Comparative Evaluation of Itraconazole Oleogel and Nanoemulgel Against Candida albicans: Influence of Excipients on Different parameters

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ABSTRACT
Background: Itraconazole (ITZ), a hydrophobic triazole antifungal drug, has poor solubility in water, and its topical efficacy depends on the formulation design and excipients used. Despite extensive studies involving individual Nanoemulgel (NEG) and Oleogel (OG) formulations containing ITZ, no systematic comparative study on the excipient-mediated performance characteristics of such formulations has been documented till date.
Objective: This research has conducted a comparison secondary analysis on already developed ITZ loaded NEG and OG formulations in order to examine the effects of formulation excipients on the physical-chemical properties, rheology, drug release, and antifungal properties against *C. albicans*.
Methods: Formulation data from the previously developed and characterised ITZ topical formulation system was used for comparative analysis. Important factors such as viscosity, drug loading, spreadability, adhesion property, drug release, drug kinetics, and antifungal activity were standardized and compared to understand the mechanistic effect of the excipient's structural arrangement. Surfactant-co-surfactant effects in NEG and lipid gelators' effects in OG were evaluated in regard to diffusion behavior.
Results: NEG showed superior dispersibility, greater spreadability, and more rapid diffusion of the drug as a result of the lowering effect of interfacial tension caused by tween 80 and PEG 400 that allowed for easy drug solubilization and drug delivery. OG systems were characterized by high viscosity, structural stability, and greater retention because of the formation of a three-dimensional structure of the drug from glyceryl monostearate (GMS) and Stearic acid (SA). Evaluation of the kinetics of release indicated that both formulations provided sustained release as per the diffusion-controlled mechanism but OG had a more sustained effect due to higher drug retention. The use of various excipients was shown to influence antifungal properties of the formulations; OG showed better antifungal properties against *C. albicans*.
Conclusion: The investigation indicates that the structure of excipients is a critical factor for dictating the efficacy of the topical ITZ systems. Although the NEG excipient system had better diffusion and spreadability, OG excipient system offered better retention and antifungal efficacy. These findings may help to understand the therapeutic effects of different formulations and contribute to designing effective topical antifungal formulations.
Keywords: Candida albicans, nanoemulgel, oleogel, release kinetics.
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1. INTRODUCTION

Fungal infections resulting from *C. albicans* continue to be a significant global problem, especially in immunocompromised and diabetic patients. Candidal infection is characterized by erythema, irritation, inflammation, pruritus, recurrences, and poor quality of life of the affected patient. Though various antifungals for topical administration have been reported, treatment of localized candidiasis still poses difficulty as a result of poor permeation of the drug into skin and poor bioavailability after topical application. Itraconazole (ITZ) is a broad-spectrum antifungal drug belonging to the triazole group of compounds that acts against *C. albicans* by interfering with ergosterol biosynthesis. The use of ITZ in topical formulations has been limited by its poor aqueous solubility, lipophilicity, low diffusion capability, and poor skin bioavailability. Such drawbacks have led to the synthesis of various lipid-based carriers as means to improve drug delivery of ITZ. Lipid-based topical carriers are receiving much attention in terms of enhancing dermal drug delivery while minimizing systemic exposure. Nanoemulsion (NE)-based carriers have been extensively used because of their small-sized droplets, high surface area, kinetic stability, and better capability of solubilizing hydrophobic drugs. When incorporated into gels, such NE carriers produce nanoemulgels (NEG) carriers with increased diffusion capability and good rheology (1,2).
The use of essential oils within NE systems could enhance the therapeutic efficacy due to their dual

functionality as a carrier for oil phase and as an agent enhancing the biological activity. Clove oil (CO), containing eugenol as one of its active components, demonstrates the potential of an antifungal, anti-inflammatory, antioxidant, and permeation enhancing agent. Therefore, the addition of CO in ITZ-loaded nanoformulations could increase synergistic antifungal activity, as well as facilitate drug dissolution and delivery through the skin. In addition, surfactants (e.g., Tween 80) and co-surfactants like polyethylene glycol 400 (PEG 400) provide interfacial stability, decrease droplets size, and enhance the drug penetration into tissues by increasing the interfacial area. Unlike NEGs, oleogels (OGs) are semi-solid lipidic systems formed by immobilization of liquid oils using oleogelators (e.g., Glyceryl monostearate (GMS) and Stearic acid (SA)). OGs have been considered a promising carrier due to their ability to retain moisture, higher adhesive capacity, longer skin retention and sustained drug release. The lipidic matrix, created with the use of oleogelators, creates a three- dimensional structure that limits the movement of molecules and affects the drug diffusion rate from a formulation matrix. Compared with surfactant-dominated NEG systems, OGs rely primarily on lipid matrix organization and viscosity-driven retention mechanisms to control drug release behaviour (3). Whereas there is potential shown by either NEG or OG systems regarding their capabilities to deliver topical antifungals, it appears that comparative studies analyzing the influence of the excipient structure on their performance have been scarce. Studies have mostly concentrated on formulations and not on comparative studies of excipients in relation to each other (1,2). Specifically, the role of surfactant-mediated diffusion of ITZ in NEGs as compared with lipid network retention of ITZ in OGs has never been comprehensively evaluated from an analytic comparative perspective (4).

Therefore, the current study seeks to conduct a comparative secondary analysis of previously developed ITZ-loaded NEG (2) and OG (1) formulations to explore the excipients' role and composition in modifying behavior of formulations against *C. albicans*. A comparative evaluation will be conducted based on the physicochemical characteristics, rheological properties, spreadability, kinetics of drug release and antifungal efficacy of formulations. It is important to focus on the mechanistic role played by the formulation excipients with respect to drug diffusion, retention, and sustained antifungal action.

2. MATERIALS AND METHODS

2.1 Source of Formulation Data

The current study was intended to be carried out as a comparative analysis of already prepared and characterized formulations of ITZ-loaded NEG and OG systems by the authors (1,2). The experimentation, formulation and optimization was carried out earlier in separate studies. This is not an example of repeated development of formulations, but it provides comparative analysis of formulations focusing more on their excipient-dependent physical-chemical behavior, drug-release profile, rheology, drug content uniformity, and antifungal activity against *C. albicans*. Formulations of NE, NEG, and OG systems loaded with ITZ were prepared and characterized as per the methods explained earlier (1,2), with an analytical re-evaluation of data. The earlier results have been collated into a single frame of comparative analysis.

2.2 Comparative Study Design

The comparative analysis was created to assess how variation in the excipients affected the performance of ITZ-loaded topical delivery systems. Parameters considered for comparison were based on pharmaceutical importance and related to the delivery of topical antifungal agents, including:

- Drug content
- Rheological behavior
- Spreadability and adhesiveness
- Drug release
- Release kinetic modeling
- Fungal activity against *Candida albicans*

To reduce variation in data interpretation and facilitate cross-formulation normalization, both formulations were compared using the same analytical standards (5).

2.3 Comparative Excipient Classification

Excipients employed in NEG and OG systems were classified based on their functional roles in order to determine mechanistic links between formulation composition and observed performance. Clove oil (CO) was used as the oil phase and penetration-enhancing component in the NEG system, while Tween 80 and PEG 400 were used as surfactants and co-surfactants, respectively, to improve diffusion and stabilize droplets. The gelling polymer that produced the semisolid consistency was carbopol 940. GMS and SA functioned as oleogelators in the OG system, creating a structured three-dimensional lipidic matrix that controlled drug entrapment, viscosity, and prolonged release behavior. Thus, the impact of lipid-network-mediated retention mechanisms in OG and surfactant-mediated diffusion mechanisms in NEG was the main focus of comparative interpretation (6).

2.4 Selection Criteria for Comparative Analysis

The following criteria were used to choose optimized formulations from the previously developed formulations for comparison analysis:

- physicochemical stability

- drug content uniformity
- Appropriate consistency of semisolid
- Reproducible release behavior
- Adequate antifungal performance

Standardized delivery performance comparisons between the two carrier systems were made possible by the use of optimal formulations.

3. COMPARISON OF DIFFERENT EVALUATION PARAMETERS

3.1. Organoleptic Characteristics and Physical Appearance

The impact of excipient architecture on formulation stability, homogeneity, and topical application was examined by comparing previously published physicochemical characterization data of the optimized ITZ-loaded OG and NEG formulations (1,2). Comparative evaluation involved organoleptic appearance, homogeneity, phase separation tendency, grittiness, drug loading, viscosity, spreadability, and adhesiveness. Attention was specifically focused on appreciating the function of formulation excipients in determining physical structure and stability of the formulations. In OG formulation, GMS and SA were comparatively analyzed to understand the effect of their involvement in developing the structure of three-dimensional lipid matrix that determines improved consistency, opacity, and immobilization of oil phase. On the other hand, NEG formulation was comparatively interpreted considering the contribution of surface active agents Tween 80 and PEG 400 towards stabilization of colloid dispersion in Carbopol gel matrix by reducing interfacial tension and stabilization of nanospheres. Comparative interpretation of drug load and homogeneity parameters helped understand the efficacy of formulation process towards incorporating and distributing the drug into the respective carriers. The effect of solubilizing drug using surfactants in NEG formulation and entrapping in lipid matrix in OG formulation on uniformity was comparatively studied.

3.2 Spreadability and Rheological Behavior

The impact of hydrated polymeric matrices and lipidic gelator networks on viscosity, spreadability, flow behavior, and retention tendency was further assessed using comparative rheological interpretation. These variables were examined to determine the connections between the formulations' topical performance attributes, structural organization, and excipient composition (7).

3.3. Drug Content Analysis

The comparative evaluation of the content of the drug was done using the assay data for the optimized formulations of NEG and OG as documented earlier (1,2). Comparative interpretation of the uniformity of drug content was done in order to analyze the effectiveness of incorporating the drug into the formulation system, as well as the compatibility of ITZ with the excipients used. Mechanistic comparison was also done to determine the effect of drug loading due to surfactant solubilization in NEG and lipid entrapment in OG.

3.4. *In vitro* Drug Release Behavior

In vitro drug release data obtained using Franz diffusion cell methodology in the original studies were comparatively reanalyzed to investigate differences in diffusion behavior between NEG and OG systems. Comparative release profiles were interpreted on the basis of excipient composition, viscosity, and structural organization of the formulations. To improve analytical interpretation, cumulative drug release patterns were comparatively evaluated over the study duration, and release behavior was interpreted in relation to surfactant-assisted diffusion in NEG and lipidic matrix-controlled diffusion in OG.

3.5. Release Kinetics and Mechanism

Drug release data from both gels were comparatively fitted to different kinetic models, including:

- Hixson-crowell
- First-order
- Higuchi
- Korsmeyer–Peppas

Comparative analysis of release kinetics was conducted to elucidate the dominant mechanism involved in the release of ITZ from different carrier systems. For the evaluation of diffusion-controlled release mechanism, the Higuchi model was employed, whereas for understanding the effect of matrix on drug release mechanism, the Korsmeyer–Peppas model was used (8).

3.6 Antifungal Activity Against *C. albicans*

Antifungal efficacy values reported in previous work against *C. albicans* have been comparatively analyzed with respect to the effect of excipients and their release properties on efficacy. Comparisons were carried out based on variations in antifungal efficacy, activity duration, and formulation retention property. Antifungal efficacy with regard to formulation viscosity and release rate were emphasized particularly during mechanism analysis, while the possible synergetic action of clove oil on antifungal efficacy was also taken into consideration.

3.7. Statistical Interpretation of Gel Performance

Comparative statistical analysis where appropriate was conducted by normalizing the formulation parameters to assess the differences between NEG and OG systems. Trends were observed among physicochemical parameters, active drug concentrations, and biological activities for the determination of excipient-related interactions that determine topical delivery performance.

4. RESULT AND DISCUSSION

4.1 Organoleptic Characteristics and Physical Appearance

Both the ITZ-loaded OG and NEG formulations showed satisfactory organoleptic qualities for their topical application. Both formulations looked homogeneous, smooth, and absence of visible phase separation and grittiness implied the successful encapsulation of the drug in its respective carriers. OG formulation looked opaque and had a highly structured semisolid structure, while NEG formulation was comparatively smoother and more hydrated gel-like structure. The variation in physical characteristics was mainly because of the structure of the excipients used. In the OG formulation, due to the presence of GMS and SA, there was the formation of a three-dimensional network in lipid form which gave structural stability and opacity. The highly structured lipid network was able to immobilize the oil phase of the formulation and minimize the problem of oil leakage and phase separation. On the other hand, the structure of the NEG formulation was based on colloid stabilizing effects.

Both formulations' lack of grittiness indicated effective drug assimilation and consistent ITZ distribution across the formulation matrix. These results show that the chosen excipients were crucial in preserving the physical stability and homogeneity of the formulation.

4.2 Spreadability and Rheological Behavior

Topical applicability, patient acceptance, and retention at the application site are all significantly influenced by spreadability and rheological behavior. Comparative analysis showed that the OG formulation had substantially higher viscosity and stronger structural consistency, while the NEG formulation had higher spreadability and reduced flow resistance. Surfactant-rich NE droplets scattered throughout a hydrated polymeric gel network may be responsible for NEG's enhanced spreadability. Tween 80 and PEG 400 improved the formulation's deformability upon application by promoting homogeneous water dispersion and lowering internal friction. In addition, the hydrated Carbopol matrix contributed to smooth spreading under mild shear conditions(9). On the other hand, the OG formulation possessed relatively higher viscosity due to the formation of a tightly packed lipoidal meshwork made up of GMS and SA oleogelators as shown in figure 1. The oleogelators were able to form a solid-like structure that could hold the oil and drug particles together within a lipoidal matrix. Even though the OG had a very stable structure, it still had good spreadability characteristics due to the lubricating nature of CO and PEG 400 (10).

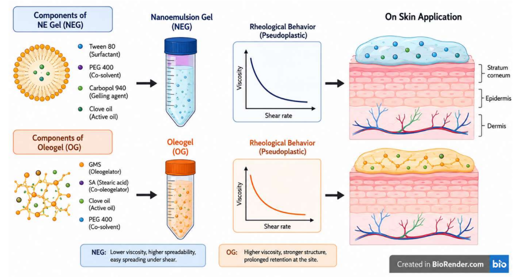

Fig 1- Figure depicting affect of different excipients on viscosity, spreadibility and skin retention.

Both the systems displayed shear thinning or pseudoplastic nature, whereby there was gradual decrease in viscosity with increased shear stress. The pseudoplastic or shear thinning property is a very favorable property of topical delivery systems since it enables the system to be easily rubbed and spread on the surface of the skin, while its higher viscosity ensures that it remains adherent on the skin. For OG, the pseudoplastic property could have been attributed to partial breakage and realignment of lipid aggregates under shear stress, while the shear thinning property of NEG could be attributed to reorganization of hydrated polymer chains and dispersed nanoparticles under shear stress as shown in table 1. It would be anticipated that OG having a relatively high viscosity would have better retention properties at the site of infection than NEG (11).

Table 1. Comparison of the optimized ITZ-loaded OG and NEG formulations' rheological and application properties

Parameter	OG	NEG	Comparative interpretation based on excipient architecture
Structural consistency	Highly structured semisolid system	Soft and hydrated gel system	GMS and SA formed a dense lipidic network in OG, whereas Carbopol-based gel matrix provided flexible consistency in NEG
Apparent viscosity	Comparatively higher	Comparatively lower	Oleogelator-induced lipid structuring

			increased resistance to flow in OG, while NE dispersion reduced viscosity in NEG
Spreadability	Satisfactory with controlled spreading	Enhanced spreading ability	Tween 80 and PEG 400 improved lubrication and reduced internal friction in NEG
Flow behavior under shear	Pseudoplastic (shear-thinning)	Pseudoplastic (shear-thinning)	Structural rearrangement of lipid aggregates in OG and polymer chains in NEG under applied stress
Adhesion and retention on skin	Greater retention tendency	Moderate retention tendency	Highly viscous lipid matrix promoted prolonged residence time in OG
Ease of topical application	Controlled application with higher consistency	Easier and smoother application	Lower flow resistance and hydrated gel structure improved applicability of NEG
Drug diffusion tendency	More controlled diffusion	Faster diffusion tendency	Dense lipidic matrix restricted rapid drug mobility in OG, whereas nanosized dispersion facilitated diffusion in NEG

4.3 Drug Content Analysis

Both OG and NEG formulations demonstrated satisfactory drug incorporation and uniform distribution of ITZ within their respective carrier systems. The observed drug content uniformity indicated efficient entrapment of the lipophilic drug and minimal drug loss during formulation processing(12). The mechanisms responsible for drug incorporation differed substantially between the two systems. In NEG, the enhanced solubilization capacity of Tween 80 and PEG 400 facilitated uniform distribution of ITZ within nanosized oil droplets. The surfactant-rich interfacial environment improved compatibility between the lipophilic drug and aqueous gel matrix while minimizing drug aggregation or precipitation. In contrast, drug incorporation in OG was predominantly governed by entrapment within the structured lipidic matrix formed by GMS and SA. The hydrophobic environment created by CO and lipid gelators favoured retention of ITZ within the semisolid matrix and reduced molecular mobility of the drug(13).

The comparatively stronger matrix organization in OG may have contributed to enhanced drug retention, whereas the nano-dispersed architecture of NEG facilitated homogeneous drug dispersion throughout the formulation. These findings suggest that both surfactant-mediated solubilization and lipidic matrix entrapment were effective approaches for improving incorporation of poorly soluble ITZ into topical systems.

Table 2. Comparative interpretation of drug content behavior

Formulation	**Drug incorporation behavior**	**Excipient-mediated mechanism**
OG	Efficient drug entrapment	Lipid matrix immobilization by GMS and SA
NEG	Uniform drug dispersion	Surfactant-assisted solubilization and nano-dispersion

4.4 *In vitro* Drug Release Behavior

The OG, and NEG formulations showed notable variations in release behavior, underscoring the significance of formulation architecture and excipient selection in regulating drug diffusion. Due to the drug's crystalline structure and poor aqueous solubility, the pure ITZ suspension showed incredibly restricted release. On the other hand, by increasing drug solubilization and dispersion, both OG and NEG systems greatly improved drug release behavior (14). NEG possessed relatively fast and diffusion-dependent release kinetics. This could be explained by the fact that nanosized NE droplets provided relatively larger interfacial surface area as well as a shorter pathway for diffusion. Both Tween 80 and PEG 400 decreased the interfacial tension and facilitated movement of ITZ from the NE droplets into the surrounding media. Moreover, hydration of the Carbopol matrix facilitated diffusion without resulting in any sudden burst release of ITZ. The OG preparation showed similar sustained release kinetics, but it involved gradual diffusion due to its structured lipidic matrix of GMS and SA. These interacting lipid compartments provided a tortuous pathway for diffusion that hindered the rapid movement of drug particles. The initial phase of release would be from the drug fractions present at the surface, while the later phases would be determined by diffusion within the lipid matrix (15).

Differences in release mechanisms show different drug transportation mechanisms by the excipients. While NEG was more of enhanced diffusion due to surfactant-induced solubilization and nanodispersion, OG was more for sustained release through lipid entrapment and diffusion control.

Table 3. Comparative interpretation of drug release behavior

Parameter	OG	NEG	Excipient-mediated effect
Release rate	Sustained and slower	Faster and diffusion-enhanced	Surfactant-assisted diffusion in NEG
Drug mobility	Restricted	Enhanced	Lipidic network limited diffusion in OG
Release mechanism	Matrix-controlled	Interfacial diffusion-controlled	GMS/SA vs Tween 80/PEG 400
Retention tendency	High	Moderate	Structural rigidity prolonged release in OG

These findings indicate that both systems successfully transformed ITZ into controlled-release topical formulations, although the mechanisms responsible for release modulation differed substantially because of excipient architecture.

4.5 Release Kinetics and Mechanism

Release kinetic analysis indicated that both formulations predominantly followed diffusion-controlled release behavior. The release patterns were best explained by diffusion-based kinetic models along with anomalous non-Fickian transport mechanisms (16). In NEG, the release mechanism was mainly governed by diffusion of ITZ from nanosized droplets through the hydrated polymeric gel network. The presence of surfactants improved drug mobility and facilitated movement of drug molecules through aqueous diffusion channels. Simultaneously, relaxation of the polymeric matrix contributed to controlled release behavior. In OG, release occurred through a more complex interplay of diffusion and matrix relaxation. The structured lipidic network formed by GMS and SA restricted rapid migration of drug molecules and created prolonged diffusion pathways. Gradual relaxation of the OG matrix additionally contributed to sustained release behaviour(17).

Mechanically, the improved diffusion capacity of NEG could be due to an increase in surface area and better interfacial movement due to the NE system while the sustained release potential of OG could be due to stronger entrapment in the matrix and higher viscosity. These results support the claim that the design of excipient structure affects the main mechanism of release and diffusion of formulations.

4.6 Antifungal Activity Against *C. albicans*

It was observed that both OG and NEG preparations showed enhanced antifungal activity against *C. albicans* in comparison with control preparation as shown in figure 2. The antifungal activity of the preparations differed due to differences in the composition of excipients and mechanism of drug release. In particular, the antifungal activity of NEG was higher because it possessed better initial activity with lower concentrations required for inhibition, which may be explained by enhanced diffusion of drugs and interaction between nanodroplets and fungus. The smaller size of globules increased surface area of contact between the ITZ and fungus. In addition, Tween 80 and PEG 400 improved drug solubilization and availability at the target site(18). The presence of eugenol-rich clove oil may have further contributed synergistically to antifungal activity through membrane destabilization and permeability enhancement. Thus, the combined effects of nanoscale dispersion, improved solubilization, and intrinsic activity of clove oil likely contributed to the enhanced antifungal efficacy of NEG(19). In contrast, OG demonstrated comparatively prolonged and sustained antifungal activity because of its highly viscous and adhesive lipidic matrix. The structured network formed by GMS and SA prolonged formulation retention at the application site and allowed sustained release of ITZ over an extended period. This prolonged residence time may have enhanced maintenance of therapeutic drug concentrations at the infected region (20).

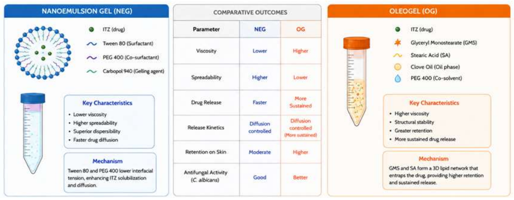

Fig 2- Comparative schematic representation of ITZ-loaded NEG and OG formulations highlighting their composition, mechanism of drug delivery, and comparative physicochemical and antifungal performance characteristics.

Zone of inhibition studies further confirmed strong antifungal activity for both systems. The enhanced activity observed in OG and NEG compared with the marketed formulation demonstrates the critical role of excipient selection in improving topical delivery performance (21).

Table 4. Comparative interpretation of antifungal performance

Parameter	OG	NEG	Mechanistic influence of excipients
Antifungal onset	Moderate	Faster	Enhanced diffusion from nanosized droplets in NEG
Sustained activity	High	Moderate-high	Lipid matrix retention prolonged drug availability in OG
Drug diffusion	Controlled	Enhanced	Surfactant-mediated transport in NEG
Retention at site	High	Moderate	Viscous lipidic matrix improved residence time in OG
Contribution of clove oil	Sustained local action	Synergistic diffusion enhancement	Eugenol-mediated antifungal activity

Overall, the comparative findings establish that excipient architecture critically governed the physicochemical behavior, release kinetics, and antifungal performance of both topical delivery systems. NEG favored enhanced diffusion, spreadability, and rapid antifungal action, whereas OG favored prolonged retention, sustained release, and extended antifungal activity.

4.7 Statistical Interpretation of Formulation Performance

Comparative interpretation of the normalized formulation parameters revealed distinct excipient-dependent differences between the OG and NEG systems with respect to physicochemical behavior, drug release characteristics, rheological properties, and antifungal performance. While both the systems showed good topical delivery efficiency along with improved efficacy than the standard suspension of ITZ, it is important to mention here that the mechanisms behind this improved performance for both the drug delivery systems were significantly different due to variations in excipients structure. On normalization of rheological properties and topical application, it was found that OG-based system displayed a higher degree of matrix stability, higher retention ability, and better sustained release property. This can be explained based on the reason that the 3-Dimensional lipid network created by GMS and SA helped in controlling the molecular movement and increased matrix stability.

In contrast, the NEG system exhibited comparatively enhanced spreadability, improved dispersibility, and greater diffusivity. This behavior was strongly associated with the surfactant-rich NE architecture, where Tween 80 and PEG 400 reduced interfacial tension and stabilized nanosized droplets within the hydrated Carbopol matrix. The increased interfacial surface area and improved drug solubilization facilitated enhanced mobility of ITZ and promoted comparatively faster release behavior. Comparative interpretation of drug content and formulation homogeneity suggested that both systems efficiently incorporated ITZ; however, the mechanisms responsible for drug stabilization differed. In NEG, drug incorporation was primarily governed by surfactant-assisted solubilization and nanoscale dispersion, whereas in OG, the structured lipidic matrix favored immobilization and retention of the lipophilic drug within hydrophobic domains. Normalization of release behavior and antifungal parameters further demonstrated that the NEG system favored enhanced immediate antifungal interaction because of improved diffusion and closer contact between nanosized droplets and fungal cells. On the other hand, the OG formulation had a long-lasting antifungal effect because of the slow drug release and increased retention at the application site. This is evident that diffusion-enhancing ability and retention-enhancing capability are two separate excipient-based drug delivery methods in topical application of ITZ.

In conclusion, it can be clearly seen from the statistical comparison that there is a definite link between the function of excipients and their effectiveness. Colloidal stabilization through surfactants in NEG mainly enhanced properties pertaining to diffusion, while lipid matrix formation in OG promoted increased retention and slow-release properties (22).

5. CONCLUSION

It is evident from the current secondary comparison analysis that the design of the excipient had a decisive impact on the physical and chemical properties, rheological activity, drug release pattern, and antifungal efficacy of the loaded ITZ-containing OG and NEG formulations for the treatment of *C. albicans* infection. Even though both the lipid carriers managed to enhance the release properties of poorly water-soluble ITZ as compared to the traditional formulation, there were notable disparities regarding the mechanism of operation and efficacy as a result of the differential composition of the formulations. The use of the NEG was associated with increased spreadability, better drug penetration, and faster antifungal activity because of the use of nanosized droplets as well as drug transportation facilitated by the use of Tween 80 and PEG 400. On the contrary, the OG formulation exhibited higher viscosity, greater structural stability, increased residence time, and sustained antifungal activity due to the formation of a well-structured lipid network created from GMS and SA. In addition, the lipid network successfully inhibited the movement of the drug molecules and induced prolonged release behavior. Release kinetics revealed that both types of formulations were subjected to the same modes of diffusion and non-Fickian transport mechanisms. However, the mechanism of release depended on the different modes of excipient network creation. Finally, the anti-fungal results indicated that the presence of CO in the preparations is not only an oil carrier but also a bioactive excipient capable of improving therapeutic efficacy. In summary, the results illustrate the correlation between excipient and NE/OG performances. The comparison reveals that NEG may be the preferred choice when diffusion and quick response are required, while OG could exhibit an advantage in situations that require prolonged residence time and sustained anti-fungal activity. NEG is more suitable for superficial fungal infections requiring enhanced penetrations while OG is more suitable for dry and scaly fungal infections.

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7. CRediT Statement

Anjali Rajora: Methodology, Data Curation, Investigation, Writing- Original Draft, Formal Analysis.

Kanchan Kohli: Supervision, Validation.

Kalpana Nagpal: Conceptualization; Project Administration; Supervision; Writing – review & editing; Visualization; Resources.

8. Competing Interests

The authors state that there are no conflicting interests

9. Declaration of Generative AI Use

Generative Artificial Intelligence (AI) tools, specifically OpenAI's ChatGPT (GPT-5), were used solely to refine the language, enhance readability, and correct grammatical and structural errors in this manuscript. The AI was not involved in data generation, analysis, interpretation, or drawing scientific conclusions. All experimental designs, results, and discussions are entirely the original work and intellectual contribution of the authors. The AI assistance was limited to improving the clarity and linguistic quality of the final document.

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