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Formulation and Evaluation of Luliconazole Emulgel for Topical Drug Delivery

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ABSTRACT

The aim of the present study was to develop an emulgel formulation of Luliconazole using carbopol 934 as a gelling agent. The Luliconazole has anti-Fungal activity. It acts by inhibiting lanosterol demethylase, which is major component of fungus cell wall. Emulgel has emerged as a promising drug delivery system for the delivery of hydrophobic drugs. The prepared emulgel were also evaluated for their physical properties, pH, drug content and rheological properties. Candida albicans was used as a model fungus to evaluate the antifungal activity of the prepared formulations. Stability studies revealed no significant differences in formulation.

It was concluded that Luliconazole emulgel formulation (F3) prepared by using Carbapol 934 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 and antifungal activity.

Keywords: Emulgel, Luliconazole, Topical drug delivery.

INTRODUCTION

Topical formulations apply a wide spectrum of preparations both cosmetic and dermatological, to healthy or diseased skin [1]. These formulations range in consistency from solid through semisolid to liquids. When gels and emulsions are used in a combined form, the dosage forms are referred to emulgel. [2, 3]As the name suggests they are the combination of emulsion

micro-emulsion and gel. Novel polymers with complex fuctions as emulsifires and thickeners have been widely used due to their gelling capacity which allows the formulation of stable emulsion by decreasing surface and interfacial tension and also by increasing the viscosity of the aqueous phase. Oil/water and water/oil emulsions are used as vehicles to deliver various drugs to the skin [4]. Emulsion gels are has importance due to many reasons; they have better application property in comparison to classical formulation as creams and ointment, they have faster and more complete release of the drug from the vehicle to the skin, also they are convenient to apply on hairy skin due to the absence of greasiness and lack of residue upon application. They permit the incorporation of both aqueous and oleaginous ingredients, so hydrophobic or poorly water soluble drugs as antifungal agents are easily incorporated in such type of vehicles through the proper choice of the oily phase [5].

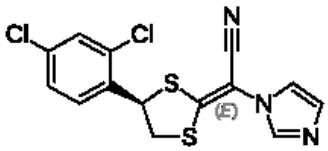

Fig. 1: Structure of Luliconazole

Luliconazole has anti-fungal activity. Luliconazole is inhibiting the enzyme lanosterol demethylase. Lanosterol demethylase is needed for the synthesis of ergo-sterol, which is a major component of the fungus cell membranes. For skin care and the topical treatment of dermatological diseases, a wide choice of vehicles including solid, semisolids and liquid Preparation is available to physician and patients. Within the major groups of semisolid preparations, the use of transparent emulgel has expanded, both in cosmetics and pharmaceuticals. Emulgel or jellified emulsion is stable one and better vehicle for hydrophobic or water insoluble drugs as Luliconazole. Also emulgel has a high patient acceptability since they possess the advantages of both emulsions and gels. Therefore, they have been recently used as vehicles to deliver various drugs to the skin. [6-7]

METHODOLOGY

Materials:

Luliconazole was obtained as a gift sample from A. S. Life Science, Haryana, India. Carbopol 940 was obtained from Loba chemicals Mumbai. Liquid paraffin, propylene glycol, ethanol was procured from Naprod life science, Mumbai. Methyl parabens and propyl parabens procured from Chem. Pure pvt.ltd. Mumbai. All other chemicals used were of analytical grade and were used without any further chemical modification.

Method:

Preparation of Luliconazolee Emulgels:

Emulgel was prepared using carbopol 940, as gelling agents (Table 1). The gels in formulations were prepared by dispersing carbopol in purified water with constant stirring at a moderate speed and then the pH are adjusted to around 6 using tri-ethanol amine. The oil phase of the emulsion was prepared by dissolving span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving tween 20 in purified water. Methyl and propyl parabens were dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. Finally the emulgel was prepared by mixing the both gel and emulsion in 1:1 ratio. The composition of different formulations has been discussed in **Table 1**.

Table 1: Composition of different formulation batches (%w/w).

Ingredient	F1	F2	F3	F4
Luliconazole	1	1	1	1
Carbapol 940	1	1	1	1
Liquid paraffin	5	5	7.5	7.5
Tween 20	0.5	1	0.5	1
Span 20	1	1.5	1	1.5
Propylene glycol	5	5	5	5
Ethanol	2.5	2.5	2.5	2.5
Methyl parabene	0.03	0.03	0.03	0.03
Ethyl parabene	0.01	0.01	0.01	0.01
Purified water	q.s	q.s	q.s	q.s

Evaluation of Emulgel:

1. Physical Appearance and pH Determination:
The prepared Luliconazole emulgel were inspected visually for their colour, homogeneity, Consistency and pH. The pH values of 1% aqueous solutions of the prepared emulgels were measured by a pH meter (Orion Research, Inc., USA). [12]

2. Drug Content Determination:
The drug content of Luliconazolee emulgel was measured by dissolving a known weight of the emulgel formulation (one gram) in 100 ml methanol, appropriate dilutions were made and the resulting solution was then filtering using millipore filter (0.45 µm). Absorbance was measured at 296 nm using UV-spectrophotometer (Shimadzu UV 1800). [11] Drug content was calculated using the slope and the intercept obtained by linear regression analysis of standard calibration curve.

3. Rheological Studies:
The viscosity of different Luliconazole emulgel formulations was determined at 25˚C using a Brook-filled Viscometer. Viscosity was measured by using spindle (52).

4. Skin Irritation Test (Patch Test):
A set of 8 rats was used in the study. The emulgel was applied on the properly shaven skin of rat. Undesirable skin changes, i.e., change in colour, change in skin morphology were checked for a period of 24 h.

5. Spreading Coefficient:
Spreading coefficient was determined by apparatus suggested by Mutimer. It consists of a wooden block, which is attached to a pulley at one end. Spreading coefficient was measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide was fixed on the wooden block. An excess of emulgel (about 2 g) under study was placed on this ground slide. The emulgel preparation was then sandwiched between this slide and second glass slide having same dimension as that of the fixed ground slide. The second glass slide is provided with the hook. Weight of 500 mg was placed on the top of the two slides for 5 min to expel air and to provide a uniform film of the emulgel between the two slides. Measured quantity of weight was placed in the pan attached to the pulley with the help of hook. The time (in s) required by the top slide to cover a distance of 5 cm was noted. A shorter interval indicates better spreading coefficient.

6. *In-Vitro* Release Studies:
The study was carried out using the modified USP apparatus type II (Hanson SR8-plus 80, USA). Two grams of each emulgel was spread on the cellophane membrane previously soaked overnight in the dissolution medium. The loaded membrane was stretched over a glass cup of diameter 3 cm, and then the cup was immersed in 100 ml of the dissolution medium (25%v/v DMF in 0.02N HCl) to maintain sink condition, the temperature was maintained at 37±0.5°C with paddle agitation speed 50 rpm. An aliquot of 5 ml was withdrawn at different intervals of time. The withdrawn samples were replaced by equal volumes of fresh release medium. The samples were assayed using spectrophotometer at λ max 296 nm. The effect of gelling, the liquid paraffin concentration and emulsifying agent concentration was studied. [5].

7. Antifungal Activity Studies: The prepared emulgel formulations were tested against candida albican strain using agar cup method. Cups of 10mm diameter were made aseptically in savoured dextrose agar after being inoculated with the tested fungal suspension strain (106cfu/ml) by spreading on the agar surface..

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

The cups were filled with each prepared formulation by sterile syringe. The zone of inhibition of each cup was observed and the radius of the zone of inhibition was measured. [17]

8. Stability Studies:

The prepared Luliconazole emulgel were packed in aluminium tubes (5 grams) and subjected to stability studies at 25°C/60% relative humidity (RH) and 40°C/75% RH for period of 3 months. Samples were withdrawn at time intervals of 15 days and evaluated for physical appearance, pH, rheological properties, drug content and drug release. [18]

RESULTS AND DISCUSSION

Physical Appearance:

Emulgel formulations were white viscous creamy preparation with a smooth homogeneous texture and glossy appearance. Results have been discussed in **Table 2**.

1. pH Determination:

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 5.76-6.236 which considered acceptable to avoid the risk of skin irritation upon application to skin.

Table 3: pH of emulgel formulation

Formulation	F1	F2	F3	F4
pH	5.83	5.76	6.19	6.23

2. Spreading Coefficient:

The spreading coefficient of various emulgel formulations are given below in **Table 4.** It was concluded that all the developed formulation showed acceptable spread ability, **F3** formulation has more spread ability as compare to other formulation i.e**.** 24.2±0.2.

Table 4: Spreading coefficient of the formulation F1–F4(mean ± SD).

Formulation	F1	F2	F3	F4
Spread ability (gm.cm/sec.)	23.7±0.2	21.4±0.1	24.2±0.2	21.5±0.4

3. **Drug Content:**

The drug content of different emulgel formulations was estimated by using UV Spectrophotometer at 200-400 nm range. The release of drug through prepared formulation was found to be 96.82, 97.65, 98.25and 98.06 respectively.

Formulation	F1	F2	F3	F4
% Drug content	96.82	97.65	98.25	98.06

Table 5 :Drug content of Luliconazole emulgel Formulation.

4. Skin Irritation Test:

Skin irritation study was performed. No allergic symptoms like inflammation, redness, irritation appeared on rats up to 24 h.

5. Rheological Studies:

The tests were performed by using Brook-field Viscometer. Results are given in Table 6, highest viscosity was found in formulation F3. It may be due to high level of the liquid paraffin concentration and low level of emulsifying agent concentration.

Viscosity (mPas)				
RPM	F1	F2	F3	F4
10	3349±0.54	3371±0.98	3671±0.65	3584±0.75

Table 6: Rheological study of emulgel formulation (mean± SD, n =3)

6. **Antifungal Activity:**

The antifungal activity of Luliconazole emulgel was studied (**Table 7)**. The zone of inhibition was measure for antifungal activity of drug. The greatest activity was observed in **F3** formulation i.e. 49.5mm and the lowest activity were found with F1.

Table 7: antifungal activity of Luliconazole emulgel

	FORMULATION			
Inhibition zone (mm)± SD	F1	F2	F3	F4
	40.1	43.7	49.5	46.8

7. *In-Vitro* Release Study:

The study revel that, the release of the drugs from emulsified gel formulation can be ranked in the following descending order: F3 > F4 > F1> F2 where the amounts of drug release after 240 min were 90.12%, 83.58%, 79.50%, 71.98% respectively **(Fig. 2, Table 8).**

Table 8: Data for in vitro cumulative % drug release data of formulations F1–F4.

Time (min)	F1	F2	F3	F4
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
5	08.90 ± 0.010	11.02 ± 8.65	11.82 ± 6.83	14.55 ± 30.44
10	12.20 ± 0.05	14.92 ± 9.64	26.54 ± 13.30	20.76 ± 10.20
15	20.78 ± 1.30	23.43 ± 6.83	35.44 ± 10.2	28.24 ± 15.70
20	31.70 ± 2.25	32.04 ± 10.2	41.74 ± 0.03	36.75 ± 0.020
30	38.10 ± 31.70	40.95 ± 24.9	52.14 ± 0.38	41.84 ± 0.03
60	48.23 ± 2.85	53.42 ± 2.31	63.25 ± 0.49	56.01 ± 2.30
120	62.59±1.25	65.86±2.28	76.12±0.47	68.25±1.374
240	71.98%±0.26	79.50%±0.39	90.12%±1.41	83.58%±0.65

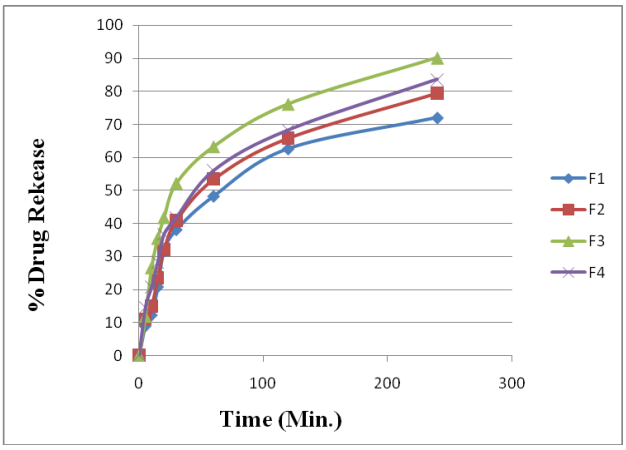

Fig. 2: ***In-vitro*** **cumulative % drug release of formulation F1–F4**

8. Stability Study:

All the prepared emulgel formulations were found to be stable upon storage for 3 months, no change was observed in their physical appearance, pH, rheological properties and drug content.

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 Luliconazole emulgel was prepared by using carbopol 934 showed acceptable physical properties, pH, drug content, viscosity and antifungal activity. Stability studies revealed no significant differences before and after storage for the selected formula. *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 F3 showed maximum release of 90.12% in 240 min. So Luliconazole emulgel can be used as an anti-Fungal agent for topical drug delivery.

Conflicts of interest: The authors stated that no conflicts of interest.

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