3 months according to ICH guideline. Also all the formulations showed no signs of irritation or erythema in the patch test. However of all the formulations, the Lutrol F127 based formulation F3 proved to be the formula of choice, since it showed the best antifungal activity, highest drug release along with acceptable percent drug content. In conclusion, the formulation F3 prepared using Lutrol F127 as the gelling agent can be used as an effective anti-dandruff hair emulgel in the near future. However the long term stability studies and further clinical trials would be required to market the formulation as an effective anti-dandruff emulgel.

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