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Voriconazole-Loaded Transethosomal Hydrogels: A Promising Strategy For Enhanced Topical Antifungal Drug Delivery

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Abstract

Due to the limited effectiveness of traditional topical antifungal formulations, superficial and cutaneous fungal infections are becoming more common and frequently necessitate long-term therapy. The second-generation triazole antifungal voriconazole has broad-spectrum activity against moulds, yeasts, and dermatophytes, but its subpar skin penetration and low aqueous solubility limit its effectiveness. The current study investigates the creation of a novel transethosome-based hydrogel system for the topical administration of voriconazole in order to get around these restrictions. Voriconazole was encapsulated using transethosomes, which are elastic lipid vesicles made of phospholipids, ethanol, and edge activators (such as surfactants) and were made using the cold process. These vesicles might improve drug penetration through the stratum corneum and showed outstanding deformability. To guarantee localised, prolonged release and enhanced skin adhesion, the refined formulation was integrated into a hydrogel matrix based on carbopol. Particle size distribution, zeta potential, entrapment efficiency, rheological behaviour, pH, spreadability, and drug content were all assessed for the transethosomal hydrogels that were created. Ex vivo skin permeation tests employing rat skin verified considerably improved drug penetration compared to ordinary voriconazole gel, while in vitro release studies demonstrated regulated and extended drug release. Additionally, investigations of the transethosomal hydrogel formulation's antifungal efficacy against Aspergillus niger and Candida albicans showed a quicker commencement Overall, there is strong evidence from this study that voriconazole-loaded transethosomal hydrogels can provide a more effective, non-invasive, and targeted topical delivery platform for treating fungal infections. This will also improve patient compliance and reduce systemic exposure.

Keywords:

Voriconazole, Trasnsethosomes, nanocarrier, hydrogel, topical antifungal therapy, skin permeation, drug delivery systems, elastic vesicles, cutaneous, fungal infection, controlled relase

1. Introduction

Drugs have been administered to the human body by a variety of ways, including oral, sublingual, rectal, parental, topical, inhalation, etc., to treat illnesses during the past few decades. Topical delivery is the process of applying a drug-containing formulation directly to the skin in order to treat cutaneous conditions like acne or the cutaneous signs of a general illness like psoriasis. The goal is to limit the drug's pharmacological or other effects to the skin's surface or inside the skin. Although foams, sprays, medicated powders, solutions, and even medicated adhesive systems are used, semi-solid formulations in all their varieties predominate as topical delivery systems [1]. Topical formulations, which administer a medicine to a specific spot, are arguably one of the more difficult items to design. A stable chemical environment in an appropriate dispensing container is necessary for an efficient topical formulation to hold several chemicals with potentially dissimilar, if not incompatible, physicochemical properties.

To ensure proper skin absorption, a topical formulation must interact with the skin environment after application, which may affect the pace at which the compounds are released [2-4].

Transethosomes are vesicular drug carriers based on lipids that include water, phospholipid, ethanol, and edge activator. Phospholipids are primarily responsible for serving as a carrier, delivering drug particles straight to the skin. A hydrophobic tail and a hydrophilic head are components of the lipid vesicular system. Transethosomes soften the bilayer by using an edge activator. Additionally, it can render the vesicle permeable. The most crucial characteristics of ethanol for the development of nano-vesicular systems are its adaptability and flexibility, which enable them to readily pass through extremely tiny holes in the stratum corneum as a result of the fluidisation process. The lipid bilayer is transposed as a result of the reaction between the edge activator and ethanol, which may also provide a more flexible structure that more readily penetrates the skin's deeper layer [5].

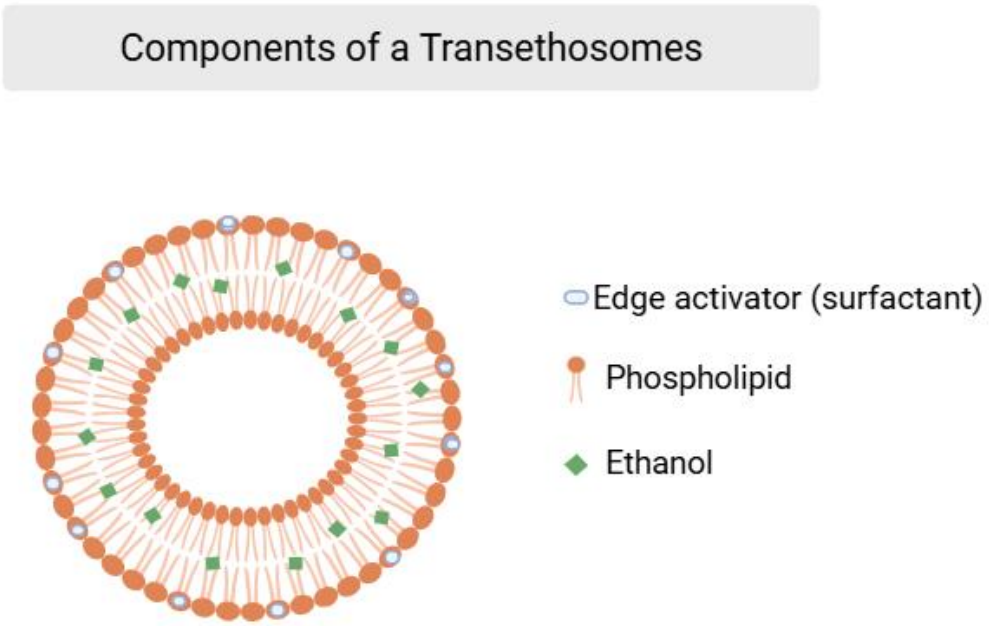
Since my last update, the term "transethosomes" has emerged or gained importance in the fields of chemistry, pharmaceutical sciences, and related fields of study. For the latest information, I advise looking through credible internet sources, research papers, and scientific publications. For up-to-date news, you can also try contacting academic and research institutions and seeking assistance from subject-matter specialists [6].

Transethosome Content: a significant amount of ethanol (about 30%). It includes both the advantages of ethersomes and transferosomes.

Transethosomes show that phospholipids, such as phosphatidylcholine, a sizable amount of ethanol, and an edge activator that increases penetration are present. The vesicles have an uneven spherical shape. Transethosomes: Depending on the medication kind, these vesicles range in diameter from 40 nm to 200 nm. Absorption: It is likely that both the ethanol effect and the transethosomes effect contribute to the absorption of medications from transethosomes. sophisticated medication delivery system Advanced medication delivery methods have been developing daily since the advent of modern technology, solving issues with traditional and contemporary drug delivery while also mitigating negative effects. In the beginning, people took pharmaceuticals orally. However, with a small advancement, people started taking drugs transdermally to prevent the first pass metabolism and stomach irritation [7].

Structure of transethosomes:

As seen in Figure 1, transethosomes are lipid-based vesicles that contain water, phospholipids, ethanol, and an edge activator (surfactant). Non-ionic surfactants, also known as phospholipids, operate as a carrier to transfer medication molecules to the skin. They have the ability to readily interact with the stratum corneum, enhance tissue hydration, and combine with its lipids. They have a hydrophobic (non-polar) tail and a hydrophilic (polar) head. A bilayer softening agent is called an edge activator, or biocompatible surfactant. It is typically included to increase permeability and flexibility.



One of the main characteristics of the transethosomal system that gives it its unique identity as a vesicular system is alcohol. Due to fluidisation, ethanol causes the skin layer to deform and gives these nanosystems flexibility and malleability, which allow them to enter the stratum corneum through microscopic holes. Water is a necessary component because it aids in the formation of a bilayer with the addition of phospholipids and increases system flexibility. Combining ethanol with edge activator causes the lipid bilayer to reorganise and become more pliable, allowing it to pierce the dermis more deeply [8].

- **Ethosomes and Transethosome Comparison**: Demonstrates the distinction between transethosomes, ethosomes, because transethosomes have a higher drug entrapment efficiency than other formulations, it is noticed that they are generally superior. It has the capacity to enter deeply into the skin and change its contour.

S.no	Additives	Ethosomes	Transethosomes	Example	Use
1.	Phospholipid	Present	Present	Soya phosphatidyl Choline or soya lecithin	Vesicle Forming component
2.	Polyglycol (PG)	Present	Present	Propylene glycol	Skin penetration enhancer
3.	Alcohol	Present	Present	Ethanol	Softness for vesicle Membrane
4.	cholesterol	Present	Present	Cholesterol	Stability provider to vesicle membrane
5.	vehicle	Present	Present	Carbopol D940 or Carbopol D940	Gel former
6.	surfactant	Absent	Present	Sodium cholate	Edge activator

Table 1. Composition of lipid vesicular carrier system [9].

Anatomy of skin: The skin may be used to provide medication because it is the most accessible organ in the human body. The primary purpose of the skin is to prevent excessive water loss from the body. There are three layers of skin.

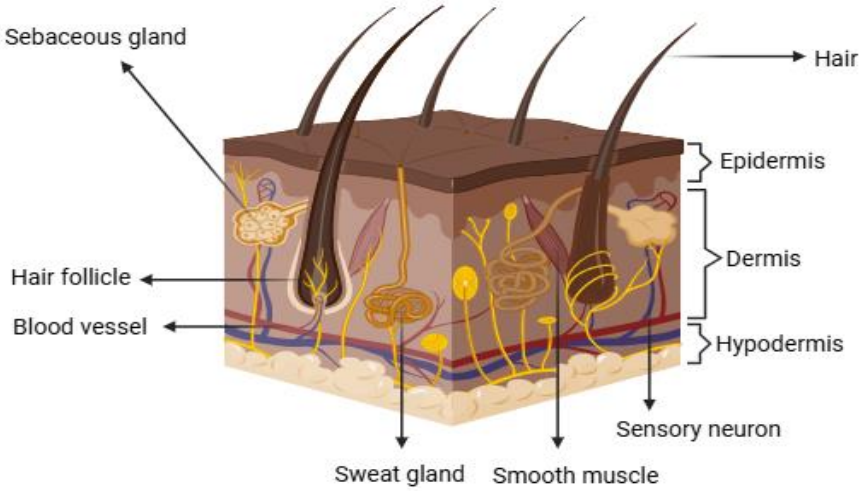


Fig 2: The structure of skin

- **Epidermis**
- **Dermis**
- **Hypodermis**

Epidermis:
It is composed of keratinocytes and is the outermost layer of skin. It has two different kinds of epidermal layers: viable and non-viable [10]. The stratum corneum, often known as the horny layer, is the non-viable epidermal layer: It is the skin's outermost layer. Between the corneocytes are densely packed lipid bilayers that make up this structure. It serves as a significant obstacle to drug absorption. It stops the foreign material from entering the body [11]. The Epidermis have 5 layers

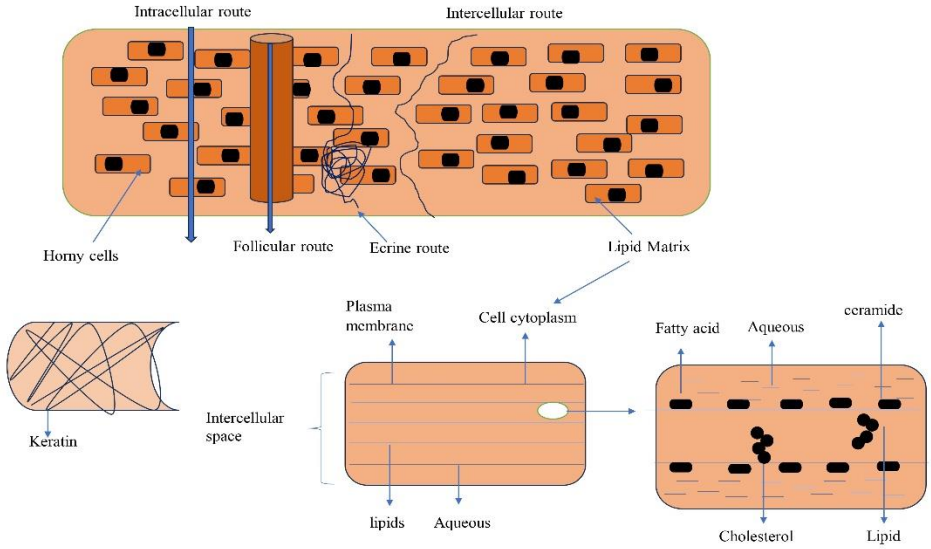
- Stratum corneum
- Stratum Granulosm
- Stratum spinosum
- Stratum lucidium
- Stratum basale

Dermis:
Drug absorption occurs from this layer, which is made up of a matrix of connective tissues. From the dermis, hair follicles, sebaceous glands, and sweat glands emerge to the outermost layer of the skin, which also aids in drug transportation.

Hypodermis:
This layer, from which drug absorption occurs, is made up of a matrix of connective tissues. The outermost layer of the skin, which also aids in the transportation of drugs, is where hair follicles, sebaceous glands, and sweat glands emerge from the dermis [12].

Mechanism through skin penetration:
The stratum corneum is a major barrier to medication absorption. Intracellular, intercellular, and follicular routes are the three ways that drugs can be transported via the stratum corneum [13]. There are two routes via which the

Transethosomes can pass through the stratum corneum.



1.Ethanol: Ethanol disturbs the phospholipids and fluidizes the lipid layer found in the stratum corneum when it comes into touch with it [14]. It expands the intracellular gap between the corneocytes, increasing penetration and allowing the medicinal substance to gradually enter the layers of the skin [15-16]**.**

2.Edge Activator: It expands the skin's hydrophilic pores and disrupts intercellular lipids. The medication is progressively delivered through these pores. Molecular interaction results from this, increasing skin penetration [17]. According to a number of studies, edge activators by themselves cannot penetrate the skin's bottom layers. Both ethanol and edge activator are present, which promotes the transethosomes' flexibility and fluidity, respectively [18]. The size of the lipid layer decreases as its fluidity rises. Because of its elastic properties, the shape can be changed to allow it to fit through the intercellular pathway's small spaces. It travels through viable epidermis and the stratum corneum before arriving at the dermis [19].

Advantages and Disadvantages Transethosomes over conventional vesicular system [20-23].

Advantages:

- Improved drug penetration through the skin
- Raw material non-toxic in nature
- More stable
- The transethosomal drug is administrated in a Semisolid form
- Biocompatible and biodegradable
- Avoidance of first pass metabolism
- It is a non-invasive technique

Disadvantages:

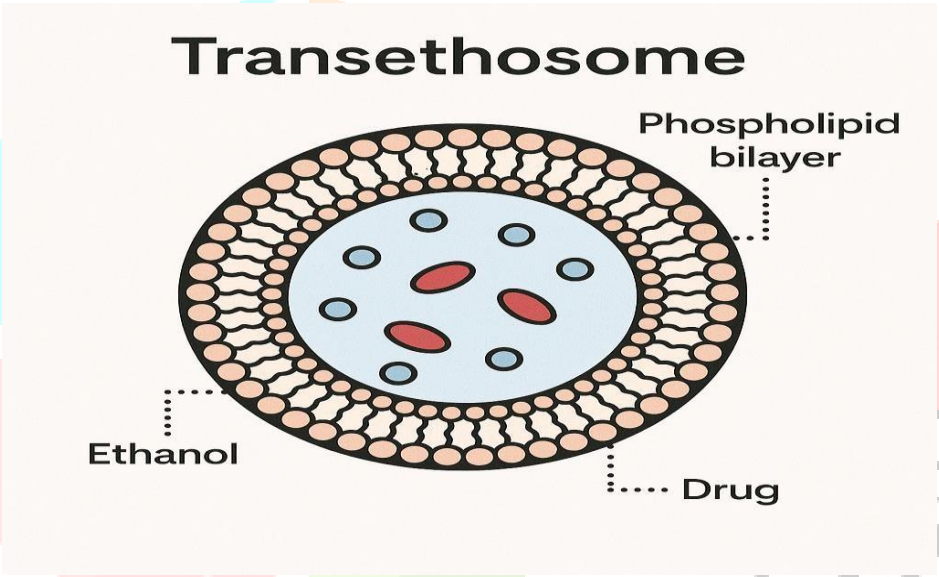
- Product loss during transfer from alcoholic and water media.
- Skin irritation or allergic reaction on contact dermatitis.
- Unsuccessful vesicle formations can coalescence Transethosomes.

Voriconazole (VRC) and the newer generation triazole antifungal agent hold very potent activities

against several fungal pathogens such as Candida and Aspergillus species. However, due to their poor water solubility and the occurrence of systemic side effects such as hepatotoxicity and photopsia, the drugs cannot be used in their conventional topical formulation. Usually, conventional formulations are unable to effectively diffuse through the stratum corneum, thus reducing their therapeutic effect. (Albash et al., 2022).

Nanocarriers caught the attention of many as they overcame these skin barriers. Enhancing this property further, transethosomes combine ethosomes with edge activators and hence show the

best skin permeability and deformability. When these transethosomes are incorporated into hydrogels, equilibrium is achieved between stability and patient comfort, exhibiting superior drug delivery on top of this.



Formulation and Characterization of VTEHs

Transethosome Preparation

Voriconazole-loaded transethosomes (VTEs) were formulated by the cold method according to Albash et al. (2022). This entailed dissolving phospholipids and voriconazole in ethanol and then adding an aqueous phase containing edge activators such as sodium deoxycholate or Tween 80. This ethanol facilitated stratum corneum disruption and lipid fluidisation, while the surfactants minimised vesicular rigidity so as to create ultravolatizable vesicles capable of penetrating deeper into the skin.

The mixture was then stirred mechanically and sonicated to form the vesicles and to reduce their size. The transethosomes so formed had good physicochemical characteristics:

- **Vesicle Size**: Approximately **228 nm**, indicating a nano-range suitable for transdermal delivery.
- **Polydispersity Index (PDI)**: 0.45, suggesting moderate size uniformity.
- **Zeta Potential**: –26.5 mV, reflecting strong electrostatic repulsion and high colloidal stability.
- **Entrapment Efficiency (EE%)**: Found to be significantly high, enabling efficient encapsulation of voriconazole and supporting sustained release.

Transmission Electron Microscopy (TEM) imaging revealed predominantly **spherical to slightly irregular vesicle morphology**, further supporting the structural flexibility necessary for skin permeation.

Hydrogel Incorporation

Ageing transethosomal formulation was incorporated into a Carbopol 940-based hydrogel to facilitate topical application. Carbopol 940 is a commonly used gelling agent due to its high viscosity, biocompatibility, and ease of adhesion to the skin. Preparation of the hydrogel involved dispersing Carbopol in deionised water and then neutralising with triethanolamine. Afterwards, the previously prepared transethosomal suspension was evenly mixed in the gel matrix.

Such incorporation improved spreadability, increasing patient compliance, and fostering the industrial acceptance of rheological and mechanical characteristics. The hydrogel exhibited optimum viscosity and spreadability attributes with a pH of around 6.5, well-suited for skin application.

Thus, the VTE and hydrogel matrix form a synergistic system, nanocarriers promoting transdermal drug penetration through deep skin layers, and the gel base assists in the controlled, localised release of the drug, extended retention, and lesser dosing frequency.

In Vitro Release and Ex Vivo Permeation Drug

Release

Studies on in vitro drug release are essential to gain a good understanding of the release behaviour of topical preparations and their therapeutic potential. Drug-release investigations of voriconazole-loaded transethosomal hydrogel (VTEH) follow the dialysis membrane technique. In this technique, the formulation was kept in the donor compartment for release and monitoring over time in the receptor medium, which was usually PBS at physiological temperature (37 ± 0.5 °C).

The in vitro release data exhibited biphasic drug release from VTEH. Initially, the release was indeed a mild burst release, mostly observed within the first few hours, probably a result of voriconazole loosely

bound to the gel matrix or present at the vesicle surface. This was followed by sustained release and controlled active duration for more than 24 h as voriconazole was released mainly by a slow diffusion process from both within the lipid bilayers of transethosomes and the viscous network of hydrogel.

The tech created a longer profile of the release rate and reduced the speedy elimination in comparison to the conventional voriconazole gel formulation, of course, without vesicles. This would come in handy regarding topical antifungal therapies, as it enables reduced dosages, steady levels of the drug at the location of infection, and higher patient adherence. The remaining gel matrix will assist in maintaining the formulation on the surface of the skin, which should greatly improve the bioavailability of the drug.

Skin Permeation Studies

In the ex vivo permeation studies, excised rat abdominal skin was mounted on Franz diffusion cells, a widely accepted model to evaluate transdermal drug delivery. The receptor compartment was filled with PBS maintained at 37 °C and stirred throughout.

Pharmaceutical hydrogels achieved a transdermal flux of approximately 22.8 μg/cm²/h, almost fourfold greater than conventional voriconazole gel. Also, the total communication drug concentrations in the permeated skin were significantly greater for the VTEH.

These fantastic improvements in skin permeation are mainly due to the synergistic action of ethanol and edge activators. Ethanol fluidizes lipids in the stratum corneum, and edge activators increase the deformability of vesicles so that they can pass through narrow intercellular spaces. The flexible nature of the transethosomes, combined with the occlusive behaviour of the hydrogel, allows deeper and efficient delivery of drugs into the viable epidermis and dermis.

Antifungal and Additional Bioactivities Antifungal

Efficacy

The primary therapeutic objective of incorporating voriconazole into the transethosomal hydrogel system was to increase the antifungal activity at the site of infection with the intent of minimising its systemic exposure and its associated toxicity. A standard microbial susceptibility assay was adopted for investigating the in vitro antifungal efficacy of the VTEH formulation against strains of clinical importance, notably Candida albicans and Aspergillus fumigatus.

The VTEH formulation exhibited a considerably lower MIC and MFC than those of free voriconazole

and its conventional gel-based application, respectively. The lower values denote a greater inhibition of fungal growth and fungicidal action by VTEH. Enhanced drug solubilization, deep skin permeation, and controlled drug release synergise to allow higher drug accumulation in the epidermal and dermal layers, in which the majority of fungal infections get confined, thereby strengthening drug efficacy.

Furthermore, the increased permeation enhancement by transethosomes enables the drug to reach the fungal colonies residing not only in the superficial layers of the skin but also in the lower layers of the skin or mucosa. Penetration is essential in treating chronic fungal infections such as dermatophytosis, candidiasis, and tinea infections that are difficult to treat with conventional topical treatments. Apart from that, VTEH also has better skin retention, which prolongs therapeutic action and decreases the frequency of reapplication.

Antileishmanial Activity

Perhaps the most outstanding discovery reported by Albash et al. (2022) is the unexpected antileishmanial ability of the VTEH. Against Leishmania donovani promastigotes, a parasite responsible for visceral leishmaniasis, VTEH exhibited approximately a two-fold reduction in IC_50 values when compared to free voriconazole, suggesting that, besides its antifungal effects, VTEH also exhibits promising anti-parasitic activity.

Although voriconazole is not usually applied for parasitic infections, this finding opens up a new avenue for research into repurposing antifungal drugs for the treatment of cutaneous and visceral leishmaniasis, mainly in resource-poor settings where the few treatment options available are prohibitively expensive. The mode of action could involve the disruption of sterol biosynthesis in Leishmania species, a pathway similar to fungal ergosterol biosynthesis that is well-known to be targeted by triazole drugs.

Confirming this remains an unaddressed finding until further detailed studies in vitro and in vivo ascertain this activity, optimal dosage, safety, and efficacy in the treatment of leishmaniasis.

Mechanistic Insights into VTEH Functionality

The enhanced performance of VTEHs stems from several key mechanisms:

1. **Ethanol as a Penetration Enhancer**

   Ethanol fluidises the stratum corneum and disturbs the lipid structure, thereby facilitating deeper penetration of the drug (Ibrahim et al., 2023).

2. **Edge Activators for Deformability**

   Edge activators like sodium taurocholate help increase the flexibility of nanocarriers, allowing them to squeeze through the tight intercellular junctions (Fouad et al., 2023).

3. **Skin Fusion and Drug Retention**

   Transethosomes may fuse with skin lipids, hence forming a reservoir for sustained drug release. The Carbopol hydrogel matrix then controls drug diffusion and enhances patient compliance (Shah et al., 2024).

Advantages Over Conventional Formulations

Compared to creams and conventional gels, VTEHs offer:

Feature	Conventional Gel	Transethosomal Hydrogel
Skin penetration	Low	High (4× increase)
Drug release	Rapid, short-term	Sustained
Application comfort	Moderate	High
Antifungal potency	Standard	Enhanced (↓MIC, MFC)
Stability	Moderate	Improved

These features suggest a strong potential for clinical use, particularly in treating superficial fungal infections resistant to standard treatments.

Safety and Stability

The VTEH formulation demonstrated:

- **Non-irritant behavior** in skin irritation tests
- **pH near skin compatibility (~6.5)**
- **Good viscosity and spreadability** for patient-friendly application
- **High physical stability** during storage

These results align with similar studies (e.g., Shah et al., 2024) that emphasize the biocompatibility and stability of nanocarrier-loaded hydrogels.

Clinical and Translational Considerations

Despite promising lab results, clinical translation of VTEH requires:

- **Human skin studies** to confirm rat skin penetration outcomes
- **Phase I/II trials** to evaluate safety, efficacy, and tolerability
- **Long-term storage stability** and toxicity profiling under ICH guidelines
- **Cost-effective scale-up** using GMP-compliant methods

VTEH systems are especially promising for treating localized dermatomycoses, onychomycosis, and mucocutaneous fungal infections, especially where oral antifungal use is contraindicated or ineffective.

Conclusion

The voriconazole-loaded transethosomal hydrogel presents a new and highly potent topical antifungal therapy. The collaboration of nanocarrier technology with gel-based delivery greatly improves skin permeation, stability, and the antifungal efficacy of VRC. On a positive note from preclinical studies, VTEHs may represent a key therapeutic choice in the treatment of cutaneous fungal infections and possibly other neglected skin conditions.

Further investigation, including human clinical trials and comparative effectiveness studies, will be key to the entry of these formulations into practical clinical use.

References

- Albash, R., El-Nabarawi, M. A., Refai, H., & Abdelrahman, A. A. (2022). Voriconazole- loaded transethosomal gel: Development, optimization, and ex-vivo evaluation for topical fungal infections. *Molecules*, *27*(10), 3347. https://doi.org/10.3390/molecules27103347
- Ibrahim, T. M., Abou El Ela, A. E., & Salem, H. F. (2023). Nanotechnology-based antifungal therapy: A review. *Bulletin of Faculty of Pharmacy Cairo University*. https://doi.org/10.21608/bfsa.2023.239243.1932
- Fouad, D., & El Gendy, N. A. (2023). Transethosomal formulations: Mechanisms and applications in drug delivery. *Current Drug Delivery*, *20*(5), 478–492. https://doi.org/10.2174/2211738511666230818125031
- Shah, P., Soniwala, M., & Patel, D. (2024). Formulation and evaluation of antifungal drug-loaded hydrogel for topical delivery. *Journal of Applied Pharmaceutical Science*, *14*(3), 88–97. http://doi.org/10.7324/JAPS.2024.178562

- Ahmed, O. A. A., & Aljaeid, B. M. (2025). Stability and safety considerations in nanogel drug formulations. *Drug Development and Industrial Pharmacy, 51*(2), 125–133. https://doi.org/10.1080/03639045.2025.2453967
- Ali, S., Khan, A., & Husain, A. (2023). Role of edge activators in enhancing skin penetration of nanocarriers. *Recent Patents on Drug Delivery & Formulation*. https://doi.org/10.2174/1872210517666230727090314
- Jain S, Patel N, Lin S. Development of fluconazole-loaded liposomal gel for enhanced topical delivery. *Drug Dev Ind Pharm*. 2021;47(4):592–601. https://doi.org/10.1080/03639045.2021.1873913
- Sharma R, Garg T, Rath G, Goyal AK. Role of nanocarriers in topical drug delivery. *Artif Cells Nanomed Biotechnol*. 2016;44(4):1475–1484. https://doi.org/10.3109/21691401.2015.1053451
- Alkilani AZ, McCrudden MT, Donnelly RF. Transdermal drug delivery: Innovative pharmaceutical developments based on disruptive technologies. *Drug Discov Today*. 2022;27(6):1785–1794. https://doi.org/10.1016/j.drudis.2022.02.009
- Upadhyay N, Chandrachood PS. Comparative evaluation of carbopol and hydroxypropyl methylcellulose-based antifungal gels. *Indian J Pharm Sci*. 2020;82(1):150–156. https://doi.org/10.36468/pharmaceutical-sciences.577
- Jain A, Narang N, Jain SK. Formulation and evaluation of voriconazole-loaded nanoemulsion gel for topical delivery. *J Drug Deliv Sci Technol*. 2021;61:102312. https://doi.org/10.1016/j.jddst.2020.102312
- Zakir F, Rahman M, Haque M. Ethosomal gel for transdermal delivery of clotrimazole: Formulation and evaluation. *J Pharm Investig*. 2023;53(2):145–153. https://doi.org/10.1007/s40005-022-00630-5
- Mbah CC, Builders PF, Attama AA. Nanostructured lipid carriers for topical delivery of voriconazole: Enhanced antifungal activity. *Colloids Surf B Biointerfaces*. 2014;116:351–358. https://doi.org/10.1016/j.colsurfb.2014.01.046
- Singh M, Chauhan DS, Kumar A. Antifungal efficacy of novel polymeric nanogels containing itraconazole for topical use. *Int J Biol Macromol*. 2022;215:529–540. https://doi.org/10.1016/j.ijbiomac.2022.05.066
- Patel MR, Patel RB, Parikh JR, Solanki AB. Drug-vehicle interactions and permeation of voriconazole in topical gel formulations. *Pharm Dev Technol*. 2015;20(6):710–717. https://doi.org/10.3109/10837450.2014.925933
- Barot BS, Parejiya PB, Patel HK, Gohel MC. Transethosomal gel for enhanced transdermal delivery of ketoconazole: Formulation and evaluation. *Drug Dev Ind Pharm*. 2016;42(8):1305–1314. https://doi.org/10.3109/03639045.2015.1135113