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Formulation and Evaluation of Luliconazole for dermal use

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ABSTRACT:
Luliconazole is an FDA-approved new azole antifungal medicine that treats fungal infections caused by Trichophyton rubrum and Epidermophyton floccosum, especially tinea pedis, cruris, and corporis. It is available as a topical gel and a 1% topical cream. Topical Formulations have several advantages, such as avoiding first pass metabolism, ease of administration, avoiding oscillation in drug planes, quiet discontinuation when desired, and increased bioavailability.
Luliconazole is a proven potential prescription drug for treating fungal infections on the skin. Its water solubility and skin permeability are, however, limited. Pre-formulation investigations were carried out, including solubility tests and UV-Vis Spectroscopy procedures with the Calibration Curve approach. Luliconazole gel formulation was formulated in which, Carbopol 940, a polymer, and Triethanolamine were used to create a luliconazole gel. Physical appearance, spreadability, and viscosity of the prepared gel were all examined. In addition, Franz Diffusion was used to assess the in vitro release of the formed gel. Luliconazole's antifungal activity was determined using a microbiological technique.

KEYWORDS: Luliconazole, antifungal, topical, gel, formulation, evaluation

I. INTRODUCTION

Luliconazole (LCZ) is an imidazole-class drug with broad antifungal action and high potency against dermatophytes. It is also used to treat various types of fungal infections such as tinea cruris, tinea corporis, and tinea pedis.Chemically, luliconazole is [(2E)-2-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]. -2-imidazol-1-yl acetonitrile]. The chemical formula is C14H9Cl2N3S2, with a molecular weight of 354.28 and a melting point of 148°C-152°C.

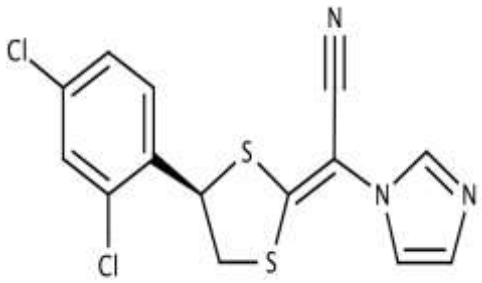

Figure 1: Chemical Structure of Luliconazole

The mechanism of action of luliconazole against dermatophytes is uncertain; however, it appears to decrease ergosterol production via blocking the enzyme lanosterol demethylase. Azoles inhibit the action of this enzyme, resulting in lower levels of ergosterol, a component of fungal cell membranes, and an increase in lanosterol. Luliconazole may be metabolized by CYP2D6 and 3A4. The literature review found that only few analytical methods were described, such as the simple and quick stability-indicating liquid chromatographic method developed and validated for luliconazole, and the UV Spectrophotometric method for estimating luliconazole in marketed formulations.

UV spectrophotometric (Calibration curve) method was done for estimation of LCZ in preformulation studies. Further, to formulate and evaluate the luliconazole gel.

Luliconazole is an imidazole antifungal API with a unique skeleton, since the imidazole molecule is absorbed into the ketene dithioacetate configuration. The potent antifungal activity of luliconazole may be due to a combination of potent in-vitro antifungal activity and favorable pharmacokinetic properties in the skin. Even when used only once per day, luliconazole 1% cream is effective. It was former official in Japan in 2005 and was approved by the FDA in November 2013. The enzyme lanosterol demethylase is thought to

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be inhibited by luliconazole. Lanosterol demethylase is required for the formation of ergosterol, which is the primary component of fungal cell membranes. It is available as a 1% topical cream. Topical drug delivery techniques are restricted drug distribution strategies.

Topical drug distribution methods are limited drug distribution methods for constrained transmission of healing substances through skin to treat the cutaneous ailment. These approaches are often useful for indigenous skin contagion. Topical dermatologic formulations treat a variety of skin problems. Ointments, gels, creams, lotions, solutions, suspensions, foams, and shampoos are all examples of topical products. The advantages of topical drug delivery systems include avoiding primary clearance metabolism, simplicity of solicitation, ease of drug discontinuation, discriminating site exact drug distribution, avoiding GI unsuitability, and better patient amenability. There are minor drawbacks, such as skin irritation and allergic reactions.

While luliconazole is applied topically, clinical investigations have indicated that following the initial dosage in individuals with tinea pedis, a maximum plasma concentration of 0.40 0.76 ng/mL (mean SD) occurred in 16.9 9.39 hours. Luliconazole has a plasma protein binding rate of more than 99%. There was no significant harm recorded in clinical studies, only minor contact dermatitis and cellulitis at the site of application.

II. MATERIALS

Luliconazole bulk powder was procured from Glenmark Pharmaceutical. While other materials like Calibrated Glasswares, Methanol, Distilled Water, Ethanol Triethanolamine, Carbopol 940, Propylene glycol, Methyl paraben, Potassium dihydrogen phosphate, Sodium Hydroxide, Sodium alginate, HPMC K 100, Na CMC, Chitosan and Sabouraud's dextrose agar was procured from laboratory.

III. METHODS

1. Pre-formulation studies:

1.1 Luliconazole's organoleptic characteristics:
The organoleptic properties of Luliconazole, including color and odor, were tested physically.

1.2 Determination of Melting point of Luliconazole:
The drug was placed in one end of an open capillary tube, and the temperature at which the drug began to melt was measured using a thermometer.

1.3 Determination of solubility:
The shake-flask method was used to conduct solubility tests. A little quantity of solvent is added to an accurately weighed amount of drug in a test tube with various solvents such as water, methanol, and ethanol. Following each addition, the mixture was agitated and visually examined to detect any undissolved particles.Solubility of drug was expressed in terms of solute and solvent.

1.4 For UV- Spectrophotometric method (In methanol):

1.4.1 Determination of λmax of luliconazole:
The UV Spectrophotometric technique was used to determine the max in the 200-400 nm wavelength range. The maximum absorbance of luliconazole in methanol was determined to be 295 nm.

1.4.2 Preparation of standard stock solution:
To make the standard stock solution, weigh and dissolve 10 mg LCZ in 100 mL of methanol to reach a final concentration of 100 mcg/mL.

1.4.3 Calibration curve UV-Spectrophotometric method:
To determine the analytical wavelength range, appropriate volumes 0.2 - 1.0 mL were transferred from the standard stock solution into a series of 10 mL volumetric flasks, followed by volume make up to obtain final concentrations ranging from 2 to 10 mcg/mL and scanned in the spectrum mode from 200 nm to 400 nm. The wavelength range of 200-400 nm was chosen for the study from the LCZ spectra. The calibration curve was created with concentrations ranging from 2 to 10 mcg/ml. A calibration curve was used to determine sample solution concentrations.

1.4.4 Linearity:
Several aliquots of luliconazole ranging from 2.0 to 10.0 mL were put into a series of 10 mL volumetric flasks and the volume was brought up to the mark with methanol to get concentrations of 2, 4, 6, 8, and 10 mcg/ml, respectively. A spectrophotometer was used to scan the solutions in the UV range 200-400 nm. The linearity range was determined.

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Figure 2: Solubility and UV method Development

1.5 For UV- Spectrophotometric method In Phosphate buffer (PBS) (pH 7.4):

1.5.1 Determination of λmax of luliconazole:

The UV Spectrophotometric technique was used to determine the max in the 200-400 nm wavelength range. The maximum absorbance of luliconazole in phosphate buffer (pH 7.4) was determined to be 296 nm.

1.5.3 Preparation of Phosphate buffer pH 7.4 (250 ml):

62.5 ml of 0.2M Potassium dihydrogen phosphate in 250ml volumetric flask and add 48.875 ml 0.2M NaOH.

1.5.3 Preparation of calibration curve of Luliconazole in Phosphate buffer (pH 7.4):

In a volumetric flask, 100mg of pure Luliconazole drug was liquefied in 10 ml of ethanol and made up to 100 ml with phosphate buffer pH 7.4. Dilutions of 100-500 mcg/ml were primed with buffer from the stock solution. At 296 nm, the absorbance of the solutions was measured. A calibration curve was created by comparing drug concentrations (mcg/ml) to absorbance (nm), and the regression equation was designed.

1.5.4 Linearity:

Several aliquots of luliconazole ranging from 100 mcg/ml to 500 mcg/ml were taken. A spectrophotometer was used to scan the solutions in the UV range 200-400 nm. The linearity range was determined.

1.6 Comparison between polymers for best suitable gelling agent using various Placebo gels:

On the basis of a literature survey which was done for determining the suitable polymer of best compatibility with luliconazole in terms of consistency and physical characteristics. According to the literature survey, we finalized and selected the below mentioned 5 polymers that can show best gelling properties.

1. Carbopol 940
2. Sodium alginate
3. Chitosan
4. HPMC K 100
5. Sodium Carboxymethyl Cellulose

1.6.1 Preparation of 10 gm Carbopol 940 placebo gel:

Accurately 0.1gm of carbopol 940 was dispersed in sufficient amount of water with constant stirring for 1 hr.

1.6.2 Preparation of 10 gm Sodium alginate placebo gel:

Accurately 0.1 gm of sodium alginate was dispersed in sufficient amount of water and it was kept overnight.

1.6.3 Preparation of 10 gm Chitosan placebo gel:

Accurately 0.1 gm of chitosan was dissolved in an acetic acid solution (pH=4**).** The prepared solution is injected drop by drop using a syringe in a gelling solution (solution of sodium hydroxide 3M). The obtained solution is maintained for 6 hours at room temperature (25°C).

1.6.4 Preparation of 10 gm HPMC K 100 placebo gel:

Accurately 0.1 gm of Hydroxy propyl methyl cellulose was dispersed in sufficient amount of water and the solution was heated and it was allowed to hydrate for a few hours.

1.6.5 Preparation of 10 gm Sodium Carboxymethyl Cellulose placebo gel:

Accurately 0.1 gm of Sodium Carboxymethyl Cellulose was dispersed in sufficient amount of water and the solution was heated and it was allowed to hydrate for a few hours.

2. <u>Formulation studies:</u>

2.1 Preparation of Luliconazole gel:

1. The gel phase was prepared by dispersing carbopol 940 in purified water with constant stirring for 1 hour.
2. Accurately 0.1gm luliconazole was dispersed in appropriate quantity of propylene glycol, methyl paraben..
3. The above dispersed drug mixture was added to carbopol gel phase.
4. The pH of the gel was adjusted to pH 6.8 - 7 by adding triethanolamine.

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Luliconazole gel formulation

Figure 3: Luliconazole gel formulation

3. Evaluation studies:

3.1 Drug content:

The drug concentration was measured by dissolving the gel formulation in a volumetric flask containing 100 ml of pH 7.4 PBS, then sonicating and filtering it. At 296 nm of LCZ, the solution is analyzed in a UV Spectrophotometer.

3.2 Spreadability test:

The spreadability of gel formulation was tested using the horizontal plate method, which involved inserting 1gm of gel sample between two glass slides and compressing it to a consistent thickness by applying 125 gm of weight to it for a set period of time (5min). Also observed is the time it takes for the gel to slide from one plate to another.

The spreadability was then computed as S= ML / T (where S = spreadability, M = weight applied, L = length moved by glass slide, and T = time).

3.2. Physical appearance and pH determination:

The color, homogeneity, consistency, and pH of the produced gel were measured using a digital pH meter after immersing the electrodes in it.

3.3 Viscosity measurement:

The viscosity of the gel formulation was determined using a Brookfield Viscometer spindle (52) at 1.5 rpm at 37± 0.5°C. It demonstrates that when polymer concentration increases, so does viscosity.

3.4 Comparative in vitro diffusion study:

An in vitro permeation research was carried out to evaluate the permeability of marketed luliconazole cream with designed luliconazole gel. A Franz diffusion cell with a durapore membrane (0.45 m) was used for the experiment. The membrane was properly positioned between the donor and receptor chambers in two cells prior to the diffusion. 1 gm of formulated gel and 1 gm of marketed formulation were weighed and evenly distributed on the durapore membrane. As dissolving media, 10 ml of phosphate buffer (pH 7.4) was added to each receptor medium. The donor and receptor compartments were kept in contact, and the entire assembly was held at a constant temperature of 32±0.5°C. Magnetic beads were utilized to agitate the receptor chamber solution. After each time interval, 1 ml of sample was removed and replaced with a new dissolving medium. At 296 nm, the sample absorbance was measured spectrophotometrically.

3.5 Comparative in vitro antifungal study:

An in vitro antifungal activity, zone of inhibition experiment with Candida albicans was done for both the improved formulation of the luliconazole gels utilizing four different polymers and the marketed luliconazole cream. To measure antifungal activity, a dextrose agar well diffusion test was done using the 'pour plate technique' on autoclave-sterilized uniform-sized Petri plates. The test plates were loaded with fungal inoculums and Sabouraud's dextrose agar (SDA) medium. These plates were allowed to cool and dry at room temperature for 15 minutes. Wells were cut from SDA with sterilized iron bores 1 cm in diameter. In addition, each well received prepared gels and marketed cream. The inhibitory zones of the prepared gel formulation were assessed and compared using formulated luliconazole gels (1%) and marketed luliconazole cream (1%) as standards. The formulated gels were used as a control. When the solution had settled, the plates were left at room temperature for 48 hours before measuring and comparing the inhibition zones around the wells to those of the standard.

IV. RESULTS AND DISCUSSIONS

1. Pre-formulation studies:

1.1 Physical Characterization of drug:

Luliconazole (LCZ) was discovered to be a solid, off white to light yellow crystalline powder with acceptable flow characteristics, as described in the literature.

1.2 Determination of Melting Point: The capillary technique was used to estimate the drug's melting point, which was found to be 149°C. The drug's melting point verified its identity as LCZ.

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1.3 Determination of Solubility:

According to the results, luliconazole was sparsely soluble in PBS (pH 7.4) and insoluble in aqueous solution, indicating low aqueous solubility. The organic solvents in which luliconazole was soluble were as follows: methanol (soluble), and ethanol (sparingly soluble).

1.4 Determination of λmax of luliconazole:

The maximum absorbance of luliconazole in methanol was determined to be 295 nm.
The maximum absorbance of luliconazole in phosphate buffer (pH 7.4) was measured to be 296 nm.

1.5 Calibration Curve UV-Spectrophotometric Method (In Methanol):

Concentration	Absorbance
2 ppm	0.120
4 ppm	0.248
6 ppm	0.372
8 ppm	0.514
9 ppm	0.686

Table 1: Calibration Curve UV-Spectrophotometric Method (In Methanol):

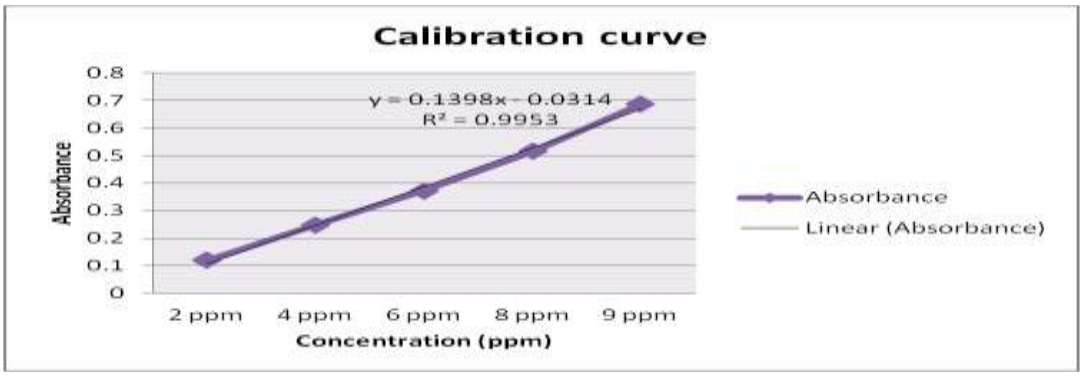

Figure 4: Calibration curve for luliconazole in Methanol

Linear Regression coefficient value (R^2 value = 0.9953)
Linearity range = 2 to 10 ppm

1.6 Calibration Curve UV-Spectrophotometric Method (In Phosphate Buffer pH 7.4):

Concentration	Absorbance
100 ppm	0.179
200 ppm	0.289
300 ppm	0.361
400 ppm	0.484
500 ppm	0.555

Table 2: Calibration Curve UV-Spectrophotometric Method (In Phosphate Buffer pH 7.4)

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Linear Regression coefficient value (R^2 value = 0.9934)
Linearity range = 100 to 500 ppm

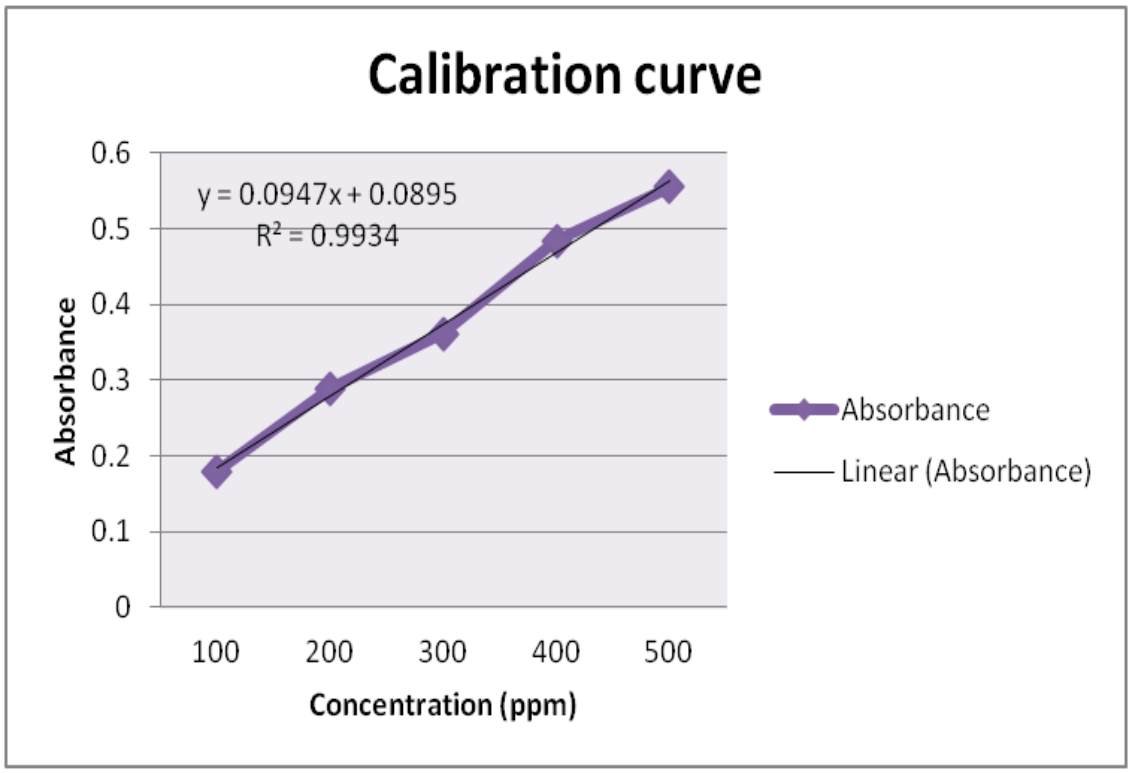

Figure 5: Calibration curve for luliconazole in Phosphate buffer pH 7.4

1.7 Comparison between polymers for best suitable gelling agent using various Placebo gels:
On the basis of comparative studies of placebo gels of different polymers, It was concluded that Carbopol was the best suitable polymer for luliconazole in terms of gelling properties, consistency and physical characteristics.

2. Formulation and evaluation studies:

2.1 Visual inspection and pH determination of gel:
The luliconazole gel prepared with Carbopol 940 and triethanolamine is white, thick, and smooth.

The pH value was discovered to be 7.2, which eliminates the possibility of skin irritation when applied to the skin.

2.2 Spreadability and Viscosity measurement:
The spreadability value of 7.4 g.cm/sec indicates that the gel is spreadable.
The viscosity of the gel formulation was determined using a Brookfield Viscometer spindle (52) at 1.5 rpm at 37± 0.5°C. It demonstrates that when polymer concentration increases, so does viscosity.

2.3 Comparative in vitro diffusion:
For Cream (Marketed formulation):

Time (hrs)	Concentration (µg/ml)	Dilution factor (*10)	Concentration in 10 ml Diffusion cell (µg/10ml)
1	0.712	7.12	71.2
2	0.681	6.81	68.1

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3	0.638	6.38	63.8
4	0.607	6.07	60.7
5	0.575	5.75	57.5

Table 3: Concentration of drug permeation of Marketed formulation:

For Formulated gel:

Time (hrs)	**Concentration (µg/ml)**	**Dilution factor (*10)**	**Concentration in 10 ml Diffusion cell (µg/10ml)**
1	0.744	7.44	74.4
2	0.712	7.12	71.2
3	0.670	6.70	67.0
4	0.638	6.38	63.8
5	0.607	6.07	60.7

Tale 4 : Concentration of drug permeation of Formulated gel:

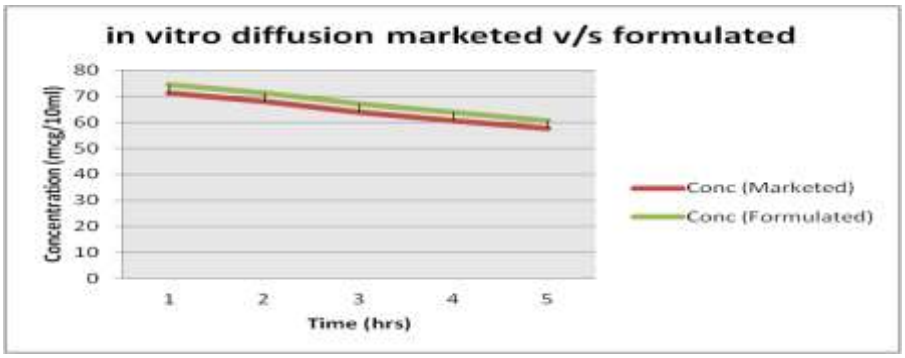

Figure 6: in vitro diffusion of Formulated gel v/s Marketed Formulation

According to the results, the drug release from the test formulation was comparable in fact slightly superior as compared to the marketed product. The diffusion of the drug from the hydrophilic base was better than the lipophilic base.

Luliconazole is a proven topical dermal antifungal drug, and has lower skin permeation and shorter skin retention. Hence there is very less diffusion of drug reaching systemic circulation and it only retains on skin.

2.4 Comparative in vitro antifungal activity:

The agar well diffusion technique (Pour-plate method) was utilized to conduct an in vitro antifungal activity. Sabouraud's dextrose agar was employed as the media for fungal strain growth (Candida albicans). All four gels were placed in the wells of the petri plates using different polymers (Carbopol, HPMC, Na CMC, Na alginate) in comparison to the marketed preparation, and after settlement of the solution, the plates were kept for 48 hours at room temperature, after which the inhibition zones surrounding the wells were measured. The zone of inhibition was measured in millimeters and compared to the standard. Carbopol luliconazole gel was found to be more similar to the marketed product in terms of zone of inhibition than the other three gels.

Zone of inhibition for carbopol gel = 12mm

Zone of inhibition for markets preparation = 15mm

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Figure 7: Comparison of Antifungal activity of gels using different polymer to that of marketed formulation

Figure 8: Zone of inhibition of different gels and marketed formulation
(M- Marketed formulation, C - Carbopol, S - Sodium alginate, H - HPMC, SC - Sodium CMC)

V. CONCLUSION

Luliconazole is a topical antifungal drug with low bioavailability due to its inability to dissolve in water. Luliconazole's dermal bioavailability can be enhanced by increasing its aqueous solubility.

Preformulation studies such as melting point, solubility tests, and UV technique development were completed successfully, indicating that the medicine Luliconazole produces effective outcomes. The suggested study's findings demonstrate that the proposed UV spectrophotometric Calibration curve approach is simple, quick, precise, and accurate. The UV spectrophotometric Calibration curve approach devised was shown to be acceptable for determining luliconazole. Statistical analysis shows that the procedure is reproducible and selective for Luliconazole analysis. As a result, it can be stated that the approach can reduce time and be employed in small laboratories with an accurate and large linear range.

The formulation and assessment of LCZ gel for locally acting antifungal agent was effectively completed in this study. Luliconazole is synthesized as a gel by the gelling process, which employs the polymer Carbopol 940 and the reagent triethanolamine. Luliconazole is formulated as gel by gelling method using polymer Carbopol 940 and reagents propylene glycol, methyl paraben and

triethanolamine. We can also infer from the formulation and assessment studies that the evaluation of gel qualities such as visual appearance, pH, spreadability, and viscosity of the formulation

Luliconazole gel was excellent and acceptable. The results showed that the luliconazole topical gel formulation was not permeable enough across the Franz diffusion cell. The comparative antifungal analysis found that carbopol polymer luliconazole gel had a larger zone of inhibition. The current study suggests that gel formulations may be a superior alternative for the delivery of a wide range of formulations for transdermal administration and other topical agents than equivalent commercial dosage forms that are already available.

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