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Formulation and Evaluation of Film Forming Gel for Prolonged Dermal Delivery of Griseofulvin

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ABSTRACT:

This study investigates the preparation and assessment of a film-forming gel for the topical administration of the antifungal medication griseofulvin over an extended period of time. Improved drug concentration, extended resistance time, and a decrease in side effects such redness, skin irritation, dryness, oedema, and skin peeling are all provided by film-forming gel-based drug delivery systems. The goal of the current study is to create a griseofulvin dosage form that is in the form of a "film forming gel," eliminating the need for frequent reapplication. Leaves a thin, clear layer on skin after application. Stay on the afflicted area longer and resist being removed by the patient's clothing.Using design expert software and the three-quarter full factorial design method, an experimental design was created that may provide a sustained release action by achieving the ideal concentrations of carbopol 940 and euragit RS 100 for viscosity and diffusion. For every test, every formulation produced results that fell within an acceptable range. Drug release from the improved formulation was 99.05%. It is possible that this formulation will shorten the course of treatment, gain greater patient acceptance, and represent a breakthrough in the management of fungal skin infections.

Keywords: Film forming gel, Griseofulvin, Eudragit RS 100, Carbopol 940.

1. INTRODUCTION

Instead of conventional topical and transdermal formulations, film-forming gels are innovative drug delivery technologies that have been utilized recently to administer a variety of medications to the skin[Abeer Khastaghi et al.,2019].In order to reduce the efficacy and resistance time of conventional topical formulations, which are typically used to treat for antifungal activity, 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[Harshali Mahale et al.,2023].

Griseofulvin is a well-known antifungal medication that is applied topically but does not enter skin. It is taken orally to treat fungal infections of the nails, especially those of the fingernails and toenails. Because of its reduced solubility and absorption in water, griseofulvin must be taken at a relatively high dose (500 mg/kg, twice daily in adults). It was thought that adding griseofulvin to topical film would aid to increase efficacy, which would then increase topical absorption and bioavailability[Prashant Malpure et al.,2023].

Film-forming compositions are a relatively new idea. Formulations that produce films can be gels, emulsions, or solutions. The resulting coating is thick enough to give the skin a continuous medication release. Commercially accessible film-forming compositions include BeeGentleTM and GELNIQUE[Saudagar et al.,2017 and Gelnique,2008].In this study, Eudragit RS100, a film-forming polymer, was used to create a dermal gel containing griseofulvin. A gelling agent is hydroxy propyl methyl cellulose. In this case, carbopol was the viscosity modifier. As a plasticizer, triethyl citrate was employed. Using a 3^2 factorial design, we assessed the effects of two factors: the concentration of Carbopol 940 and Eudragit RS100 on the antifungal activity and drug release rate.

2. MATERIALS AND METHODS

Materials

Griseofulvin was Sample, gifted from Glenmark pharmaceuticals Ltd. Eudragit RS100 was received from jiozuo zhongwei special products Pvt. Ltd. Carbopol 940, HPMC K4M, Triethyl citrate, Propylene glycol were brought from college.

Method of preparation of Film forming gel:

The formulation design was done using Design Expert e stat software version (7.0)

Experimental Work

Color: A little sample of Griseofulvin was taken in butter paper and examined under bright illumination.

Odor: A small amount of Griseofulvin sample was smelled in order to identify the scent.

Appearance: The appearance was detected following the application of a pinch of Griseofulvin between two fingers.

Melting point determination: The melting point serves as the initial barometer of the sample's purity. The open capillary method was used to find griseofulvin's melting point. One end of a glass capillary that has been sealed with flame is filled with griseofulvin. After submerging the capillary in liquid paraffin and inserting it into the M.P. apparatus, the melting point was ascertained.

Study of solubility: The solubility of griseofulvin was assessed in a range of solvents. 20 mg of griseofulvin and 10 mL of the required solvent were added to a test tube. Particles were observed after ten minutes of sonication of the mixture. The solvents used in the solubility study were methanol, dimethyl sulfoxide [DMSO], dimethyl sulfoxide [DMF], and water.

Analysis using UV-Visible spectrophotometry: UV Spectroscopy: Griseofulvin's ultraviolet spectrum was acquired. Spectra Manager Software and the Shimadzu UV 1800

Spectrophotometer were employed in the analysis. After thoroughly cleaning the glassware twice with distilled water, it was dried.

Materials and reagents: Methanol was used as a solvent to create the dilution,

Method: All of the reagents were analytical grade. 1000 µg/ml was obtained by dissolving 10 milligram of griseofulvin in 10 ml of methanol. A 20 µg/ml sample was created by diluting 0.2 ml of the resultant solution with 10 ml of methanol. After that, the generated spectra were examined.

Calibration Curve for Methanol

Stock solution: To prepare a stock solution, 10 mg of griseofulvin was dissolved in 10 ml of methanol, resulting in a concentration of 1000 µg/ml.

Solution A: One milliliter of the sample was collected from the inventory solution and diluted with ten milliliters of methanol to yield 100 µg/ml.

Dilutions: Two milliliters (ppm), four milliliters (ppm), six milliliters (ppm), eight milliliters (ppm), and ten milliliters (ppm) of solution A were extracted and diluted up to ten milliliters with solvent (methanol), accordingly, at a wavelength of 295 nm.

Drug excipient compatibility study: When developing new medications, excipient compatibility studies are a crucial stage. An evaluation of the drug ingredient's chemical structure, the kind of delivery system needed, and the recommended production technique may be prudent before a drug component is synthesized into the intended dosage form. Usually, excipients with specialized functions are combined with drug molecules. Excipients are pharmacologically inert; but, in the correct circumstances, they can undergo chemical reactions and physical interactions with drug molecules under favorable environmental conditions.

Compatibility Examine drug excipients to see if they have been approved or rejected for usage in pharmaceutical formulations. The API alone and in combination with different excipients were administered in high concentrations and mixed well. The mixture was sieved, put into glass vials, and stored in a balancing chamber at 40+2°C/75±5%RH [Kathpalia et al., 2023].

Table 1. Drug-Excipient Compatibility

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

Formulation of Film Forming Gel by Dispersion Method:

The formulation design was created using the program Design Expert e stat. The gelling agent, HPMC K4M, was stirred into the solvent at 1200 RPM for 30 minutes. The medication was dissolved in ethanol and water. We dissolved triethyl citrate in the required volume of ethanol and propylene glycol. The solution containing the triethyl citrate was used to dissolve Eudragit RS 100. The Eudragit mixture was introduced after 5 milliliters of ethanol were used to dissolve the carbopol 940. All of the preparations were homogenized between 1200 and 1500 RPM in order to produce a stable gel preparation [Mundada et al.,2012 and Telange et al.,2022].

Table 2. Formulation Strategy

Sr No.	Ingredients	Quantity								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Griseofulvin	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

2.	Eudragit RS100	1.35	1.2	1.35	1.5	1.2	1.5	1.2	1.35	1.5
3.	Carbopol 940	0.3	0.45	0.6	0.45	0.3	0.3	0.6	0.45	0.6
4.	HPMC K4M	1	1	1	1	1	1	1	1	1
5.	Triethyl citrate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
6.	Propylene glycol	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
7.	Ethanol: Water (70:30)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total		10 gm								

Factorial design study:

The 3^2 complete factorial design was used to confirm the quality effects of increasing the concentrations of variables like Eudragit RS 100 (X1) and Carbopol 940 (X2) on diffusion and viscosity. The levels of two components were selected based on studies conducted prior to enforcing the experimental design. The table describes the experimental runs, factor combinations, and the application of the coded levels to the experimental units used in the study.

Table 3: Factorial Design Model Parameters

Independent Variables	**Name**	**Unit**	**Level**		
			Low(-1)	**Middle(0)**	**High(+1)**
X1	Eudragit RS100	Gm	1.2	1.35	1.5
X2	Carbopol 940	Gm	0.3	0.45	0.6

Evaluation of Film-forming Gel:

Physical Evaluation: The formulations were examined for their color, odor, and appearance.

pH: The pH meter (Chemline-111) was calibrated using buffer solutions at pH levels of 4, 7, and 9. About 0.5 g of the film-forming gel was weighed, diluted in 50.0 ml of distilled water, and the pH was measured.

Viscosity: The viscosity of the film-forming gel was evaluated using a Brookfield Viscometer (Amtech model number LVDVE) at various rpms with spindle number 64. The spindle was revolved at 10, 50, 60, and 100 rpm, and the viscosity (CP) and torque (%) were measured. Viscosity may increase as torque decreases [Telange et al.,2022].

Drying time: A film-forming gel was applied to the inner sides of a volunteer's forearm, with the investigation carried out after obtaining informed consent. After 2 minutes, a pitcher slip appeared on the film without any applied pressure. The film was considered dry if no liquid remained visible on the glass slide after removal. If any liquid was still present on the slide, the experiment was repeated until the film was completely dry.

The drug's content: A film-forming gel containing 10mg of Griseofulvin was placed in a 10ml volumetric flask containing 5ml of methanol, and the quantity was adjusted to a concentration of 1000ug/ml with methanol. An aliquot of 1ml was transferred to a 10ml volumetric flask, and the volume was adjusted with methanol to achieve a concentration of 100ug/mL. The produced solution's absorbance was measured at λmax 295 mm with a UV spectrophotometer [Telange et al.,2022].

In-vitro diffusion test: Drug release profiles from film-forming gels were measured in-vitro using a Franz diffusion cell. The cell contained two chambers: a donor compartment with an inner diameter of 24 mm and a receptor compartment with a sampling capacity. The donor compartment contained 20 milligrams of the medication, separated by a cellophane barrier. A clamp was used to hold the donor and receptor compartments together, and the assembly was fastened to a magnetic stirrer. Samples were collected, diluted with methanol, and analyzed for

drug concentration with a UV spectrophotometer [Mundada et al.,2012; Chemate et al.,2017 and Li. X. et al.,2014].

3. RESULT AND DISCUSSION

UV-visible analysis:

The ultraviolet spectrum of griseofulvin was obtained. The test was performed using a Shimadzu UV 1800 spectrophotometer. Table 4 displays absorbance values at 2, 4, 6, 8, and 10 ppm, as well as a calibration curve obtained using UV spectrophotometry.

Table 4: Calibration curve for Griseofulvin

Sr. No.	Concentration(ppm)	Absorbance
1.	2	0.145
2.	4	0.272
3.	6	0.404
4.	8	0.522
5.	10	0.648

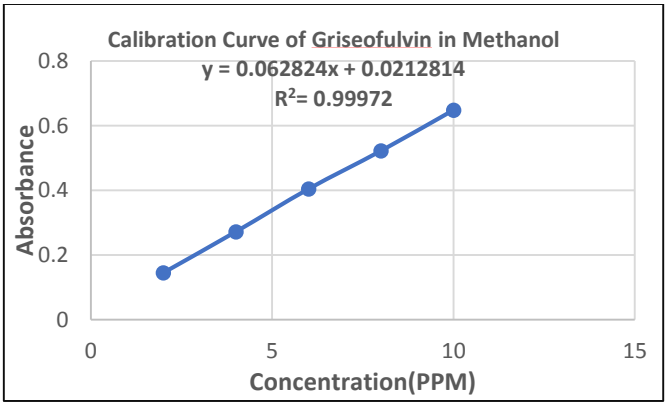

Fig 1. Calibration curve of Griseofulvin

Physical evaluation of film forming gel:

It include visual observations, pH, viscosity, and spreading time. The gel was weighed at 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 left to dry for 48 hours at room temperatures. The drug concentration was evaluated by adding 10mg of Griseofulvin to a 10ml volumetric flask containing 5ml methanol and measuring the absorbance using a UV visible spectrophotometer.A lab-assembled device with two chambers, a diffusion membrane, and a magnetic stirrer that resembled a Franz diffusion cell was used to conduct the in vitro diffusion test. The results are shown in table 5, which is provided below. Samples were gathered, diluted with methanol, and then examined for drug content using a UV spectrophotometer.

Table 5: Physical characteristics of formulated batches

Batches	Colour	Odour	Appearance	Integrity of Film
F1	Colourless	Characteristic	Smooth	Cracked and Flaky
F2	Colourless	Characteristic	Viscous	Cracked and Flaky
F3	Colourless	Characteristic	Viscous	Flaky
F4	Colourless	Characteristic	Smooth	Good
F5	Colourless	Characteristic	Smooth	Good

F6	Colourless	Characteristic	Smooth	Good
F7	Colourless	Characteristic	Smooth	Good
F8	Colourless	Characteristic	Smooth	Good
F9	Colourless	Characteristic	Viscous	Good

Batches	**pH**	**Viscosity**	**Spreadability**	**Drying time(min)**	**Drug content(%)**
F1	5.95 ± 0.1	5311 ± 105	9.5 ± 0.2	1.35 min ± 5 sec	95.89
F2	5.93 ± 0.1	5485 ± 120	8.2 ± 0.1	1.38 min ± 5 sec	97.76
F3	6.17 ± 0.1	6781 ± 145	9.1 ± 0.2	1.42 min ± 3 sec	93.21
F4	6.05 ± 0.1	6450 ± 82	7.5 ± 0.2	1.50 min ± 5 sec	98.52
F5	6.09 ± 0.1	5012 ± 111	8.3 ± 0.2	1.50 min ± 5 sec	98.62
F6	6.12 ± 0.1	5398 ± 95	9.4 ± 0.1	1.50 min ± 5 sec	96.34
F7	6.14 ± 0.1	6195 ± 108	7.8 ± 0.2	1.50 min ± 5 sec	98.14
F8	6.10 ± 0.1	6387 ± 102	8.1 ± 0.1	1.50 min ± 5 sec	97.02
F9	6.04 ± 0.1	7231 ± 75	7.7 ± 0.1	1.50 min ± 5 sec	97.69

Drug Diffusion Determination: After testing all of the created batches, it was discovered that the drug diffusion ranged from 82.79 to 99.05%. Due to the increased viscosity of the formulation and film thickness, the drug diffusion system will also slow down with time, confirming a longer-lasting effect. Table 6 and Figure 2 display the formulations' in-vitro drug delivery studies. From the in vitro diffusion study, it can be inferred that formulations F1 through F3 did not maintain the drug release for the full eight hours.

Low concentrations of polymers that modulate drug release and the formulations' sporadic viscosity may be to blame for this. Drug release was sustained for eight hours using formulas F4 and F5. Conversely, formulations F6 through F9 did not completely release the medication. Intermediate concentrations of the hydrophilic polymer HPMC and the hydrophobic polymer Eudragit were shown to sustain drug delivery. Out of the nine formulations, formula F5 was shown to have the highest release; after eight hours, 99.05% of the drug in the system became active against fungal growth [Mundada et al.,2012; Chemate et al.,2017 and Li. X. et al.,2014].

Table 6: Cumulative Drug Release of F1 to F9 batches

Time (Hrs)	**Batches**	**% Cumulative Drug Release**								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1.		13.37	15.61	14.67	15.71	15.32	14.61	13.47	12.48	11.95
2.		24.96	26.12	25.79	26.95	27.86	26.70	25.39	24.53	25.46
3.		41.80	40.75	38.92	41.37	41.99	39.13	38.53	36.33	37.52
4.		59.65	58.83	55.35	56.02	56.25	54.31	51.79	45.91	47.56
5.		75.48	76.62	77.45	68.69	67.81	67.60	62.76	56.04	59.16
6.		88.25	85.38	87.91	79.11	80.35	76.22	70.44	65.21	69.04
7.		94.12	92.95	91.69	89.32	91.12	80.46	82.34	78.13	77.60
8.		98.72	94.08	96.23	94.92	99.05	87.18	93.83	95.19	82.79

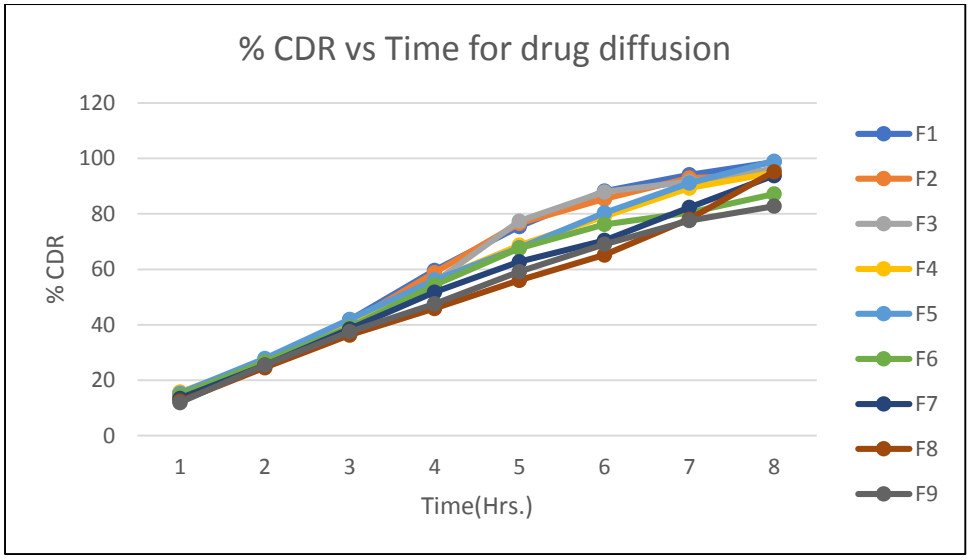

Fig 2: Graph of % cumulative Drug Release Vs Time

Optimization study: Design Expert 7.0 software was used to examine how independent factors affected replies. Nine potential batches of the experimental design layout were created.ANOVA was used to examine the software's suggested linear, 2FI, quadratic, and cubic models, among others, that fit the data the best. One factor and perturbation graphs were then created for each of the different dependent variables after regression polynomials for each dependent variable were calculated. Equations representing mathematical models were created for every distinct response or dependant variable.The response varies when two factors are modified concurrently, as indicated by the interaction terms X1 and X2, which represent the average outcome of altering one component at a time from its low to high value[Pingale et al.,2021; Patel et al.,2014 and Umrekar et al.2023].

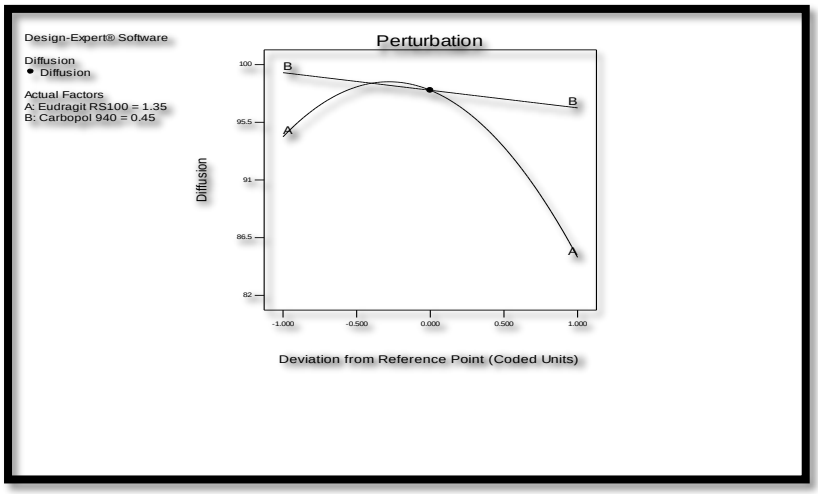

Figure 3: Effect of Eudragit RS 100 and Carbopol 940 on Diffusion

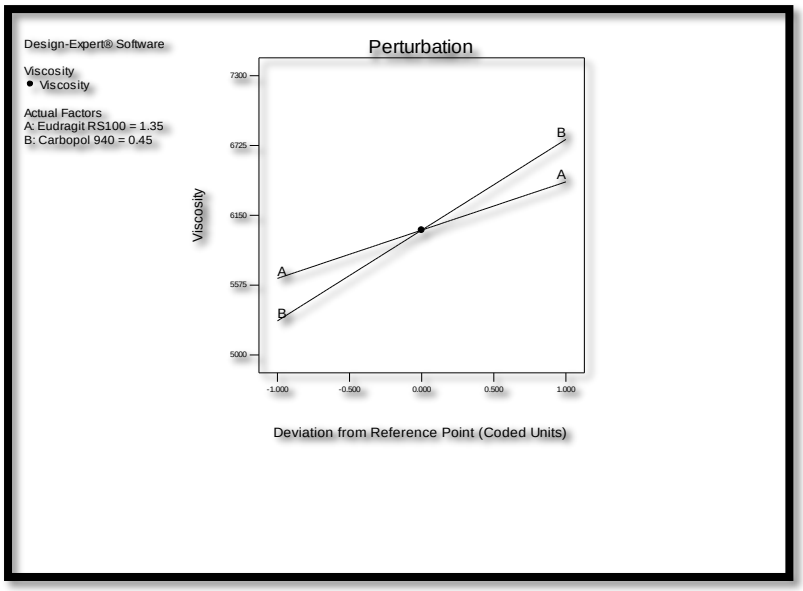

Figure 4: Effect of Eudragit RS 100 and Carbopol 940 on Viscosity

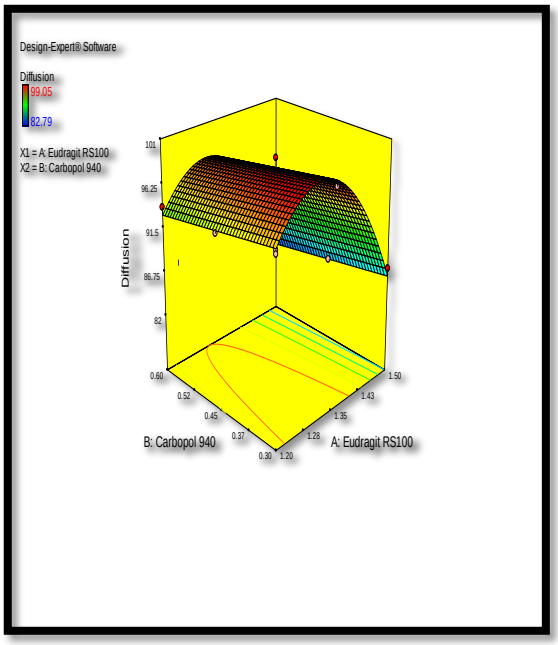

Figure 5: 3D Plot for Viscosity

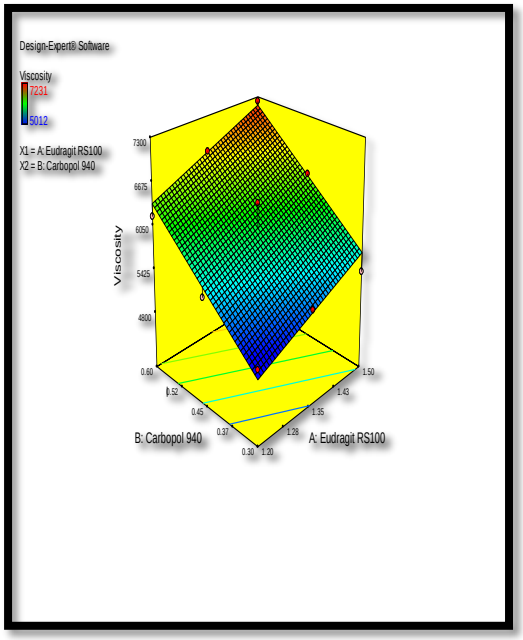

Figure 6: 3D plot for Diffusion

Antifungal study for optimized batch (F5): The antifungal investigation was conducted using the standard methodology outlined under the experimental work. It was found that the optimal batch's zone of inhibition measured 27 mm. It was shown that the zone of inhibition for the common antifungal medication Nystatin was 27 mm. Based on antifungal results, it was demonstrated that the optimized batch of film forming gel had strong antifungal activity.

Table 7: Antifungal study (Zone of inhibition)

Sr. No.	Sample	Zone of inhibition(mm)
1.	Optimized batch (F5)	27 mm
2.	Standard antifungal agent (Nystatin)	27 mm

Table 8: Summary of comparative study results

Sr. No.	Evaluation Parameter	Selected batch	Marketed formulation
1.	Physical evaluation	Smooth	Smooth
2.	pH	6.05 ± 0.1	6.1 ± 111
3.	Viscosity	5012 ± 111	7495 ± 95
4.	Spreadability	8.3 ± 0.2	8.9 ± 0.2
5.	Drying time	1.50 min ± 5 sec	-
6.	Drug content	98.62%	99.12%
7.	Drug diffusion	99.05	98.67
8.	Antifungal test	27 mm	27 mm
9.	Integrity of formulated film	Good	Good

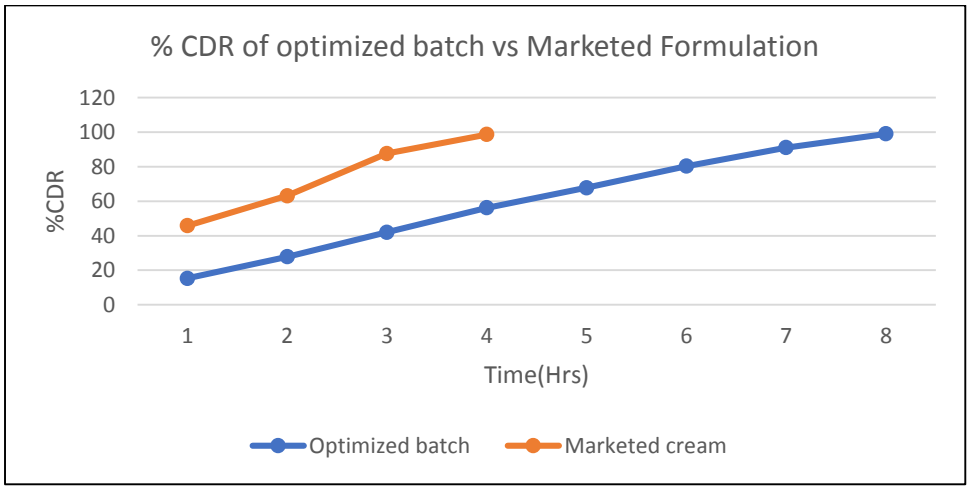

Figure 7: % CDR of Optimized batch vs Marketed formulation

Stability analysis: The optimized batch F5 of film-forming gel was used to conduct the stability analysis. At one month, the optimized formulation was assessed mostly based on its physical attributes. Diffusion investigations, pH, drug concentration, physical appearance, and temperature evaluations were conducted at 40°C and 75% humidity [Umrekar et al.2023].

Table 9: Stabilized study for optimized formulation

Evaluation parameters	Results
Colour	White
Odour	Characteristic
Appearance	Smooth
pH	6.09
Viscosity	4635
Drying time	2 min
Drug content	98.87%
Drug diffusion	97.66%

4. CONCLUSION

In conclusion this study focuses on the preparation and assessment of Griseofulvin film-forming gel. The dispersion approach was used to prepare the Griseofulvin film-forming gel. The preparation of Griseofulvin as a film-forming gel, which may provide prolonged release

action through the combination of Eudragit RS100 and Carbopol 940, is the primary goal of the study. The influence of Eudragit RS100 and Carbopol 940 concentrations on film-forming gel was investigated through the use of design expert software and the 3^2 factorial design approach to create the experimental design. Nine batches of Griseofulvin film-forming gel were made, and each batch was assessed based on a range of factors. Batch F5 was chosen as the optimal batch through the use of optimization techniques. The optimized batch underwent viscosity and diffusion tests. The identical formulation contained the highest percentage of the medication.

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.

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