Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Comparative Antifungal Study of Fluconazole and Fluconazole Enhanced with Silver Metal Colloid Creams: A 3^2 Factorial Design Optimization Approach

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ARTICLE INFO

Article history:

Received: 09 November, 2023

Revised: 26 December, 2023

Accepted: 05 January, 2024

Published: 30 January, 2024

Keywords:

Antifungal creams, *Candida albicans*, Fluconazole, Silver metal colloid, Zone of Inhibition.

DOI:

10.25004/IJPSDR.2024.160111

ABSTRACT

Antifungal resistance remains a critical health challenge within dermatology and pharmaceutical research. This study aimed to enhance antifungal creams by investigating the effectiveness of fluconazole (FLZ) and fluconazole combined with silver metal colloid (FLZ-AgMC). Employing a 3^2 factorial design, systematic exploration was conducted to assess the influence of metal colloid concentration and stearic acid content on crucial cream attributes: viscosity, spreadability, and zone of inhibition ratio. Viscosity ranged from 56132 to 58700 cP, spreadability from 28.7 to 27.8 gm.cm/sec, and the zone of inhibition increased with metal colloid concentration. Optimized cream formulations were identified using Stat-Ease Design Expert version 7. Various FLZ and AgMC concentrations were evaluated for antifungal activity against *Candida albicans*, with FLZ-AgMC exhibiting significantly enhanced efficacy, as indicated by a larger inhibition zone compared to FLZ alone. The inhibitory zone ratio demonstrated a 35 to 40% improvement, indicating enhanced fungal growth inhibition. Skin permeation and *ex-vivo* studies confirmed that the optimized Fluconazole formulation followed the Higuchi Model (R2 = 0.9847). Silver metal colloid-containing formulations demonstrated superior antifungal efficacy against *C. albicans*. The impact of silver metal colloid and stearic acid on viscosity and spreadability was established, revealing key factors influencing the cream's physical properties. This optimization approach highlights the potential for innovative antifungal formulations, contributing to improved patient care, user acceptability, and clinical application.

Introduction

Fungal infections, often overlooked in their prevalence and impact, represent a substantial global health burden. Dermatophytes, candidiasis, and other fungal skin infections affect millions of individuals worldwide, resulting in discomfort, decreased quality of life, and significant healthcare costs. In the search for effective antifungal treatments, researchers continually explore innovative strategies to enhance the effectiveness of existing antifungal agents.[1] Among these, contagion, and cutaneous mycoses are among the most prevalent, causing discomfort, disfigurement, and occasionally severe complications. The management of such infections primarily relies on the topical application of antifungal agents, which aim to inhibit fungal growth and promote the healing of infected skin.

Fluconazole is widely used as an antifungal drug and has demonstrated remarkable effectiveness against a spectrum of fungal pathogens. However, the emergence of drug-resistant fungal strains and the demand for more effective therapeutic alternatives have led researchers to seek novel methods for improving the performance of these antifungal drugs,[2] and optimizing the topical delivery remains a challenge to enhance their therapeutic outcomes.[3] Such an approach involves the incorporation of metal colloids, such as silver, into topical formulations to enhance their antifungal properties.

In recent years, nanotechnology has opened up new possibilities for improving and enhancing the efficacy of

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

antifungal treatments. Silver metal colloid (AgMC) has gained attention because of its exceptional antimicrobial properties. AgMC can effectively inhibit fungal growth by disrupting the cell membrane; intruding into the cell division, and inducing oxidative stress.[4-5] Incorporation of AgMC into antifungal creams could potentially enhance their efficacy.

The synergistic potential of silver nanoparticles (SNP) in conjunction with the antifungal fluconazole against *Candida albicans* is evidenced by comprehensive investigations including minimal inhibitory concentrations (MIC), fractional inhibitory concentration (FIC) index assessments, and morphological analyses. The combined treatment exhibits substantial antifungal efficacy, particularly noteworthy in addressing fluconazole-resistant strains, thereby indicating its clinical relevance. *In-vivo* experiments further validate the promising therapeutic outlook of the SNP-fluconazole combination. Various research has set the stage for exploring a novel and effective strategy in the battle against *Candida* infections, especially those resistant to conventional antifungal treatments.[6-8]

Factorial design optimization is a powerful statistical tool, that allows researchers to systematically investigate and optimize multiple variables simultaneously. By employing a 3^2 factorial design, the present study was intended to comprehensively evaluate the impact of two independent factors on the antifungal efficacy and consistency of the resulting cream formulations. This approach enabled us to identify the optimal combination of these variables to maximize the creams' antifungal activity.[9]

The combination of silver metal colloid with fluconazole represented a significant advancement, particularly in addressing resistance among *Candida* strains to conventional antifungal agents. This innovative therapeutic strategy not only augmented antifungal efficacy but also demonstrated potential in overcoming drug resistance, a substantial concern in global public health. The pharmaceutical advantage of this study lies in its potential to facilitate the development of more efficacious and adaptable antifungal treatments, thereby equipping clinicians with a valuable resource to address *Candida* infections amid evolving resistance patterns. The investigation addressed global concerns about fungal infections, emphasizing the need for improved antifungal therapies due to challenges like resistance and adverse effects. The study aimed to enhance patient care by optimizing fluconazole formulation and investigating its collaborative effects with AgMC to offer more effective and better treatment options.[10-12]

Materials and Methods

Materials

Fluconazole was acquired from Virupaksha Organics Limited, Boisar, Maharashtra. Beeswax, methyl paraben, propyl paraben, stearic acid, ceto-stearyl alcohol, glycerin, and carbopol-934 were purchased from Dolphin Pharmacy Instruments Pvt. Ltd. Mumbai, Maharashtra and the true colloidal silver 40 ppm was procured from Blessed Organic, Rajasthan.

Methods

Assessment of organoleptic characteristics and melting point[13-14]

The assessment of organoleptic characteristics involved observing fluconazole's color, odor, and overall appearance. The measurement of the melting point was done by the capillary method.

FTIR spectroscopy study[15]

To determine the chemical composition of fluconazole, fourier transform infrared spectroscopy (FTIR) using an IR affinity-1 was utilized. The FTIR spectrum of FLZ exhibited peaks in accordance with the reference spectra.

Assessment of drug-excipient compatibility[16]

The interaction between drugs and excipients is pivotal in ensuring the stability of pharmaceutical formulations. In order to develop a viable formulation, compatibility studies between the drug and the excipients were conducted, and the FTIR spectral pattern of the drug-excipient mixture was compared to the individual drug spectrum.

Preparation of the standard curve of fluconazole [17]

In 100 mg of fluconazole was dissolved in 100 mL of methanol. From this initial solution, 10 mL of sample was withdrawn and transferred into a 100 mL volumetric flask. Methanol was added to reach a final stock solution containing 100 µg/mL. From the stock solution, a series of dilutions (10, 20, 30, 40, and 50 µg/mL) were prepared using methanol. The absorbance of the solutions was assessed spectrophotometrically against a blank of methanol at 260 nm.

Formulation of cream

A formulation for FLZ antifungal cream was developed by preparing nine batches with variations in the concentrations of metal colloid (X1) and stearic acid (X2). The responses, including viscosity (Y1), spreadability (Y2), and zone of inhibition (Y3), were measured for each batch, as detailed in Table 1.

In preparing the cream formulation, an oil phase was formed by heating it to 65 to 70°C in a water bath.

Table 1: Independent variables

	Levels		
Factors (Independent variables)	*Low*	*Medium*	*High*
	-1	0	+1
Metal colloid (A) in percentage	0	5	10
Stearic acid (B) in percentage	0	5	10

Table 2: Formulation of topical cream

	F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
Fluconazole	300	300	300	300	300	300	300	300	300
Ag-colloid 40 ppm	0	0	0	750	750	750	1500	1500	1500
Stearic acid	0	750	1500	0	750	1500	0	750	1500
Bees wax	1500	1500	1500	1500	1500	1500	1500	1500	1500
Cetosteryl alcohol	1000	1000	1000	1000	1000	1000	1000	1000	1000
Methyl paraben	20	20	20	20	20	20	20	20	20
Propyl paraben	10	10	10	10	10	10	10	10	10
Glycerin	2000	2000	2000	2000	2000	2000	2000	2000	2000
Triethanolamine	75	75	75	75	75	75	75	75	75
Carbopol-934	200	200	200	200	200	200	200	200	200
Water	9895	9145	8395	9145	8395	7645	8395	7645	6895
Total (mg)	15000	15000	15000	15000	15000	15000	15000	15000	15000

Simultaneously, an aqueous phase was prepared. The oil phase was gradually added to the aqueous phase at 60 to 70°C, and the two phases were mixed for 10 to 15 minutes. The resulting emulsion was naturally cooled to room temperature until it transformed into a semisolid cream base.[18] The formulation of the batches is shown in Table 2.

Evaluation Parameters of Topical Cream Formulations

Physical examination[19]

The topical creams were visually examined for color, homogeneity, consistency and phase separation.

Determination of pH[19]

In this study, the pH of an antifungal cream formulation was determined using a Labline digital pH meter. The pH meter was initially pre-calibrated with a standard buffer solution. A beaker containing 50.0 mL of water served as the medium for dissolving a weighed amount of cream (5 grams), following which the pH of the resulting solution was measured. The pH investigation of the cream formulation was conducted in triplicate, and subsequently, the average of the triplicate readings was calculated, to ensure a comprehensive assessment of the pH characteristics of the antifungal cream formulation.

Determination of viscosity

A Brookfield DVE Viscometer was used to determine the viscosity of the formulated creams using spindle LV 4 at a speed of 50 rpm.

Determination of spreadability[19]

Spreadability tests were conducted using a specifically designed apparatus comprising a wooden board with a stationary glass slide and a movable glass slide attached to a weight pan mounted on a pulley. An excess sample of 2 grams was positioned between the two glass slides, and a 1-kg weight was applied to the upper slide for a duration of 5 minutes to compress the sample and eliminate entrapped air, ensuring an even thickness. An additional weight of 80 grams was then added to the pan. The time in seconds required for the upper slide to traverse a distance of 7.5 cm was measured. The spreadability tests were performed in triplicate, and the average spreadability was determined using the formula, $S = m*l / t$.

Where,

S is the spreadability (g.cm / sec)

m is the weight tied on the upper slide (in grams),

l is the length of the glass slide (in centimeters), and

t is the time taken for the upper slide to reach the specified distance (in seconds).

Drug content

The UV spectrophotometer was utilized to determine the drug content.

Determination of the type of cream

A dye test was utilized to determine the type of cream.

Zone of inhibition[20]

For *in-vitro* antifungal activity studies, the FLZ and fluconazole enhanced with silver metal colloid (FLZ-AgMC) were tested against *C. albicans*. The diameter of the inhibition zone was measured and compared to ascertain the extent of the zone of inhibition.

Optimization of Variables Using Full Factorial Design

The current investigation employed a 3^2 full factorial design to optimize variables. It included an assessment of two independent factors: Percentage of silver metal colloid (A) and Percentage of stearic acid (B), each varying across 3 levels. Experimental trials were performed for all possible combinations. The dependent variables measured in the investigation were viscosity (Y1), spreadability (Y2), and the zone of inhibition (Y3). Utilizing Design Expert Software (Version 7, Stat Ease In. 2021, Minneapolis, MN,

55413), multiple regression analysis and ANOVA were executed in order to establish a statistical relationship between the independent variables. Additionally, contour plots and 3D response surface plots were created to visualize the outcomes of this analysis.

Diffusion study[21]

Approval for the experiment was obtained from the Institutional Animal Ethics Committee (Proposal No. IAEC/VIP/2022/SEPT/P/11). The study involved *ex-vivo* skin permeation and retention tests using the skin of albino wistar rats. The skin sample was meticulously prepared, removing subcutaneous fats, and mounted on the Franz dispersion cell. A phosphate buffer at pH 6.8 was used as the diffusion medium. The formulated cream was applied to the skin, with the diffusion medium maintained at 37 ± 1°C with stirring at 40 to 60 rpm to ensure sink conditions, followed by 2 mL withdrawal of aliquots periodically and replacement with fresh medium over a time intervals of 0, 30, 60, 120, 180, 240, 300 and 360 minutes. The drug concentration in the sample was assessed spectrophotometrically using a standard calibration graph.

Skin irritation study[21-22]

The research was conducted on healthy wistar rats. The animals were divided into control and optimized formulations as per IAEC/VIP/2022/Sept./P/12/Ext. The hairs were removed from the dorsal side of rats 24 hours prior to the administration of the formulation. In the experiment, a formulation containing 1-mg of drug was uniformly applied on the shaven skin of rats, and the application site was covered with gauze by Bengal Surgical Limited and Micropore Tape, a non-reactive tape . After 1-hour, the formulation was rinsed off with dist. Water, and any remaining residue, were removed by wiping the test sites with tap water. The observations for dermal reactions were made at 60 minutes, 24, 48, and 72 hours after the initial application of the test formulation. Scores from 0 to 4 were assigned based on the irritation.

The observations were recorded as a numerical rating for each animal, as follows:

0 = no visible reaction
1 = mild Erythema
2 = intense Erythema
3 = intense Erythema with edema
4 = intense Erythema with edema and vesicular erosion.

Results and Discussion

Organoleptic Characteristics and Melting Point of Fluconazole

Fluconazole was found to be a white crystalline powder with no odor and a slightly bitter taste. The melting point of fluconazole was found to be 140°C ± 1.15 (n = 3).

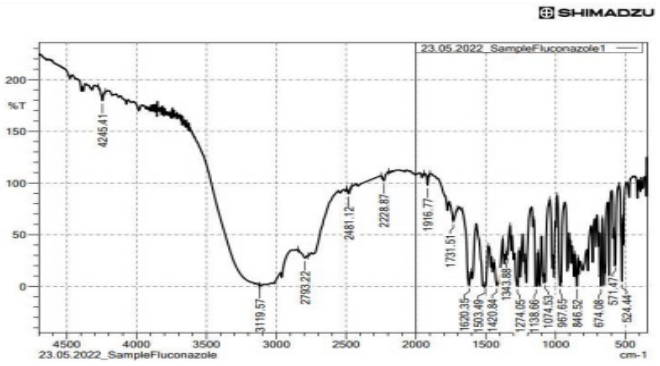

Fig. 1: FTIR spectra of fluconazole

Drug Identification *via* FTIR Spectroscopy

The FTIR of fluconazole (Fig. 1) along with the comparison of the observed peak with the reference peak, is presented below in Table 3.

Molecules absorb infrared radiation at specific frequencies because of the vibration of their chemical bonds. These absorption frequencies are characteristic of various functional groups in organic molecules and can be used as a fingerprint to identify specific compounds. The observed peak in the IR spectrum of a drug (FLZ) matched the peak reported in FLZ Table 3. Thus, it is a strong indicator that the two substances are the same or very similar.

Drug-Excipient Compatibility Study

Comparing the FTIR spectra of both the pure drug and its physical mixture (Fig. 2), it was noted that the peaks align within the designated range, indicating no significant interaction or chemical reaction between the drug and the excipients in the physical mixture. Thus, the physical mixture maintains the same molecular structure as that of a pure drug, suggesting compatibility and affirming its suitability for subsequent pharmaceutical formulation, as detailed in Table 4.

Preparation of the Standard Graph of Fluconazole

The standard graph for fluconazole was prepared (Fig. 3) using the observed absorbance at 260 nm (Table 5), as the fluconazole has the maximum absorption (λ_{max})

Evaluation Parameters of Cream Formulations

All the formulated batches F1–F9 were white to off-white, with creamy consistency and good homogeneity.

Determination of pH

All formulations had pH values falling within the range of 5 to 7, demonstrating that they meet the required pH specifications (20) for topical application and are considered satisfactory.

Determination of viscosity

Viscosity in cream is important because it determines the product's texture, spreadability, and stability. Proper

Table 3: Comparison of observed peak to reference peak of FLZ

Peak obtained in drug (frequency cm^{-1})	*Description for FLZ*	*Observed peaks (frequency cm^{-1}) [23,24]*
3424.38	OH Stretching	3219.57
2817.36	CH2 Stretching	2793.22
3013.20	CH (Aromatic Stretching)	3119.57
1616.21 and 1456.80	C = N Stretch and CH (Aromatic bending) C – H Trizole Ring	1620.35 and 1503.49
868.75		967.65

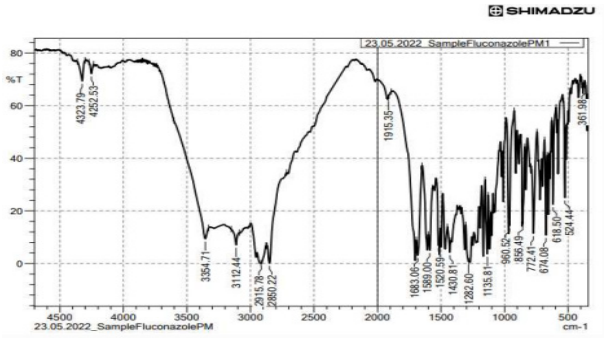

Fig. 2: FTIR spectra of fluconazole, metal colloid and physical mixture

viscosity ensures that the cream maintains its desired consistency, adheres well to the skin, and delivers a pleasant user experience.The viscosity of prepared batches is shown in Fig. 4.

Determination of spreadability

The spreadability of a cream is crucial, as it determines how easily and uniformly it can be applied to the skin. It affects the user experience and ensures even distribution of active ingredients, enhancing the cream's effectiveness and comfort. The spreadability is found as follows (Fig. 5).

Drug content

The drug content of prepared cream formulations F-1 to F-9 is indicated in Table 6.

Determination of the type of cream

The addition of scarlet red (an oil-soluble dye) to the cream and examination under a microscope revealed that

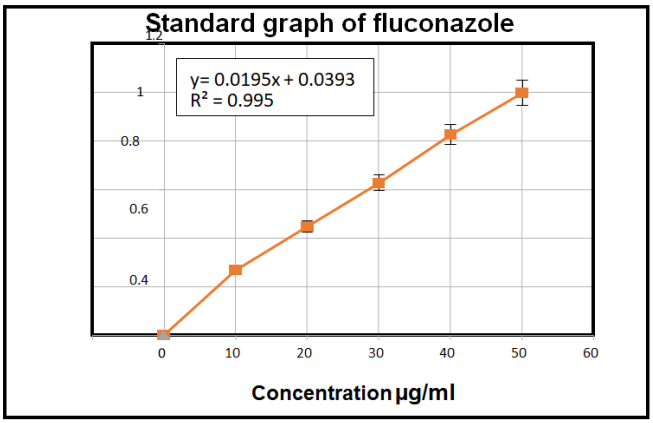

Fig. 3: Standard graph of fluconazole

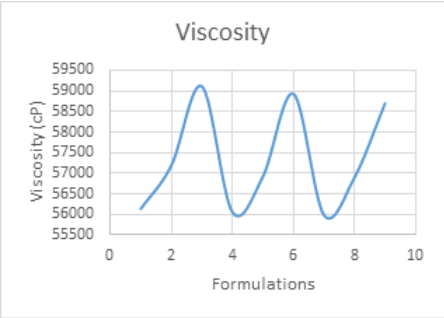

Fig. 4: Viscosity of formulation (F1-F9)

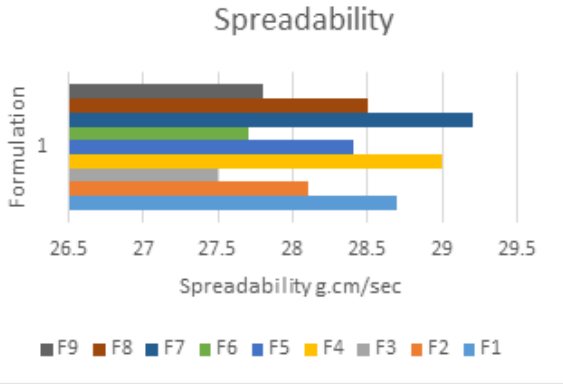

Fig. 5: Spreadability of formulation (F1-F9)

Table 4: Observed peak of FLZ and physical mixture with FLZ

S. No	*FLZ*	*Functional groups*	*FLZ+ Metal colloid + Physical mixture*
1	3424.38, 3119.57, 2793.22	O--H stretching	3219.57, 3112.44, 2915.78
2	2793.22	C ----H stretching	2850.22
3	1916.77	C---H Bending aromatic compound.	1915.35
4	1620.35	C = N Stretching	1683.06
5	1503.49	N – O Stretching	1520.59
6	1343.88,1274.05	C-F Stretching	1282.60, 1135.81
7	967.65	C-H triazole ring	960.52

Table 5: Absorbance of FLZ at 260 nm

Concentration µg/mL	*Absorbance at 260 nm (mean ± SD, n = 3)*
0	0
10	0.268 ± 0.012
20	0.448 ± 0.013
30	0.627 ± 0.002
40	0.825 ± 0.01
50	0.997 ± 0.003

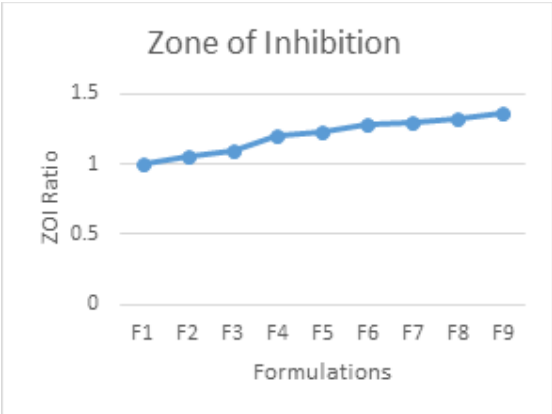

Fig. 6: Zone of inhibition of formulation (F1-F9)

the dispersed globules were red, while the background remained colorless. It indicated that the cream is of the oil-in-water (o/w) type.

Zone of inhibition

The zone of inhibition (ZOI) is a critical metric to measure the effectiveness of antifungal agents by quantifying the area where fungal growth is inhibited around a drug-soaked well. The ZOI of formulations compared with that of standard drugs was noticed as shown in Fig. 6.

3^2 Full-Factorial Design Model Assessment

The optimization of fluconazole cream was carried out through a comprehensive 3-level factorial design, incorporating two key factors—silver metal colloid (A) and stearic acid (B). The experiment focused on three critical responses: viscosity (Y1), spreadability (Y2), and ZOI (Zone of Inhibition) ratio (Y3). The values corresponding to the levels and responses were meticulously documented in Table 7, providing a detailed insight into the experimental outcomes.

Contour plots and response surface plots

Contour plots were generated to illustrate the relationships between variables A and B at constant levels of -1, 0, and 1. The use of two-dimensional contour plots facilitated the elucidation of the connections between independent and dependent variables (Fig. 7). Response surface plots were employed as valuable tools to gain insights into the primary and interactive influences of the independent variables (Fig. 8).

The complex mathematical equations for viscosity, spreadability, and zone of Inhibition ratio were derived through experimental data analysis. The viscosity (Y1) was expressed as a function of A and B with coefficients determined as 56978.22- 141.50 *+1439.00 * B-65.50 * A * B+34.1 * A2 +483.67 * B2-13.50 * A2 * B. Similarly, the spreadability (Y2) and zone of inhibition ratio (Y3) were determined by equations incorporating A and B, with respective coefficients as 28.38 +0.20 * A -0.65 * B-0.050 * A * B -0.067 * A2 -0.017 * B2 and 1.23+0.14 * A +0.035* B -7.500E-003* A * B -0.050* A2 +0.010* B2 +7.500E-003* A2 * B +7.500E- 003 * A * B2, respectively.

In Fig. 8, a response surface plot depicts the impact of varying metal colloidal and stearic acid quantities in fluconazole cream on viscosity, spreadability, and the zone of inhibition ratio. Meanwhile, Fig. 9 illustrates the utilization of an overlay plot for the optimization of fluconazole cream formulation. This optimization aimed to meet prescribed criteria, ensuring viscosity fell within the 55,000 to 65,000 cps range, spreadability ranged from 25 to 30 gm.cm/sec, and the zone of inhibition maintained a ratio between 1:1.3 and 1:1.5 (Table 8)

Evaluation of optimized formulation

The prepared batches are thoroughly evaluated for appearance, color, odor, consistency, pH, viscosity, spreadability, and drug content. These evaluations ensure that the formulations meet the standards, addressing sensory aspects, uniformity, pH balance, physical characteristics, and drug concentration. The results of the evaluation are as shown in Table 9.

Diffusion study of optimized formulation

The investigation involved a diffusion study of optimized fluconazole formulations. The findings were systematically recorded in cumulative percentage drug release depicted in the graph below (Fig. 10). Simultaneously, a drug release kinetic study was conducted for the refined formulations, with detailed results presented in Table 10 and Fig. 11.

Higuchi model was found to be best suited with an R2 value of 0.9829, which indicates that the drug molecules move passively through the cream matrix from regions of higher concentration to regions of lower concentration based on the drug release kinetic study.

Table 6: Drug content of batches F1-F9

Formulation	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
Drug content (%)	95.5 ± 0.03	95 ± 0.02	96.2 ± 0.01	95 ± 0.01	96.1 ± 0.02	97 ± 0.02	96.5 ± 0.018	97.5 ± 0.027	98 ± 0.012

Table 7: 3^2 Full-factorial design

Run	*Factor-1 metal colloid %*	*Factor-2 stearic acid %*	*Response 1 viscosity cP*	*Response 2 spreadability g.cm/sec*	*Response 3 ZOI ratio*
1	0	0	56132	28.7	1
2	0	5	57183	28.1	1.05
3	0	10	59114	27.5	1.1
4	5	0	56052	29	1.21
5	5	5	56920	28.4	1.23
6	5	10	58930	27.7	1.28
7	10	0	55980	29.2	1.3
8	10	5	56900	28.5	1.32
9	10	10	58700	27.8	1.37

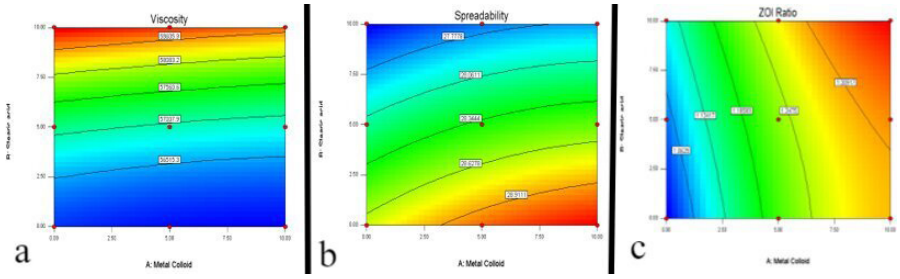

Fig. 7: Contour plot showing the impact of factors percentage of silver metal colloid (A) and percentage of stearic acid (B) over responses a. Viscosity (Y1), b. Spreadability (Y2) and c. Zone of Inhibition Ratio (Y2)

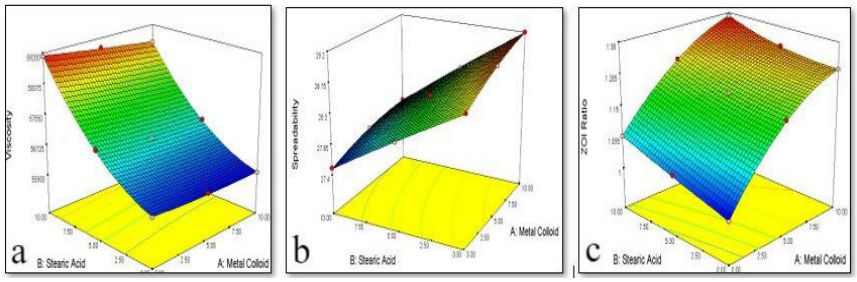

Fig. 8: Three-dimensional response surface plot depicting the impact of factors percentage of silver metal colloid (A) and percentage of stearic acid (B) over responses a. Viscosity (Y1), b. Spreadability (Y2) and c. Zone of Inhibition Ratio (Y2)

Skin irritation study

The skin irritation study was conducted in accordance with ethical committee guidelines and suggestions. The optimized cream formulation exhibited no indications of erythema or edema when topically applied to the animal's skin during the study period. Optimized formulation and standard formulations were deemed safe as they did not induce skin redness and received a score of 0. The observed outcomes affirm the outstanding dermatological safety and tolerance of the examined formulation, thereby substantiating its viability for subsequent investigation and advancement in clinical trials (Fig. 12).

In the present investigation, a cream formulation was meticulously developed by combining beeswax, stearic

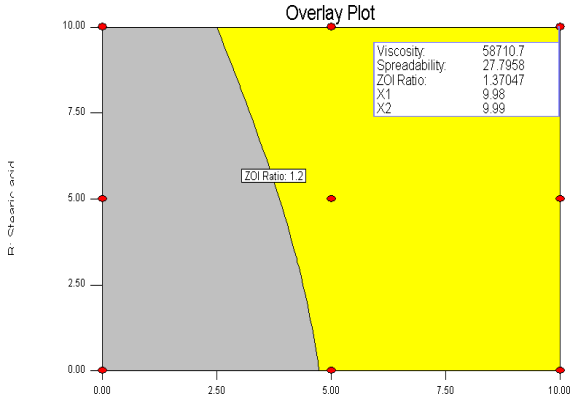

Fig. 9: Overlay plot for optimization of fluconazole cream

Table 8: Predicted solution of the optimized formula

Factor-1 metal colloid %	*Factor-2 stearic acid %*	*Response 1: viscosity cP*	*Response 2: Spreadability g.cm/sec*	*Response 3 ZOI Ratio*
9.98	9.99	58710.7	27.79	1.37

Table 9: Evaluation of optimized formulation

Parameters evaluated for an optimized batch	*Results*
Appearance	Smooth
Color	Dull white
Homogeneity	Homogeneous
pH	6.5 ± 0.46
Viscosity (cP)	56657.82 ± 48.32
Spreadability (gm.cm/sec)	27.58 ± 0.50
Drug content	96.1 ± 0.32
ZOI ratio	1.41

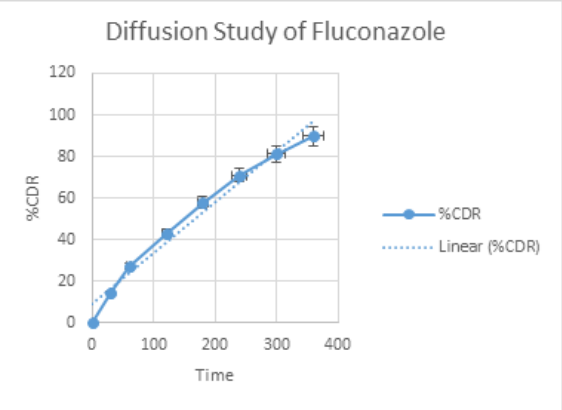

Fig. 10 : Diffusion study of optimized fluconazole

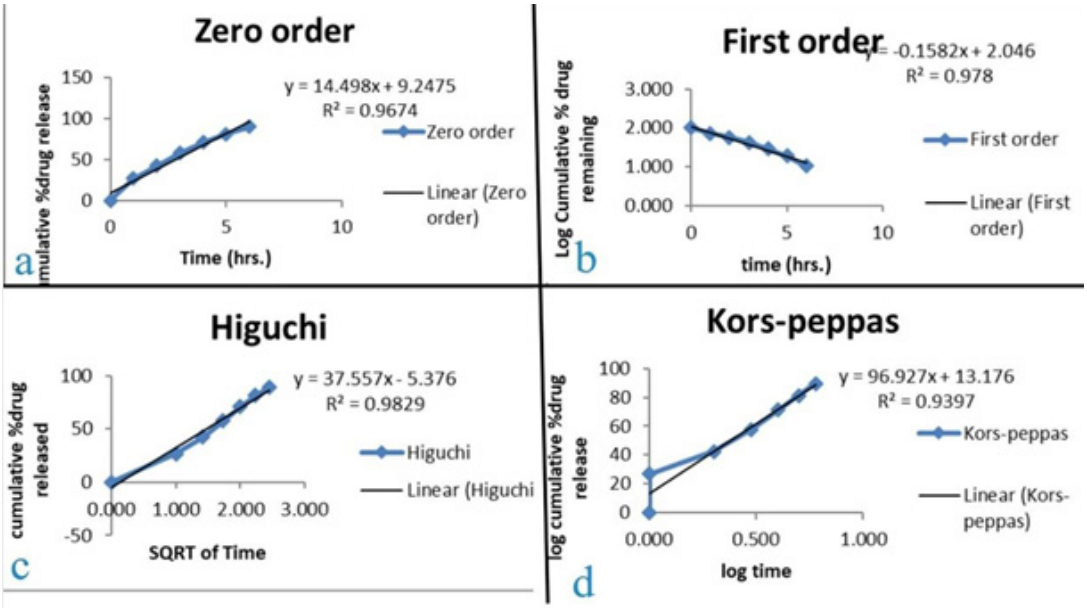

Fig. 11: Drug release kinetic study for fluconazole

Table 10: Drug release kinetic study of fluconazole

Time (Hr)	*Cumulative % drug released*	*%Drug remaining*	*Square root time*	*Log cum. %drug remaining*	*Log time*	*Log cum. % drug released*	*%Drug released*	*Cube root of %drug remaining (Wt)*
0	0	100	0.000	2.000	0.000	0.000	100	4.642
1	26.92	73.08	1.000	1.864	0.000	1.430	26.92	4.181
2	42.6	57.4	1.414	1.759	0.301	1.629	15.68	3.857
3	57.76	42.24	1.732	1.626	0.477	1.762	15.16	3.483
4	71.06	28.94	2.000	1.461	0.602	1.852	13.3	3.070
5	81.21	18.79	2.236	1.274	0.699	1.910	10.15	2.659
6	89.63	10.37	2.449	1.016	0.778	1.952	8.42	2.181

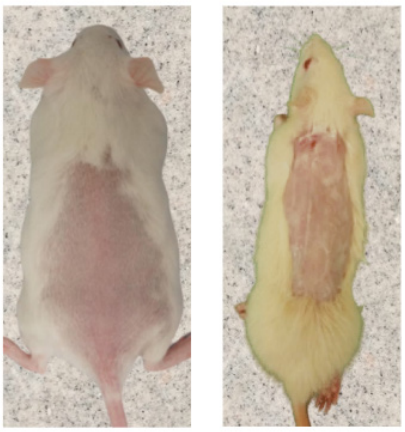

Fig. 12: Skin irritation study

acid, cetostearyl alcohol, Carbopol 934P, methyl paraben, propyl paraben, triethanolamine, and distilled water. The experimentation involved nine distinct formulations, with variations in the proportions of silver metal colloid (A) and stearic acid (B) at 0, 5, and 10%, respectively. To ensure the compatibility of the drug and excipients, a pre-formulation assessment was undertaken using FTIR analysis, which revealed no discernible interactions.

The comprehensive evaluation encompassing viscosity studies, spreadability tests, drug content analysis, drug diffusion studies, antifungal assessments, and irritation evaluations yielded consistently favorable outcomes. The culmination of these investigations identified an optimal batch formulation, featuring fluconazole enriched with silver metal colloid. This formulation demonstrated a pH of 6.5 ± 0.46, viscosity (cP) of 56657.82 ± 48.32, spreadability (gm.cm/sec) of 27.58 ± 0.50, drug content of 96.1 ± 0.32, and a zone of inhibition (ZOI) ratio of 1.41.

Significantly, the amalgamation of fluconazole with silver metal colloid exhibited heightened efficacy in comparison to the use of the allopathic drug alone during individual testing against *Candida albicans*. This observation suggests that the synergy between the drug and metal colloid holds promise for augmenting antifungal therapy, addressing challenges associated with conventional antifungal treatments. The enhanced performance observed prompts further inquiry into the potential topical application of this combination for treating fungal diseases.

In conclusion, the meticulous formulation, thorough characterization, and promising efficacy observed in this study underscore the potential of the fluconazole-silver metal colloid combination as a viable strategy for advancing antifungal therapies. Further investigations are warranted to explore the applicability and nuances of this combination in topical treatments for fungal diseases.

Acknowledgments

The authors express their gratitude to VIVA Institute of Pharmacy, Virar (E), Maharashtra, India, for their generous provision of materials, equipment, and invaluable infrastructure support for conducting this research, and to RK University, Rajkot, Gujarat, India, for providing the plagiarism report.

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HOW TO CITE THIS ARTICLE: Pandey S, Mehta D. Comparative Antifungal Study of Fluconazole and Fluconazole Enhanced with Silver Metal Colloid Creams: A 3^2 Factorial Design Optimization Approach. Int. J. Pharm. Sci. Drug Res. 2024;16(1):76-85. **DOI:** 10.25004/IJPSDR.2024.160111