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LULICONAZOLE EMULGEL: CHARACTERIZATION, PREPARATION, AND EVALUATION

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ABSTRACT

The objective of this work is to develop emulgel of Luliconazole which will increase skin penetration of drug in comparison with present marketed preparations of the drug. The Luliconazole has anti-fungal activity. It acts by inhibiting lanosterol demethylase, which is major component of fungus cell wall. It was concluded that Luliconazole emulgel formulation based on solubility studies Oleic acid as oil, Tween 80, and Span 80 as emulsifiers and propylene glycol and cetostearyl alcohol as co-surfactant were selected for preparation of emulgel. The emulgels were prepared using different combinations of oil, emulsifiers, co-surfactant and carbomer (Carbapol 940). The prepared emulgel were also evaluated for their physical properties, pH, Rheological study, drug content determination and in-vitro drug release. In-vitro release study demonstrated diffusion controlled release of luliconazole from formulation up to 8 hours. The drug release profile exhibited zero order kinetics.

KEYWORDS: Topical drug delivery, Emulgel, Luliconazole.

INTRODUCTION

Topical formulations apply a wide spectrum of preparations both cosmetic and dermatological, to healthy or diseased skin.[1] Topical therapy has been used for centuries for the treatment of dermatological disorders. The spectrum of drugs/agents applied directly to the skin ranges from antiinflammatory, antiseptic, antibacterial, antifungal, antiviral, anti-acne, antipigmentary, anesthetic compounds to skin emollients and protectants. Topical route has the main advantage of direct delivery of drug to the target tissue i.e. skin and mucous membranes, bypassing the firs-pass effect.[2]

Topical formulations are prepared in different consistency such as solid, semisolid, and liquid. The topical delivery system is failed in the administration of hydrophobic drug. In each formulation with the active ingredients many excipients are used. Sometimes more than one formulation can be combined to enhance the drug delivery; emulgel is such type of combination. It is the combination of emulsion and gel.[3]

Gel and emulsion are used in a combined form, the dosage forms are referred to emulgel.[4] Emulgel is prepared both in oil- in- water and water- in- oil type emulsion mixed with gel. Oil- in- water type is used for lipophilic drugs and water- in- oil type is used for hydrophobic drugs' delivery. The emulgel have many advantages like greaseless, easily spreadable, easily removable, emollient, non-staining, bio-friendly, pleasing appearance, transparent and cosmetically acceptable, which also have a good skin penetration and long shelf-life.[3]

Luliconazole a topical broad-spectrum imidazole antifungal drug belonging to dichlorobenzene class of organic compounds is an optically active R- enantiomer. Luliconazole has anti-fungal activity. It was approved by FDA for the treatment of fungal infections.[5]

Fig 1: Structure of Luliconazole.

MATERIALS AND METHODS

Materials

Luliconazole was received as a gift sample from Schon Pharmaceutical Limited, Indore (India). Carbapol 940 was obtained from Loba chemia Mumbai. Oleic acid, Span 80, Tween 80 and Propyl Paraben procured from S D Fine Chem Limited, Mumbai. Cetostearyl alcohol procured from Vishal Chem, Mumbai. Propylene Glycol procured from Himedia. All other chemicals used were of analytical grade and were used without any further chemical modification.

Methods

Preformulation Study[5]

Organoleptic properties- The pure drug sample was studied for their organoleptic properties like colour, odour, taste and crystallinity and pH.

Determination of Melting Point- Melting point of drug sample was determined by using melting point apparatus. Drug sample was filled in one end open capillary tube. The capillary was placed in melting point apparatus and gradually temperature rises when drug sample was melted the melting point of sample powder was recorded.

Determination of λmax By UV spectrophotometer- 100mg of Luliconazole sample was weighed and transferred to 100ml volumetric flask and adding 1:1 methanol: water as solvent upto the mark to give 1000µg/ml solution. 10ml of the above solution was pipetted out in a 100ml volumetric flask and diluted up to the mark. From this 1ml of the solution was pipetted out and transferred into a 10ml volumetric flask and diluted up to the mark with methanol to form 10µg/ml that was scanned in the range of 200-400nm using UV-visible Double Beam Spectrophotometer (Shimadzu 1800).

Preparation of Calibration curve of Luliconazole- The calibration curve of luliconazole were prepared in distilled water and methanol by using Shimadzu 1800 UV visible spectrophotometer. Accurately weighed 100mg of luliconazole was transferred into a 100ml volumetric flask and adding 1:1 methanol: water as solvent upto the mark to give 1000µg/ml standard stock solution of luliconazole. 10ml of standard stock solution was transferred to a 100ml of volumetric flask and volume was made up to the mark to give 100µg/ml of working solution from which further dilutions of 2-20µg/ml was prepared by pipetting out 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, 1.6, 1.8 and 2 ml of working solution to different 10ml volumetric flasks. Observed absorption maxima, λmax 299nm was used for further analysis of absorption for concentration ranging from 2 to 20µg/ml. The linear plot was constructed and correlation coefficient value was determined.

Partition Coefficient- The partition coefficient determination of luliconazole was performed using n-octanol as the oil phase and water (1:1) as the aqueous phase. The two phases were mixed in equal quantities (50 ml) by adding 50 mg of drug in a separating funnel and was saturated with each other at room temperature for 24 hour to separate the two phases. The test compound in each phase was sampled and quantitated using UV spectroscopy. The ratio of

obtained concentration in octanol phase to the concentration in the buffer phase was determined and the log10 of the ratio was calculated.

Solubility Analysis- The solubility of luliconazole in various medium was determined by equilibrium solubility method. In this method 5 ml of each solvent was taken into a separate vial and excess amount of luliconazole was added to each solvent and stirred magnetically. After stirring for 24 hours at 37℃, the equilibrate sample was centrifuged for 10 min. at 5000rpm. Supernatant was filtered and properly diluted with water. Concentration of luliconazole was determined by UV spectroscopy.

FTIR spectroscopy- FTIR analysis for Luliconazole was done by FTIR NICOLET 6700. Each sample was mixed with potassium bromide in 1:100 and compressed to form pellets later observed at the range from 4000 to 400cm^{-1}.

Preparation of Luliconazole Emulgel

The composition of different formulations has been discussed in **Table 1.** The gels in formulations were prepared by dispersing carbapol in purified water with constant stirring at a moderate speed and then pH are adjusted to around 6 using tri-ethanol amine. The oil phase of the emulsion was prepared by first Cetostearyl alcohol is melted then mixed Oleic acid, Span 80 and Methyl salicylate while the aqueous phase was prepared by dissolving Tween 80 in purified water. Preservative Propyl paraben dissolve in Propylene glycol. Drug was dissolve in ethanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70℃ to 80℃, the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. Finally the emulgel was prepared by mixing of both gel and emulsion in 1:1 ratio.[6][7]

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

Ingredients(%w/w)	F1	F2	F3	F4
Luliconazole	0.5	0.5	0.5	0.5
Oleic acid	20	20	20	20
Propylene glycol	5	5	5	5
Methyl salicylate	10	10	10	10
Cetostearyl alcohol	4	4	4	4
Span-80	0.9	1.9	0.9	1.9
Tween-80	1.1	2.1	1.1	2.1
Carbapol 940	0.5	0.5	0.75	0.75
Water	58.9	57.9	58.9	57.9
Propyl paraben	0.02	0.02	0.02	0.02
Triethanolamine	Adjust pH 6 to 7			

Evaluation of Emulgel

1. **Physical Appearance-** The prepared Luliconazole emulgel were inspected visually for their color, homogeneity, consistency.
2. **pH-** It is determined by using digital pH meter. The pH meter is dipped into the emulgel and the pH is checked; it is repeated for 3 times.
3. **Rheological Study-** The viscosity of different Luliconazole emulgel formulations was determined at 25℃ using a Brook-filled Viscometer. Viscosity was measured by using spindle 7 and rpm 10.
4. **Drug Content Determination-** The drug content of Luliconazole emulgel was measured by dissolving a known weight of the emulgel formulation (1 gram) in 100 ml flask and adding 1:1 methanol: water, appropriate dilutions were made and the resulting solution was then filtering. Absorbance was measured at 299nm using UV- Spectrophotometer (Shimadzu UV 1800). Drug content was calculated using the slope and the intercept obtained by linear regression analysis of standard calibration curve.
5. **In- Vitro Release Study-** The study was carried out using the modified USP apparatus type II. 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 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 299 nm. The effect of gelling, the liquid paraffin concentration and emulsifying agent concentration was studied.
6. **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 by spreading on the agar surface. The cups were filled 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.
7. **Stability Studies-** The prepared luliconazole emulgel were packed in aluminium tubes (5 gram) and subjected to stability studies at 25°C/60% relative humidity (RH) and 40°C/75% RH for period of 1 month. Samples were withdrawn at time intervals of 15

days and evaluated for physical appearance, pH, rheological properties, drug content and drug release.

RESULTS AND DISCUSSION

Preformulation Studies

Organoleptic properties- The drug was studied for their organoleptic properties like color, odour, taste, crystallinity and pH observation was recorded in table 2.

Table 2: Organoleptic properties of Luliconazole.

Parameters	Result
Colour	Light yellow to yellow solid
Odour	Odourless
Taste	Extremely bitter in taste
Crystallinity	Crystallinity in nature
pH	6.13

Melting point- Melting point of drug was determined by capillary method was found to be 147℃ (Table 3). The observed value was identical to the reported value i.e. 149℃. The observed melting point confirmed the drug as Luliconazole.

Table 3: Melting point of luliconazole.

Drug	Observed	Reference
Luliconazole	147±2℃	148-150℃
Luliconazole	148±2℃	-
Luliconazole	147±2℃	-

Determination of λmax by UV- Identification of drug was also carried out using UV Visible Spectrophotometer. Methanol was used as the medium and observed absorption maxima were compared with the reported value. The wavelength of maximum absorbance acts as a characteristic value for a compound. Observed value for the obtained sample of pure Luliconazole was 296nm found to be identical to the reported value that confirmed the obtained sample as Luliconazole.

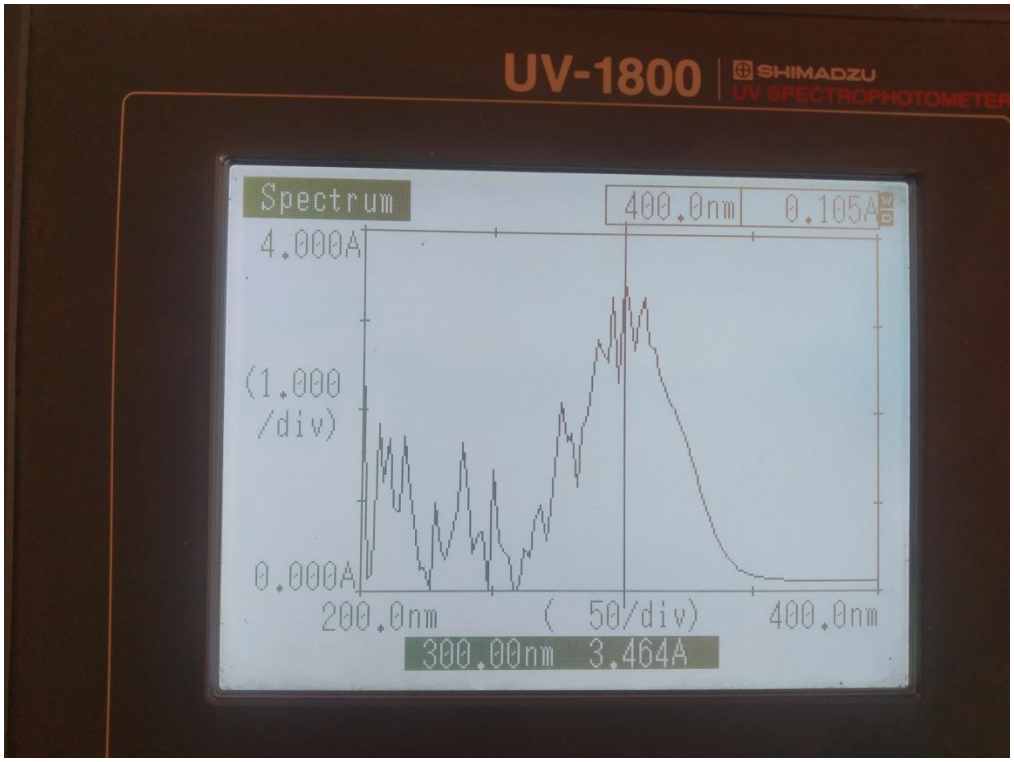

Fig. 2: λmax of Luliconazole is 300nm.

Calibration curve of Luliconazole- The wavelength of maximum absorbance, λmax for luliconazole in distilled water and methanol (1:1) was determined with the help of UV-Visible Spectrophotometer. Prepared solution of concentration 15µg/ml was scanned in the range of 200-400nm. The λmax observed was 299nm. Observed absorption maxima, λmax 299nm was used for further analysis of absorption for concentration ranging from 2 to 20µg/ml. The linear plot was obtained and concentration range 2 to 20µg/ml and correlation coefficient (r2) value was found to be 0.9994. The results were plotted as in Fig 3.

Table 4: Absorbance data of luliconazole for preparation of calibration curve at 299 nm.

S. No.	Concentration (µg/ml)	Absorbance
1.	0.2	0.054
2.	0.4	0.109
3.	0.6	0.157
4.	0.8	0.198
5.	1	0.253
6.	1.2	0.299
7.	1.4	0.346
8.	1.6	0.402
9.	1.8	0.453
10.	2	0.493

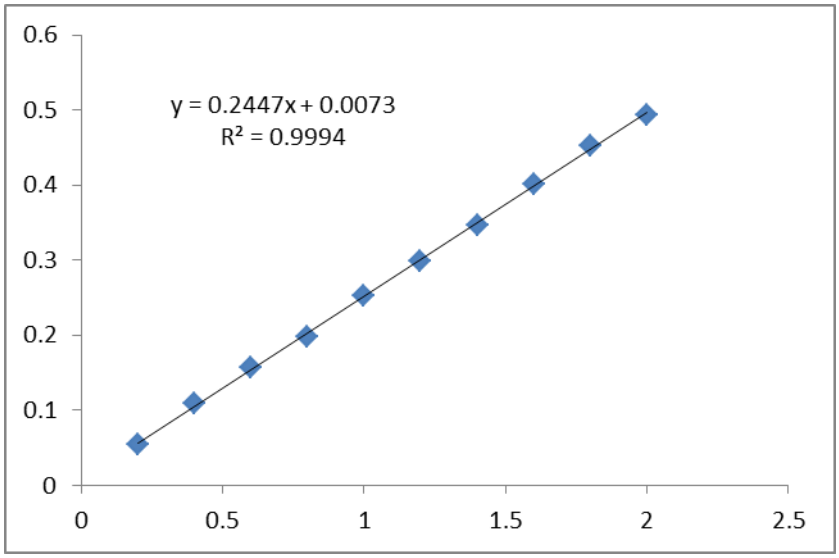

Fig 3: Calibration curve of luliconazole.

Partition coefficient- $\log_{10}$ P is the logarithmic value of partition coefficient (P), the ratio of an amount of solute in the organic phase to aqueous phase that helps to determine the partition coefficient of drug. In this research partition coefficient of drug was determined by interpreting the value of log P calculated from calibration curve equation. The value for $\log_{10}$ P was obtained as 3. 830 close to the reported value of 4.07. The result reflected the lipophilic nature of drug and thus Luliconazole found to have high permeability.

Solubility Analysis- The solubility of luliconazole in various medium was studied and the results of study were shown in table **5.**

Solvent	Solubility (mg/ml) Mean±SD
Water	0.065±0.05 mg/ml
Ethanol	1.067±0.02 mg/ml
Methanol	1.092±0.04 mg/ml
DMSO	0.494±0.01 mg/ml
DMF	0.160±0.06 mg/ml
Acetonitrile	0.532±0.05 mg/ml

FTIR- FTIR Spectrum of luliconazole was obtained by scanning the drug in the range of 4000 to 400cm-^{1}. Major peaks observed were as 3114.75, 3075.75 & 3040.00cm-^{1}, minor peaks observed were as 7.59.29 & 1101.04cm-^{1} whose presence resembled the structure of luliconazole (Fig 4). Observed FTIR spectra and standard value were as depicted in Fig. 3. The observed value was within the range or very close to the characteristic peaks of standard value confirming drug as luliconazole.

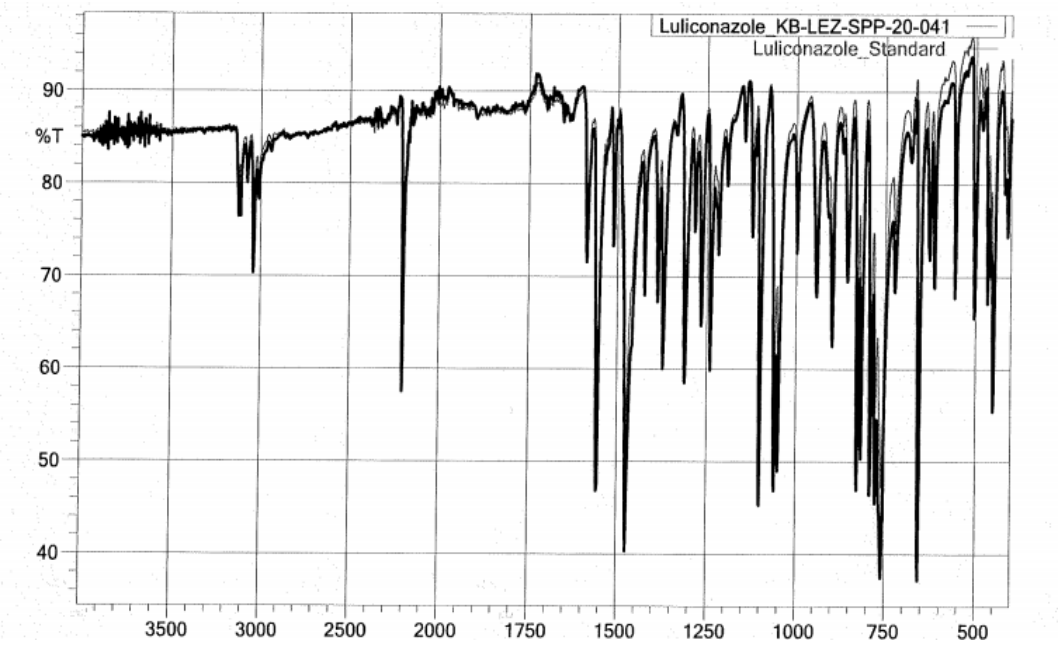

Fig 5: FTIR spectra of luliconazole.

Evaluation of Emulgel

1. Physical appearance- Emulgel formulations were white viscous creamy preparations with a smooth homogeneous texture and glossy appearance. Results have been discussed in Table 6.

Table 6: Physical parameter of formulation batches.

Formulation	Colour	Homogeneity	Consistency
F1	White	Excellent	Excellent
F2	White	Excellent	Excellent
F3	White	Excellent	Excellent
F4	White	Excellent	Excellent

2. pH determination- pH of prepared emulgel was measured by using pH meter. The pH of the emulgel formulations was in the range of 5.76-6.36 which considered acceptable to avoid the risk of skin irritation upon application to skin.

Table 7: pH of emulgel formulation.

Formulations	F1	F2	F3	F4
pH	5.79	6.15	5.83	5.73

3. Rheological study- Viscosity of different formulations was determined at 25℃ using Brookfield viscometer was measured by using spindle 61 and rpm 10.

Table 8: Viscosity (mPas) of emulgel formulation.

RPM	F1	F2	F3	F4
10	3136±0.54	3504±0.98	3686±0.65	3328±0.75

4. Drug Content Determination- 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 95.24, 97.89, 96.40 and 97.57 respectively.

Table 9: Drug content of Luliconazole emulgel formulation.

Formulation	F1	F2	F3	F4
% Drug content	95.24	97.89	96.40	97.57

5. In-vitro drug release study- The release of the drugs from emulsified gel formulation can be ranked in the following descending order: F4>F3>F1>F2 where the amounts of drug release after 240 min were 90.12%, 83.58%, 79.50%, 71.98% respectively (Table 10).

Table 10: 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
5	11.01	09.80	14.55	11.82
10	14.27	13.17	20.76	26.54
15	22.43	21.45	27.35	35.40
20	31.08	31.63	38.71	41.07
30	42.87	38.10	40.89	51.14
60	53.95	47.47	55.78	62.57
120	65.86	63.56	69.09	76.49
240	79.50	71.98	83.53	90.12

6. Antifungal activity study- The antifungal activity of luliconazole emulgel was studied (Table 11). The zone of inhibition was measure for antifungal activity of drug. The greatest activity was observed in F4 formulation i.e. 49.8mm and the lowest activity were found in F1.

Table 11: Antifungal activity of luliconazole emulgel.

Formulation	F1	F2	F3	F4
Inhibition zone	41.8	44.2	49.4	46.8

7. Stability Study- All the prepared emulgel formulations were found to be stable upon storage for 2 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 940 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 F4 showed maximum release of 90.12% in 240 min. So Luliconazole emulgel can be used as an anti-Fungal agent for topical drug delivery.

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