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FORMULATION AND EVALUATION OF A BIFONAZOLE-LOADED CHITOSAN-HONEY INVASOMAL HYDROGEL FOR ENHANCED TOPICAL ANTIFUNGAL ACTIVITY

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ABSTRACT
Background: To develop a novel bifonazole-loaded chitosan-honey invasomal hydrogel to improve the drug's topical antifungal efficacy. In this formulation, invasomal vesicles, composed of phospholipids, ethanol, and terpenes, were utilized to enhance the penetration of bifonazole through the skin. **Methodology:** These invasomal carriers were incorporated into a chitosan-based hydrogel matrix, which provided structural stability and bioadhesive properties, allowing for better retention on the skin. Additionally, natural honey, known for its antibacterial and wound-healing properties, was included to enhance the therapeutic benefits of the hydrogel. **Results & Discussion:** Invasomes were prepared using soya phosphatidylcholine, ethanol (30% v/v), and d-limonene (0.5%) and then incorporated into a chitosan-honey gel matrix. Among the six formulations (IF1–IF6), IF5 showed optimal results, with 93.32% drug release over 12 hours, a viscosity of 6545 ± 26 cps, a pH of 6.85, and antifungal inhibition zones of 17 mm (*Candida albicans*) and 11 mm (*A. flavus*). The formulation was characterized in terms of its physical properties, including viscosity, gel strength, and spreadability, and evaluated for its drug entrapment efficiency, in vitro drug release profile, and ex vivo skin permeation. This study demonstrates a synergistic system enhancing skin permeation, drug retention, and antifungal efficacy. **Conclusion:** This formulation represents a promising alternative for the effective and patient-friendly treatment of superficial fungal infections, offering improved drug delivery, enhanced therapeutic efficacy, and a reduced dosing frequency.

INTRODUCTION

Superficial fungal infections of the skin, including dermatophytosis, candidiasis, and tinea infections, are common dermatological conditions that affect millions worldwide. These infections not only cause discomfort but can also lead to chronic recurrence if not treated effectively [1]. Because they can be applied directly to the infection site, topical antifungal medications remain the gold standard for therapy. This reduces the risk of systemic adverse effects [2]. Among them, the imidazole derivative bifonazole has garnered considerable interest due to its antifungal properties against a wide range of yeasts, molds, and dermatophytes [3]. However, bifonazole's

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therapeutic efficiency is limited by its poor aq. solubility & limited penetration through stratum corneum, which is the skin's main barrier to drug delivery [4]. To address these limitations, researchers are increasingly turning to novel drug delivery systems that enhance drug permeation, retention, and bioavailability.

Hydrogels, which are networks of three-dimensional hydrophilic polymers that can absorb huge volumes of water or biological fluids, are one such approach. Hydrogels have gained widespread interest for topical drug delivery due to their moisturizing properties, skin compatibility, and sustained drug release capabilities [5]. Chitosan, a naturally derived polysaccharide obtained from the deacetylation of chitin, exhibits biodegradable, biocompatible, and antimicrobial properties, making it an ideal polymer for hydrogel formation [6]. Chitosan has also demonstrated the ability to promote wound healing by supporting cell adhesion and proliferation, further enhancing its applicability in skin-related therapies. When used in hydrogel systems, it can improve drug localization and prolong release, thereby enhancing therapeutic efficacy [7]. Furthermore, honey's anti-inflammatory, antimicrobial, and wound-healing characteristics have made it a staple in traditional medicine for generations [8]. Modern studies confirm that honey not only creates a protective barrier over wounds but also promotes wound healing through granulation and epithelialization. Incorporating honey into hydrogels can offer dual benefits as a natural preservative & as a healing enhancer while providing a moist environment that supports skin recovery [9]. To further improve skin penetration, invasomes have emerged as a promising vesicular system in topical drug delivery. Invasomes are lipid-based carriers that are enhanced for skin penetration by the addition of ethanol and terpenes. Due to their increased fluidity and deformability, invasomes can transport medications more efficiently and penetrate deeper into the epidermal layers than regular liposomes. The incorporation of bifonazole into an invasomal gel system can potentially overcome the limitations posed by the stratum corneum, allowing for better drug distribution and absorption [10]. The combination of these three powerful components, bifonazole as the active antifungal agent, chitosan-honey hydrogel as a biocompatible matrix, and invasomes as advanced carriers, represents a novel, synergistic approach to topical antifungal therapy [11]. By integrating these technologies, this study aims to develop a bifonazole-loaded chitosan-honey invasomal hydrogel and evaluate its physicochemical characteristics, drug release profile, skin permeation capacity, and antifungal efficacy. The successful formulation of such a system could significantly improve the management of superficial fungal infections and reduce the risk of recurrence through sustained and targeted drug delivery. The synergistic interaction arises as chitosan forms a bioadhesive matrix, enabling sustained release, while honey enhances wound healing and provides intrinsic antimicrobial activity. Invasomes facilitate deep skin penetration of bifonazole, thereby maximizing therapeutic efficacy. Despite the efficacy of bifonazole, its limited solubility and poor skin permeation hinder therapeutic outcomes. Chitosan offers mucoadhesive and antimicrobial benefits, while honey contributes to wound healing and antimicrobial action. Invasomes, lipid-based vesicles enhanced with ethanol and terpenes, further improve transdermal delivery. Therefore, this study aims to design a bifonazole-loaded chitosan-honey invasomal hydrogel for improved topical antifungal delivery. The novelty of this study lies in the integration of three components: bifonazole, invasomes, and a chitosan-honey hydrogel into a single delivery system offering controlled release, enhanced permeation, and superior antifungal activity compared to conventional gels.

MATERIAL AND METHODS

Material

The drug manufacturer, Glenmark Pharmaceuticals Ltd., based in Mumbai, India, provided a free sample of bifonazole. Sigma-Aldrich of St. Louis, MO, USA, supplied the chitosan, which had a medium molecular weight and an 85% degree of deacetylation. The honey was sourced from Dabur India Ltd. in Uttarakhand, India, and is known for its antibacterial and therapeutic capabilities. The analytical quality of ethanol and soya phosphatidylcholine is utilized in invasome synthesis.

Methods

Formulation of Bifonazole-Loaded Invasomes

A mechanical dispersion approach was used to load 10 mg of bifonazole into invasomes. Vortexing was used to dissolve soya phosphatidylcholine in ethanol. The terpenes and medication were incorporated into the mixture by vortexing it first, followed by five minutes of sonication. The final invasomal preparation was achieved by adding a fine stream of phosphate-buffered saline while continuously vortexing the mixture for an extra five minutes. Invasomes were prepared using soya phosphatidyl-choline, ethanol (30% v/v) & d-limonene (0.5%). The hydration

temp. was maintained at 40°C with stirring at 1000 rpm for 30 min [12].

Formulation of Bifonazole loaded invasomal chitosan and honey hydrogel

The cold mechanical approach was used to generate several formulations of invasomal hydrogel loaded with bifonazole. The hydrogel, chitosan, and polyacrylic acid polymer (Carbopol 934) were prepared by dissolving a definite amount of the polymer in distilled water while stirring constantly with a magnetic stirrer for 1 hour, or until the polymer had absorbed all the water. The pH of the hydrogel was maintained by adding TEA while stirring continuously to neutralize the carbopol. After that, the preservative methyl paraben was added in the appropriate amount, and the mixture was allowed to sit for 24 hours to allow the polymer to fully expand and settle. Lastly, Bifonazole-loaded invasomes were added to the mixture at varying concentrations, and the mixture was stirred continuously until the invasomes and honey were completely dissolved in the hydrogel.

The ultimate weight was brought to 100 g using the water solution. To finish the development of the hydrogel, the finished formulations were packed into wide-mouth glass containers and closed with screw-top plastic lids. The containers were then stored in the refrigerator. Hydrogels were prepared using the cold mechanical approach, wherein chitosan and Carbopol 934 were stirred at 1000 rpm for 1 hour at room temperature (25 ± 2°C). The invasomal dispersion was added and homogenized at 500 rpm for 30 minutes [13].

Table 1: Different Bifonazole invasomal gel batches

Composition	IF1	IF 2	IF 3	IF 4	IF 5	IF 6
Invasomes eq to%	1	1	1	1	1	1
Carbopol 934 (%)	1.0	1.5	2.0	2.5	3.0	3.5
Chitosan (%)	0.5	1.0	1.5	0.5	1.0	1.5
Honey (%)	-	-	-	0.25	0.5	1.0
Methyl paraben%	0.02	0.02	0.02	0.02	0.02	0.02
Triethanolamine%	0.2	0.2	0.2	0.2	0.2	0.2
Dist. H_2O ml (Qs)	100	100	100	100	100	100

Evaluation of Bifonazole-loaded Invasomes gels

Physiochemical properties

The gel's organoleptic properties, occlusion, washability, and overall appearance were assessed by visual inspection. Using a pH meter, the pH of the Bifonazole invasomal gel was tested three times to ensure precision. The average pH value was then calculated [14].

Grittiness and Homogeneity

To determine the texture of the invasomal gel, a small amount was squeezed between the thumb and index finger. To determine the thickness of the gel, we felt for any coarse material on our fingertips. To ensure the gel was homogeneous, a small amount was placed on the back of the hand, and its uniformity was examined [15].

Spreadability

Two glass slides, each measuring 6×2 inches, were selected. To evaluate the gel formulation's spreadability, one slide was coated with it. The two slides were arranged such that they stretched 6 cm along the slide, and the formulation was sandwiched between them. By evenly pressing 100 grammes of weight onto the upper slide, the gel mixture between the two slides was thinned out to form a layer. Once the weight was removed, the excess gel formulation that had adhered to the slides was carefully scraped off. Twenty grams of weight were fastened to the string after a basic pulley had been used to fasten the lower slide to the apparatus board. The upper slide had been fastened to the board using a string. With the weight applied, the upper slide was timed to travel 6 cm and separate from the bottom slide.

For each gel formulation, we ran the experiment again and averaged the results of six of these analyses [10].

$$\boldsymbol{Spreadability}\ (\boldsymbol{gcm/sec}) = \frac{\boldsymbol{m.l}}{\boldsymbol{t}}$$

Where, m = weight tied to the upper slide (20 grams), **t** = time taken (seconds), **l** = length of glass slide (6cms).

Content uniformity analysis

To ensure homogeneity of Bifonazole in the invasomal gel, 0.5 g samples were collected from three different sections of the gel. Ten milliliters of methanol were used to extract each sample, which was subsequently spun at 3,000 revolutions per minute for 15 minutes. A UV-visible spectrophotometer operating at 256 nm was used to evaluate the Bifonazole content after filtering the supernatant.

Viscosity

At 37°C, using spindle No. 7, the invasomal gel's viscosity was measured using a Brookfield viscometer. After measuring the gel's viscosity, a spatula was used to apply an appropriate amount of gel to the center of the viscometer plate, just under the spindle [16].

pH Determination

pH of formulation was resolved by a pH meter [10]

***In-vitro* drug release**

A study on the in vitro release of drugs was conducted using a Franz diffusion cell. Its effective permeability area is 0.196 cm^2, and its receiver cell capacity is 10 ml. On top of the receptor cell, which was filled with phosphate-buffered saline (pH 7.4), was placed the invasomal gel-containing donor cell. A pre-treated dialysis membrane with a molecular weight cutoff of 12–14 kD was clamped between the donor and receptor compartments. For the duration of the experiment, a temperature of 37 ± 1°C and a constant magnetic stirring speed of 600 rpm were maintained. At1,2,3,4,5,6,8, and 12 hours, samples were obtained from the receptor cell to be analyzed for Bifonazole content using a UV spectrophotometer. To keep the receptor compartment under sink conditions, a new release medium was supplied at each time point [17]. The invasomal gel's release kinetics were examined using suitable release data for several kinetic models:

- **Higuchi's Model**: Cumulative percentage drug released vs. the square root of time
- **Zero Order Kinetics**: Cumulative percentage drug release vs. time
- **First Order Kinetics**: Log cumulative percentage drug remaining vs. time
- **Korsmeyer-Peppas Model**: Log cumulative percentage drug release vs. log time

In vitro antifungal study of Bifonazole loaded invasomal hydrogel

This study used three different concentrations of invasomal hydrogel (10, 20, and 30 µg/ml) against *Aspergillus flavus* and *Candida albicans*. Invasomal gel and hydrogel in various concentrations were poured into the perforations (50µl in each well). Used as a control: distilled water. Then, after 48 hours of incubation at 28°C, the Petri plates were checked for distinct inhibition zones surrounding the well. The average diameter of zones of inhibition produced around the well was measured in millimeters (mm) [18].

Stability Study

The optimized formulation of Bifonazole invasomal hydrogel (IF5) was subjected to accelerated stability studies to assess its physicochemical stability over time. The formulation was stored at two different conditions, 4 ± 0.5 °C and 28 ± 0.5 °C, in screw-capped, amber-colored glass bottles to protect from light exposure. Samples were withdrawn at predetermined intervals of 0, 15, 30, 60, and 90 days for analysis. The drug content was determined spectrophotometrically to indirectly estimate the amount of Bifonazole retained within the gel matrix, reflecting its chemical stability. Additionally, viscosity measurements were performed using a Brookfield viscometer to assess any changes in the rheological properties of the hydrogel over time, which indicates physical stability. These parameters were evaluated to regulate the effect of storage temperature on overall stability & shelf-life of formulation [19].

RESULTS AND DISCUSSION

Results

The developed bifonazole-loaded chitosan-honey invasomal hydrogels (IF1–IF6) were evaluated for various physicochemical and biological parameters to identify the optimal formulation.

Drug Content and Viscosity

As shown in Table 2, all formulations exhibited high drug assay values, indicating uniform distribution of the drug. Among them, IF5 displayed the highest drug content (99.45 ± 0.25%) and suitable viscosity (6545 ± 26 cps), balancing spreadability and structural integrity.

Table 2: Evaluation of drug content & viscosity of bifonazole loaded chitosan-honey hydrogel formulations (IF1–IF6)

Formulation	% Assay	Viscosity (Cps)
IF1	97.45 ± 0.12	6950 ± 15
IF2	96.65 ± 0.32	6875 ± 20
IF3	95.45 ± 0.45	6812 ± 23
IF4	98.78 ± 0.36	6645 ± 24
IF5	99.45 ± 0.25	6545 ± 26
IF6	98.12 ± 0.32	6485 ± 25

pH, Spreadability, and Extrudability

Formulations maintained a skin-compatible pH range (6.45–6.95). IF5 demonstrated appropriate spreadability (8.45 ± 0.25 gm·cm/sec) & extrudability (195 ± 6 g), as indicated in Table 3.

In Vitro Drug Release

The in vitro release profile of IF5 exhibited a sustained drug release up to 12 hours, reaching 93.32% release (Table 4). This slow & controlled release is suitable for prolonged antifungal therapy Figure 1.

Table 3: Spreadability and Extrudability

Code	pH	Spreadability (gm.cm/sec.)	Extrudability (g)
IF1	6.89 ± 0.32	12.25 ± 0.15	185 ± 53
IF2	6.95 ± 0.25	10.65 ± 0.32	192 ± 7
IF3	6.72 ± 0.15	9.85 ± 0.14	190 ± 4
IF4	6.45 ± 0.33	10.10 ± 0.33	185 ± 9
IF5	6.85 ± 0.41	8.45 ± 0.25	195 ± 6
IF6	6.74 ± 0.38	7.65 ± 0.12	175 ± 5

Table 4: Cumulative drug release of optimized formulation (IF5) over 12 hours

Time(h)	√Time(h)	Log Time	Cumulative % Drug Release (Mean ± SD)	Log Cum. % Drug Release	Cum. % Drug Remaining	Log Cum. % Drug Remaining
0.5	0.707	-0.301	18.85 ± 0.45	1.275	81.15	1.909
1	1.000	0.000	32.25 ± 0.52	1.509	67.75	1.831
2	1.414	0.301	43.32 ± 0.47	1.637	56.68	1.753
3	1.732	0.477	51.12 ± 0.39	1.709	48.88	1.689
4	2.000	0.602	59.98 ± 0.43	1.778	40.02	1.602
6	2.449	0.778	68.85 ± 0.42	1.838	31.15	1.493
8	2.828	0.903	76.65 ± 0.48	1.885	23.35	1.368
10	3.162	1.000	88.85 ± 0.53	1.949	11.15	1.047
12	3.464	1.079	93.32 ± 0.41	1.970	6.68	0.825

Note: All data expressed as Mean ± Standard Deviation (n = 3)

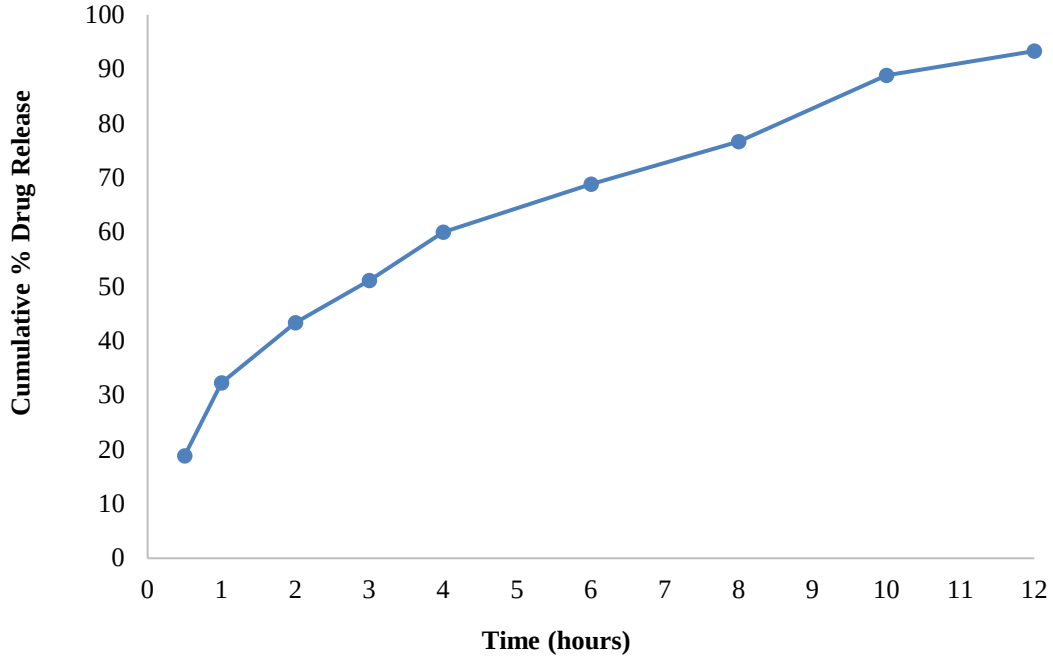

Figure 1: In vitro cumulative drug release profile of bifonazole-loaded invasomal hydrogel (IF5) over 12 hours. Data are expressed as Mean ± Standard Deviation (n = 3)

Drug Release Kinetics

Regression analysis (Table 5) revealed that the drug release followed Higuchi's model ($R^2 = 0.9915$), indicating a diffusion-controlled release mechanism. The Korsmeyer-Peppas model ($R^2 = 0.9861$) supported this finding with an anomalous transport mechanism. The n-value (0.67) for the Korsmeyer–Peppas model indicates non-Fickian (anomalous) diffusion, suggesting that drug release was governed by both diffusion and polymer relaxation.

Antifungal Activity

Antifungal testing (Table 6) demonstrated significantly enhanced activity of IF5 compared to plain bifonazole. At 30 µg/ml, the optimized formulation achieved a 17 mm zone of

inhibition against Candida albicans and an 11 mm zone against *Aspergillus flavus* (Figure 2).

Table 5: Release Kinetic Models for IF5

Model	R^2
Zero Order	0.9374
First Order	0.9752
Higuchi's Model	0.9915
Korsmeyer-Peppas Model	0.9861

Stability Study

The stability of IF5 over 90 days under different temperatures is detailed in Table 7. Refrigerated samples retained better drug content (98.95%) and viscosity (6420 cps) compared to those stored at room temperature (97.15% and 6310 cps). Stability studies were conducted in accordance with ICH guidelines at 25 ± 2°C / 60% RH and 40 ± 2°C / 75% RH for a period of 90 days. Results indicate that IF5 remained stable, with only minor variations in drug content and viscosity.

Table 6: Antifungal Activity

Fungus	Bifonazole 30 µg/mL (Zone in mm)	IF5 Formulation 30 µg/mL (Zone in mm)
Candida albicans	15.00 ± 0.40	17.00 ± 0.15
Aspergillus flavus	9.00 ± 0.35	11.00 ± 0.20

Note: Zones of inhibition are reported as Mean ± Standard Deviation (n = 3)

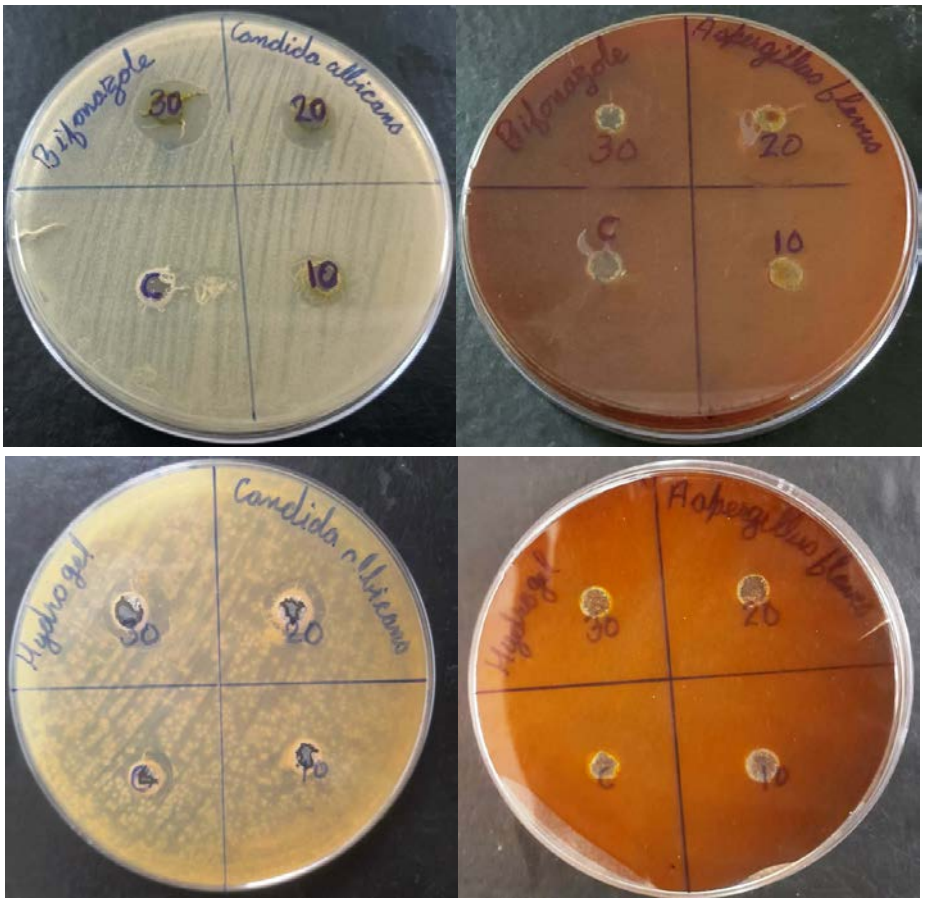

Figure 2: ***Antifungal activity of bifonazole-loaded invasomal hydrogel (IF5) and plain bifonazole at 30 µg/mL against Candida albicans and*** **Aspergillus flavus*. Results represent Mean ± SD (n=3). Error bars indicate standard deviation.**

Table 7: Stability Study for IF5

Day	Drug Content (%) @ 4°C	Drug Content (%) @ 28°C	Viscosity (cps) @ 4°C	Viscosity (cps) @ 28°C
0	99.45 ± 0.25	99.45 ± 0.25	6545 ± 26	6545 ± 26
90	98.95 ± 0.20	97.15 ± 0.25	6420 ± 13	6310 ± 13

DISCUSSION

The formulation of a bifonazole-loaded chitosan-honey invasomal hydrogel, with IF5 emerging as the optimal composition, was strategically designed to enhance topical antifungal therapy by improving drug permeation, bioadhesion, and sustained therapeutic presence at the site of infection. The study outcomes collectively reinforce the scientific rationale behind this multifaceted delivery system. The assay results (Table 2) revealed that all hydrogel formulations exhibited satisfactory drug content, with IF5 achieving the highest assay value (99.45 ± 0.25%), indicating excellent drug encapsulation and uniform distribution within the matrix. This consistency is critical for ensuring reliable therapeutic efficacy across applications.

The viscosity of IF5 (6545 ± 26 cps), although slightly lower than that of IF1 to IF3, remained within the optimal range for topical formulations. The moderate viscosity enhances spreadability without compromising gel structure, contributing to patient comfort, ease of application, and better coverage over the skin surface. The addition of honey not only improved the hydrogel's physical appearance and handling characteristics but also contributed biologically beneficial properties, including antimicrobial and wound-healing effects. Honey, known for its humectant capacity, helps maintain a moist environment, which can promote epithelial regeneration and reduce skin irritation. Moreover, its natural antibacterial and antifungal components, such as hydrogen peroxide and phenolic acids, may work synergistically with bifonazole, thereby enhancing the formulation's overall antimicrobial activity.

The viscosity range of 6400–6950 cps provides a balance between structural integrity and ease of application. It allows for sufficient skin adherence without being too stiff, ensuring proper spreading and patient compliance. The measured pH values of all hydrogel formulations ranged from 6.45 to 6.95 (Table 3), indicating good dermal compatibility. This minimizes the risk of skin irritation or barrier disruption upon topical application. The spreadability of IF5 (8.45 ± 0.25 gm.cm/sec.) was optimal for smooth application, while the extrudability (195 ± 6 g) ensured that the gel could be conveniently dispensed from containers without requiring excessive force. Together, these parameters indicate a user-friendly and cosmetically appealing formulation. A negative Pearson's correlation ($R^2 = 0.96$) was observed between honey concentration and spreadability, suggesting that increasing honey content reduces gel flow due to increased viscosity and crosslinking. The in vitro release profile of IF5 (Table 4) showed a sustained release of bifonazole for up to 12 hours, with approximately 93.32% cumulative drug release, indicating that the hydrogel can maintain therapeutic concentrations over an extended period. This sustained behavior is crucial for enhancing treatment adherence by reducing the need for frequent reapplication.

Kinetic modeling of the release data (Table 5) indicated that the Higuchi model ($R^2 = 0.9915$) best fit the release profile, implying that the drug diffusion from the hydrogel matrix followed a square root time-dependent mechanism, typical of diffusion-controlled systems. Additionally, the Korsmeyer–Peppas model ($R^2 = 0.9861$) indicated anomalous (non-Fickian) transport, suggesting that both diffusion and matrix relaxation/swelling mechanisms contributed to drug release. This dual mechanism is beneficial for maintaining consistent drug levels over time. The high R^2 values for the Higuchi and Korsmeyer–Peppas models, along with $n = 0.67$, confirm that drug release follows a non-Fickian mechanism involving both diffusion and swelling-relaxation of the gel matrix, which is ideal for sustained delivery.

The antifungal activity assay results (Table 6) clearly demonstrated superior activity of the optimized invasomal hydrogel compared to pure bifonazole formulations. The zone of inhibition against *Candida albicans* reached 17 ± 0.15 mm at 30 µg/ml concentration in the IF5 gel, whereas the same concentration of plain bifonazole produced only 15 ± 0.40 mm inhibition. A similar trend was observed against *Aspergillus flavus*. This corresponded to a 13.3% increase in inhibition zone over pure bifonazole (15 mm) and a 22.2% increase for *A. flavus* (from 9 mm). Compared to plain bifonazole gel (15 mm and 9 mm zones), IF5 invasomal hydrogel exhibited significantly higher antifungal activity (17 mm and 11 mm zones), demonstrating improved drug availability at the infection site. These outcomes highlight the advantages of the invasomal system in improving drug penetration through the stratum corneum, resulting in increased local bioavailability and enhanced fungicidal activity. The honey may have potentiated the antifungal effect via its own antimicrobial components.

The stability data (Table 7) revealed that the IF5 formulation retained its drug content and viscosity better under refrigerated

conditions (4.0 ± 0.5°C) than when stored at 28 ± 0.5°C over 90 days. At 4°C, the drug content decreased minimally, from 99.45% to 98.95%, while the viscosity reduced slightly, from 6545 to 6420 cps. In contrast, samples stored at room temperature exhibited a more pronounced decline in both parameters. These results suggest that elevated temperatures may accelerate hydrogel degradation and drug instability, underscoring the importance of maintaining cool storage conditions to preserve formulation integrity over time. A previous study reported 78% bifonazole release in 8 hours using a multiple emulsion system, while the present invasomal gel showed 93.32% release in 12 hours, indicating superior control and efficiency.

CONCLUSION

The present study successfully formulated and evaluated a bifonazole-loaded chitosan-honey invasomal hydrogel intended for enhanced topical antifungal therapy. The combination of invasomal vesicles with a chitosan-honey hydrogel base yielded a stable, bioadhesive, and skin-compatible formulation, characterized by improved drug encapsulation, controlled release, and enhanced skin permeation. The sustained release profile and superior antifungal activity observed in the optimized formulation suggest that this delivery system effectively overcomes the limitations of conventional topical treatments, including poor drug solubility and limited skin penetration. The synergistic benefits of chitosan and honey further contribute to the formulation's antimicrobial efficacy and wound-healing potential. With its novel hydrogel formulation, topical administration of bifonazole shows great promise for treating a wide range of superficial fungal infections, as well as for enhancing patient compliance with treatment and achieving better therapeutic results. The optimized bifonazole invasomal hydrogel (IF5) exhibited 93.32% sustained drug release, enhanced antifungal activity (17 mm zone), and stability over 90 days. The synergistic use of chitosan, honey, and invasomes demonstrated promising potential for effective topical fungal therapy.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Shivaji M. Patil collected data and performed experiments. S. Bhargav conducted the analysis. Shivaji M. Patil wrote the first draft of the manuscript, and all authors reviewed and revised previous versions. All authors contributed to the study's conception and design and gave final approval.

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