Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [11] October 2023 :140-145

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Formulation, development, and evaluation of antifungal film-forming gel for prolonged dermal delivery of luliconazole

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ABSTRACT
The goal of the current study was to create a patient-friendly medication delivery method for the preparation of a topical film-forming gel of luliconazole to treat antifungal activity. For localised therapies of diseases of our body tissues to be effective, the pharmaceutical active must be retained at the treatment site for a sufficient amount of time. Sweat, clothing, movements, and the ease with which they wash away when in contact with water have all been known to reduce the efficacy and residence time of traditional topical formulations, which are typically used to treat for antifungal activity. This necessitates a longer treatment regimen. The current project aims to develop a "film-forming gel" dosage form of luliconazole that, when applied to the skin, leaves a thin, transparent film. Hydroxypropyl methyl cellulose and carbopol were combined in various ratios, together with ethanol as a solvent and triethyl citrate as a plasticizer, to produce luliconazole film-forming gels. The optimisation used diffusion and viscosity as its variables. The effects of the concentration and ratio of the polymeric blends utilised were examined, along with the created film-forming gels and films that resulted from solvent evaporation. Design Expert 7.0 programme improved the concentrations of both polymers to achieve the optimal viscosity and diffusion. After 8 hours, it was discovered that formulation F5 had the greatest release among the nine formulations. The drug's antifungal activity was accessible in 99.13% of the formulation.
Keywords: *Film-forming gel, Luliconazole, Hydroxy propyl methyl cellulose, propylene glycol.*

Received 29.07.2023 Revised 26.08.2023 Accepted 19.10.2023

INTRODUCTION

Recently, novel drug delivery methods, such as film forming gel, have replaced more conventional topical therapies and transdermal formulations as the preferred method of administering a range of pharmaceuticals to the skin. When applied to the skin's surface, these systems consist of a vehicle containing a medication and film-forming polymers, which evaporates to leave behind a thin, transparent film. Film-forming gels are more aesthetically acceptable to patients than conventional semi-solid topical medicines like gels and ointments, in addition to serving a medical purpose. They can be designed to provide sustained pharmaceutical release, eliminating the need for frequent reapplication. They are nonsticky, stay on the injured area for a longer period without coming off when rubbed [1-4]. An antifungal agent for external usage is luliconazole. The systemic adverse effects of luliconazole will be lessened via topical application, and by directly targeting the afflicted area, it will also achieve maximum antifungal efficacy [5]. In this work, an effort was made to create patient-friendly drug delivery systems for luliconazole film-forming gels to transport it to the site of action in fungal infection with less systemic adverse effects.

MATERIAL AND METHODS

Luliconazole was gift sample from Optimus drugs Pvt. Ltd. Hyderabad. Carbopol 940, Triethyl citrate and Propylene glycol were brought from Amishi Drugs & Chemical Pvt. Ltd. Ahmedabad, Gujarat. Eudragit RS PO and HPMC K4M were brought from Jiaozuo Zhongwei Special Products Pvt. Ltd. China.

Method

The formulation design was done using Design Expert e stat software. The gelling agent (HPMC K4M) was dispersed in solvent with stirring at 1200 RPM for 30mins. Drug was dissolved in solvent (Ethanol: Water). Triethyl citrate was dissolved in required quantity of ethanol and propylene glycol. Eudragit RS 100 was dissolved in the above triethyl citrate mixture. Carbopol 940 was dissolved in 5 ml of ethanol and added to Eudragit mixture. All the preparations were homogenized at 1200-1500 RPM to get a stabilized gel preparation [6,7].

Experimental Work

The physical and chemical characteristics of active pharmaceutical components and their interactions with other substances, such as excipients, are studied prior to formulation. It is the first stage in the formulation of suitable dose forms. Preformulation is a stage of research and development where a scientist analyses the physical and chemical characteristics of a pharmacological substance to create a stable, reliable dosage form.

Drug Characterization:

- Colour: Luliconazole was placed on a small piece of butter paper and studied in a well-lit area.
- Odour: A small quantity of luliconazole was smelled to determine the aroma.
- Appearance: Luliconazole's appearance was evaluated after a pinch was placed between two fingers.

Determination of melting point: The sample's melting point is the first sign of its purity. Luliconazole's melting point was measured using the open capillary method. It was administered in a glass capillary with a flame-sealed opening. The capillary was then placed into the melting point device, dipped into the liquid paraffin, and the melting point was recorded.

Solubility study: Luliconazole's solubility was assessed in the various solvents listed in table 1. A test tube received 10ml of the necessary solvent, and 20mg of liquorice was added to the solvent. The mixture was then subjected to a 10-minute sonication, after which any residual particles were observed. Solvents used in solubility study were methanol, dimethyl sulfoxide (DMSO), dimethyl formamide (DMF) and water.

UV-visible spectrophotometric analysis:

UV spectroscopy: Luliconazole's UV spectrum was gathered. The examination was conducted using a V 550 Spectrophotometer from Jasco Corporation in Japan using spectra manager software. The glasses were thoroughly cleaned in distilled water that had been quadrupled, then dried.

Reagents & Materials: All reagents were of analytical grade and Methanol was used as solvent to prepare dilution.

Method: 10 mg of Luliconazole was dissolved in 10 ml of solvent (Methanol) to produce 1000 µg/ml. From this prepared solution 0.2 ml of sample was taken and further diluted with Methanol up to 10ml to produce 20 µg/ml sample and spectra was observed.

Calibration Curve in Methanol:

Stock solution: 10 mg of Luliconazole was dissolved in 10 ml of solvent (Methanol) to produce 1000µg/ml.

Solution A: From stock solution 1ml of sample was withdrawn and diluted up to 10ml with solvent (Methanol) to produce 100 µg/ml.

Dilutions: From solution A 0.5 ml, 1 ml, 1.5 ml, 2 ml and 2.5 ml solution were withdrawn and diluted up to 10ml with solvent (Methanol) to produce 5 ppm, 10 ppm, 15 ppm, 20 ppm and 25 ppm and absorbances were measured at 296 nm.

FT-IR of Luliconazole: Using potassium bromide (KBr) as a blank, the IR spectra of luliconazole was recorded on a Shimadzu IR Affinity- spectra with a resolution of 4 cm over a range of 400-4000 cm. The principal peaks of the IR spectrum described in the monograph were compared with the peaks in the spectrum of luliconazole.

Drug excipient compatibility study: Studies on the compatibility of medicine excipients are a crucial stage in the development of new medications. A drug substance's chemical makeup, the type of delivery system needed, and the proposed manufacturing method must all be carefully considered before a drug substance is formed into the intended dosage form. Drug ingredients are frequently coupled with excipients, which have specific functions. Although excipients are pharmacologically inactive, under the correct circumstances they can engage in chemical reactions and physical interactions with drug molecules. Excipients for use in pharmaceutical formulation have either been approved or rejected using compatibility tests on medication excipients. The API was taken in various ratios and thoroughly mixed both on its own and with each excipient.

Table 1. Drug- Excipient Compatibility Study Ratio

Sr. No.	Sample	Ratio
1	Luliconazole: Eudragit RS100	1:1
2	Luliconazole: Carbopol 940	1:1
3	Luliconazole: HPMC K4M	1:1
4	Luliconazole: Triethyl citrate	1:1
5	Luliconazole: Propylene glycol	1:1

Factorial design model: A 32 complete factorial design was performed to the formulation that produced satisfactory results in order to create a stable film forming gel in order to examine the impact of varying the concentrations of variables like Eudragit RS 100 (X1) and Carbopol 940 (X2) on reactions like diffusion and viscosity. Prior to putting the experimental design into practice, research was done to determine the amounts of two elements.

Table summarizes the experimental runs, their factor combinations, and the translation of the coded levels to the experimental units used in the study.

Table 2. Composition of Luliconazole

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Luliconazole	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Eudragit 100	1.2	1.2	1.2	1.35	1.35	1.35	1.5	1.5	1.5
Carbopol 940	0.3	0.45	0.6	0.3	0.45	0.6	0.3	0.45	0.6
HPMC K4M	1	1	1	1	1	1	1	1	1
Triethyl citrate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Propylene glycol	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethanol: Water	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S

Evaluation of Film-forming Gel

Physical evaluation: The physical evaluation parameters i.e., Colour, odour, appearance of the prepared film forming gel were tested by visual observations.

pH: The PH meter (Labman pH system LMPH-10) was calibrated using standard buffer solutions of pH 4, 7 and 9. About 0.5gm of the film forming gel was weighed and dissolved in 50.0 ml of distilled water and its pH was measured [7].

Viscosity: Viscosity of the film forming gel was determined by Brookfield Viscometer (Amtech Model Number. LVDVE) at different rpm, using spindle number-64. The spindle was rotated at 10, 50, 60, 100 rpm and viscosity (CP) and Torque (%) was measured. Lesser the torque better will be viscosity.

Spreadability test: The film-forming gel weighed 500 mg and was placed between two slides. The upper slide was loaded with a 100g weight. Extra formulation was scraped off and weight was reduced. The apparatus's board served as the bottom slide's mounting point, and the upper slide was fastened with stiff string to which a 20 g load was applied. The time it took the higher slide to slide off was recorded.

$$S=ML/T$$

Where, S= Spreadability, M= Weight on upper slide, L-Length moved on glass slide, T-Time

Drying time: Applying and evenly spreading 1 g of the gel on a Petri dish with a diameter of about 8 cm resulted in the creation of films using the solvent evaporation technique. 48 hours at room temperature were given for the films to dry. Carefully removing the films, they were then subjected to the following additional examinations. Cosmetic experts preferred formulas that adhered to the skin in a flexible, translucent layer that was lustrous, clear, and glossy.

Drug content: Film forming gel equivalent to 10mg of Luliconazole was taken in a 10ml volumetric flask containing 5ml methanol and the volume was made up to mark with methanol to get a concentration of 1000ug/ml. An aliquot of 1ml was transferred to a 10ml volumetric flask and volume was made up with methanol to get a concentration of 100ug/ml. The absorbance of prepared solution was measured at λmax 296 mm by using UV visible spectrophotometer [7].

In-vitro diffusion test: A Franz diffusion cell was used to determine drug release profile from film-forming gels. The cell had two chambers, a donor compartment with an inner diameter of 24mm and a receptor compartment with a sampling capacity. The donor compartment contained 20 mg of the drug, separated by a cellophane membrane. The donor and receptor compartments were held together using a clamp, and the assembly was fixed on a magnetic stirrer. Samples were collected, diluted with methanol, and analysed for drug content using a UV Spectrophotometer [8,12,13].

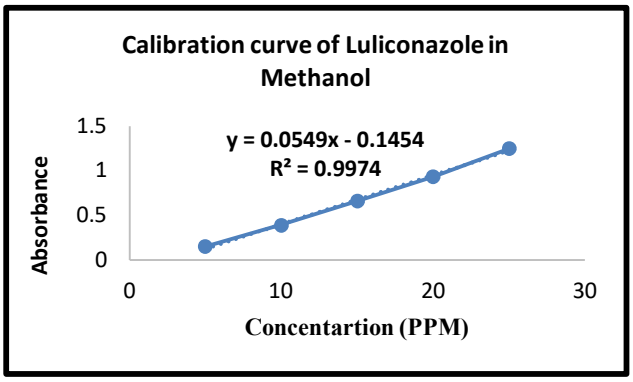
RESULT AND DISCUSSION

UV-visible and IR analysis: The UV spectrum of luliconazole was collected. The test was carried out with a V 550 Spectrophotometer from Jasco Corporation in Japan with spectra manager software. The glasses were thoroughly washed in triple distilled water before being dried. The IR spectra of luliconazole was recorded on a Shimadzu IR Affinity- spectra with a resolution of 4 cm over a range of 400-4000 cm using potassium bromide (KBr) as a blank. The main peaks of the IR spectrum given in the monograph were compared to the peaks of the luliconazole spectrum.

Table 3. Calibration curve of Luliconazole

Sr. No.	Concentration	Absorbance
1	5	0.1504
2	10	0.3920
3	15	0.6621
4	20	0.9312
5	25	1.2525

An absorbance at 5,10,15,20 and 25 ppm are shown in table 3 while calibration curve using UV spectrophotometry and Infra-red spectra of pure drug luliconazole is shown in **fig1** and **fig2** respectively.



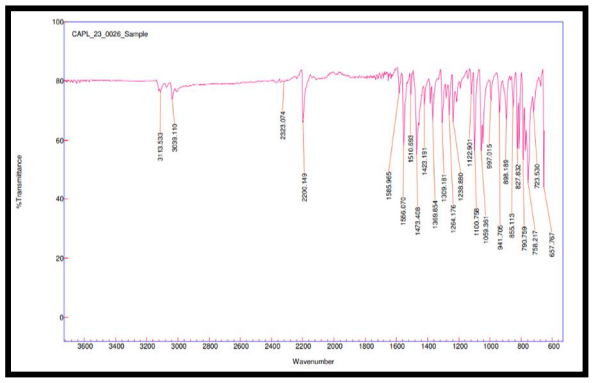


Fig1. Calibration curve of Luliconazole **Fig2. IR of pure Luliconazole**

Evaluation of prepared formulations: The physical evaluation of the prepared film forming gel involved visual observations, pH measurements, viscosity measurements, and spreading time. The gel was weighed 500 mg and placed between two slides, with the upper slide loaded with a 100g weight. The film-forming gel weighed 500 mg and was placed between two slides. The drying time was recorded, and the films were dried for 48 hours at room temperature. The drug content was determined by transferring 10mg of Luliconazole to a 10ml volumetric flask containing 5ml methanol and measuring the absorbance using a UV visible spectrophotometer. The in vitro diffusion test was performed using a laboratory-assembled apparatus resembling a Franz diffusion cell, with two chambers, a diffusion membrane, and a magnetic stirrer. Samples were collected, diluted with methanol, and analysed for drug content using a UV spectrophotometer, the results are depicted in table 4, as given below.

Table 4. Physical characteristics of formulation batches

Batches	Colour	Odour	Appearance	pH	Viscosity	Spreadability	Drug content
F1	Colourless	Characteristic	Smooth	5.94 ± 0.1	4982 ± 104	9.5 ± 0.2	96.45
F2	Colourless	Characteristic	Viscous	5.92 ± 0.1	5491 ± 125	8.2 ± 0.1	97.77
F3	Colourless	Characteristic	Viscous	6.18 ± 0.1	6233 ± 144	9.1 ± 0.2	99.84
F4	Colourless	Characteristic	Smooth	6.04 ± 0.1	5248 ± 87	7.5 ± 0.2	99.96
F5	Colourless	Characteristic	Smooth	6.09 ± 0.1	6378 ± 111	8.3 ± 0.2	99.21
F6	Colourless	Characteristic	Smooth	6.11 ± 0.1	6789 ± 95	9.4 ± 0.1	98.15
F7	Colourless	Characteristic	Smooth	6.11± 0.1	5406 ± 108	7.8 ± 0.2	99.98
F8	Colourless	Characteristic	Smooth	6.13 ± 0.1	6426 ± 102	8.1 ± 0.1	99.25
F9	Colourless	Characteristic	Viscous	6.05 ± 0.1	7211 ± 75	7.7 ± 0.1	97.78

Determination of % drug diffusion: When the drug diffusion for each batch of formulations was evaluated, it was discovered to be between 81.88 and 99.13%. The drug diffusion mechanism slows down with regard to time and exhibits prolonged effects as the formulation viscosity and film thickness rise. Table 24 and picture 23 display the results of the formulations' in-vitro drug release investigation. According to

an *In vitro* diffusion analysis, formulations F1 through F3 did not maintain drug release over an 8-hour period. Low viscosity of the formulations and low levels of drug release modifying polymers may be to blame for this. Drug release from formulations F4 and F5 was sustained for eight hours. Formulations F6 to F9, on the other hand, did not entirely release the medication.
At intermediate concentrations of the hydrophilic polymer HPMC and the hydrophobic polymer Eudragit, drug release was observed to be sustained. After 8 hours, it was discovered that formulation F5 had the greatest release among the nine formulations. The drug's antifungal activity was accessible in 99.13% of the formulation [8,12,13].

Table 5. Determination of % drug diffusion

Time (Hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	13.46	15.58	14.45	15.68	15.28	14.45	13.38	12.45	12.35
2	25.27	26.14	25.69	27.16	28.16	26.69	24.16	23.36	24.69
3	41.79	40.68	39.24	41.05	42.05	39.04	37.35	35.67	36.28
4	59.78	58.78	55.27	56.06	67.78	54.27	50.46	45.72	47.41
5	75.45	76.58	77.39	68.78	67.88	67.59	61.28	55.16	59.25
6	88.28	85.46	88.13	80.28	80.28	76.13	70.78	65.25	69.03
7	94.06	92.92	91.34	90.06	91.06	86.64	79.25	76.67	76.92
8	95.18	94.06	93.68	98.61	99.13	96.55	85.36	83.07	81.88

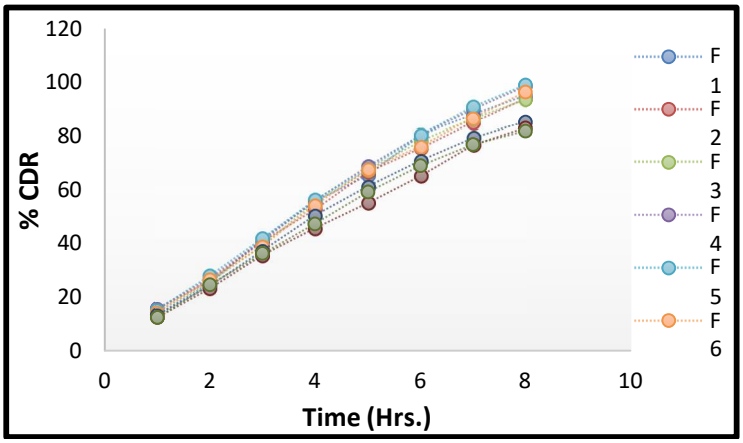


Fig3. % CDR vs Time for drug diffusion

Optimization Study: To study the effect of independent variables on responses Design Expert 7.0 software was used. Experimental design layout developed for 9 possible batches of Luliconazole film forming gel is shown in table. Out of the various models such as Linear, 2FI, Quadratic and Cubic which fit well was suggested by software and was tested for analysis of variance (ANOVA). Regression polynomials were calculated for the individual dependent variables and then one factor and perturbation graphs were obtained for each individual dependent variable. Mathematical models were generated for each individual dependent variable or response (R) and expressed as equations. X_1 and X_2 are the main effects which represent the average result of changing one factor at a time from its low to high value and X_1 X_2 are interaction terms show how the response changes when two factors are simultaneously changed [14,15].
Antifungal study for optimized batch (F5): The normal technique described under the experimental work was followed for the antifungal study. The zone of inhibition for the ideal batch was determined to be 27mm. Zone of inhibition for Nystatin, a common antifungal drug, was discovered to be 27mm. The optimised batch of film forming gel was shown to have significant antifungal activity based on antifungal data [9].
Stability study: The optimised formulation was placed in an aluminium foil tube and kept in a stability chamber at a temperature and humidity of 40 2 °C and 75 5% for a month. Physical evaluation, pH measurement, viscosity, spreadability, drying time, drug content, and diffusion studies were all performed on the formulation. The stability of the active ingredient is the primary criterion in any reasonable design of dosage forms for drugs that determines whether or not they should be accepted. According to ICH QIA (R2) criteria, stability investigations were conducted [8,14].

CONCLUSION

Utilising hydroxypropyl methyl cellulose and triethyl citrate, a film-forming gel of luliconazole was created. To get the best viscosity and diffusion, the concentrations of both polymers were optimised via Central Composite Design. The formulation F5 was chosen as the optimised formulation since it had the highest diffusion and lowest viscosity. The largest percentage of medication was also present in the same formulation. The film-forming dermal gel created in this study satisfies all criteria needed for topically applied usage. This brand-new dosage form will enhance the precision and placement of a dose when it is administered. Thus, by improving patient compliance and lowering the gastro-intestinal related toxicities associated with the oral administration of antifungals like luliconazole, the formulation may be a superior alternative for treating fungal infection.

DECLARTION OF COMPITING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACKNOLEDEGEMENT

The authors wish to acknowledge the help provided by the technical and support staff of KCT's R.G. Sapkal College of Pharmacy, Nashik.

REFERENCES

1. Rajan, S., Nair, S. S., Sreena, K., & Sabari, S. (2022). Preparation and evaluation of ketoprofen film forming gel. *European J Pharm Med Res*, *9*(9), 212-19.
2. Nikhilitha, P. (2021). Effect of natural polymer on release retarding rate of glimepiride sustained release tablet. *Journal of Advanced Scientific Research*, *12*(01 Suppl 1), 145-150.
3. Singh, V., Singh, M., Kukreti, G., Agarwal, A., & Bajaj, H. (2015). Rheumatoid arthritis: Treatment by film forming gels. *J Analgesics*, *3*, 9-14.
4. Abrar, B., Anis, S., Tanu, B., & Singh, S. (2012). Formulation and in-vitro evaluation of NSAID's gel. *Int J Curr Pharm Res*, *4*(3), 56-58.
5. Kathe, K., & Kathpalia, H. (2017). Film forming systems for topical and transdermal drug delivery. *Asian journal of pharmaceutical sciences*, *12*(6), 487-497.
6. Mundada, M., Wankhede, S., Patwardhan, S., & Avachat, A. (2012). Formulation and evaluation of topical gel of lornoxicam using a range of penetration enhancers. *Indian J Pharm Edu Res*, *47*, 168-71.
7. Telange, D. R., Pandharinath, R. R., Pethe, A. M., Jain, S. P., & Pingale, P. L. (2022). Calcium Ion-Sodium alginate-piperine-based microspheres: evidence of enhanced encapsulation efficiency, bio-adhesion, controlled delivery, and oral bioavailability of isoniazid. *AAPS PharmSciTech*, *23*(4), 99.
8. Mundada, M., Wankhede, S., Patwardhan, S., & Avachat, A. (2012). Formulation and evaluation of topical gel of lornoxicam using a range of penetration enhancers. *Indian J Pharm Edu Res*, *47*, 168-71.
9. Patel, M. A., & Pingale, P. L. (2014). High functionality coprocessed excipients: a review. *World J Pharm Sci*, *3*(3), 795-806.
10. Saudagar, R. B., & Gangurde, P. A. (2017). Formulation, development and evaluation of film-forming gel for prolonged dermal delivery of miconaole nitrate. *Research Journal of Topical and Cosmetic Sciences*, *8*(1), 19-29.
11. Patel, M. A., & Pingale, P. L. (2014). Comparative effect of different high functionality excipients on various characteristics of vardenafil HCl tablets (BCS II drug). *International Journal of Pharmaceutical Sciences and Research*, *5*(12), 5447.
12. Chemate, S. Z., & Albhar, S. N. (2017). Formulation and Development of Flurbiprofen Containing Film Forming Gel. *World Journal of Pharmaceutical Research*, *6*(11), 652-662.
13. Li, X., Zhang, R., Liang, R., Liu, W., Wang, C., Su, Z., ... & Li, Y. (2014). Preparation and characterization of sustained-release rotigotine film-forming gel. *International Journal of Pharmaceutics*, *460*(1-2), 273-279.
14. Pingale, P. L., Amrutkar, S. V., & Telange, D. R. (2021). Formulation, Characterization and In-Vitro Dissolution Studies of Metadoxine Tablets Prepared by Various Granulation Methods. *J Med Pharm Allied Sci*, 2712-9.
15. Srivastava, S., Verma, U., Kumar, R., & Bhatt, N. (2021). Preparation and Evaluation of Econazole Nitrate Containing Film-Forming Gel. *European Journal of Molecular & Clinical Medicine*, *8*(3), 2881-2895.

CITATION OF THIS ARTICLE

Harshali M, Khanderao J, Sujit J, Rishikesh B, Prashant P. Formulation, development, and evaluation of antifungal film-forming gel for prolonged dermal delivery of luliconazole. Bull. Env.Pharmacol. Life Sci., Vol 12 [11] October 2023: 140-145.