Design, Optimization, and Evaluation of Nanoemulsion-Based Drug Delivery Systems Incorporating Poorly Water-Soluble Antifungal Agents for Improved Solubility, Stability, and Therapeutic Efficacy in Topical Applications

Samaira Menon ,Dr. Niharika Vashisht

Department of Pharmaceutics and Nanomedicine, Amrita Vishwa Vidyapeetham (School of Nanosciences and Molecular Medicine), Kochi

1. Abstract

Fungal skin infections are increasingly becoming a significant global health issue, impacting millions and leading to increased morbidity, reduced quality of life, and escalating healthcare expenses. Traditional topical antifungal treatments like creams, ointments, and lotions often face challenges such as inadequate drug solubility, limited skin penetration, instability, and less than ideal therapeutic results. Many commonly used antifungal medications, such as azoles and allylamines, fall under Biopharmaceutics Classification System (BCS) class II or IV, which are characterized by poor water solubility and inconsistent bioavailability. These challenges call for innovative drug delivery methods that can improve solubility, stability, and localized therapeutic effectiveness while reducing systemic side effects.

Nanoemulsion-based drug delivery systems have gained attention as effective carriers for drugs with low water solubility due to their small droplet size (20–200 nm), large surface area, thermodynamic stability, and improved permeation characteristics. Nanoemulsions can dissolve lipophilic antifungal agents within their oil phase and enable controlled release through the skin barrier. Moreover, the addition of surfactants and co-surfactants enhances drug dissolution, thermodynamic stability, and skin penetration, leading to better therapeutic outcomes.

This research article thoroughly examines the design, optimization, and evaluation of nanoemulsion-based delivery systems that incorporate poorly water-soluble antifungal agents for topical use. It covers formulation strategies, physicochemical characterization, in vitro and ex vivo evaluation, and assessment of therapeutic efficacy. The paper integrates recent advancements in nanotechnology and pharmaceutics, including the construction of pseudo-ternary phase diagrams, high-pressure homogenization, and quality-by-design (QbD) optimization techniques. Additionally, it critically analyzes the mechanisms behind improved drug permeation, antifungal effectiveness, and stability enhancement.

Recent studies indicate that nanoemulsion formulations significantly improve solubility, drug loading, stability, skin permeation, and antifungal activity compared to traditional formulations. Optimized nanoemulsions exhibit smaller droplet sizes (<100 nm), a narrow

polydispersity index, high zeta potential, and enhanced drug release profiles. Furthermore, ex vivo permeation and in vitro antifungal tests confirm superior drug penetration and increased activity against common fungal pathogens like Candida albicans and Trichophyton rubrum.

In summary, nanoemulsion-based topical delivery systems offer a highly effective approach to overcoming the solubility challenges of antifungal agents and enhancing therapeutic efficacy. This article provides a comprehensive research-oriented framework for designing optimized nanoemulsion formulations and outlines future opportunities in the field of topical antifungal nanomedicine.

2. Keywords

Antifungal medications; Nanoemulsion; Drugs with low water solubility; Delivery of drugs through the skin; Improvement of solubility; Stability; Penetration through the skin; Nanoemulgel; Effectiveness of treatment; Nanotechnology.

3. Introduction

3.1 Background

Skin and mucosal tissue fungal infections, such as dermatophytosis, candidiasis, and onychomycosis, pose a significant global public health challenge. These infections are mainly attributed to dermatophytes, yeasts, and molds that inhabit superficial keratinized tissues, resulting in persistent and recurring conditions. Although conventional topical antifungal treatments are commonly employed, they encounter numerous obstacles, including insufficient drug penetration through the stratum corneum, limited drug solubility, low bioavailability, and the need for frequent applications.

Antifungal medications like ketoconazole, itraconazole, terbinafine, luliconazole, and econazole nitrate often suffer from poor water solubility and a lipophilic nature. These physicochemical properties impede their dissolution in topical formulations, hindering effective delivery to the intended site. Additionally, poor solubility can cause formulation instability and drug precipitation, diminishing therapeutic efficacy.

Nanotechnology-based drug delivery systems have demonstrated great promise in overcoming these challenges. Among the various nanocarriers, nanoemulsions have attracted considerable interest due to their simple preparation, stability, and capacity to enhance drug solubilization and permeation.

3.2 Nanoemulsions in Drug Delivery

Nanoemulsions are colloidal dispersions Consisting of oil, water, surfactant, and co-surfactant, these systems have droplet sizes that usually fall between 20 and 200 nm. They possess distinct physicochemical characteristics, including transparency, high kinetic stability, and an increased surface area. The small size of the droplets facilitates effective drug encapsulation and enhances diffusion through biological membranes. Nanoemulsions are especially effective for topical drug delivery as they can penetrate the stratum corneum and transport drugs to deeper skin layers. Furthermore, they can accommodate both hydrophilic and lipophilic drugs, making them adaptable carriers for antifungal agents.

Nanoemulsions provide multiple advantages:

Greater solubility for drugs with low water solubility

Better skin penetration and drug accumulation

Enhanced stability and protection against degradation

Regulated and prolonged drug release

Decreased irritation and better patient adherence

Studies show that nanoemulsion formulations can greatly improve drug penetration and antifungal effectiveness when compared to traditional creams and ointments.

3.3 Rationale of the Study

The creation of nanoemulsion-based delivery systems for antifungal drugs with low solubility is a new approach intended to address the shortcomings of traditional formulations. Nonetheless, to improve therapeutic effectiveness and stability, it is crucial to conduct systematic optimization, formulation design, and thorough evaluation. Consequently, this research article concentrates on the design, optimization, and assessment of nanoemulsion systems for the topical delivery of antifungal agents that are poorly soluble in water.

---

4. Literature Review

4.1 Challenges Associated with Poorly Water-Soluble Antifungal Agents

Numerous antifungal medications are categorized under BCS Class II, characterized by their low solubility yet high permeability. The therapeutic impact of these drugs is frequently constrained by inadequate dissolution and inconsistent absorption at the infection site.

Poor aqueous solubility can lead to:

Partial absorption of the drug

Instability of the formulation

Precipitation of the drug while in storage

Diminished therapeutic effect

As a result, enhancing solubility and permeability is a key area of interest in the research of antifungal drug formulations.

4.2 Nanoemulsion as an Advanced Drug Delivery System

By integrating lipophilic drugs into the oil phase, nanoemulsions enhance their solubilization. Additionally, they possess increased surface area and free energy, which facilitate effective drug delivery and boost bioavailability.

Their advantages include:

- Increased solubility of drugs
- Better pharmacokinetic characteristics
- Directed delivery of medication to skin layers
- Enhanced therapeutic efficacy

4.3 Recent Advances in Nanoemulsion-Based Antifungal Delivery

Recent research indicates that nanoemulsion formulations of antifungal medications like econazole, posaconazole, and luliconazole greatly enhance the solubility, stability, and antifungal effectiveness of these drugs. Likewise, nanoemulgel formulations exhibit superior cumulative drug release and increased antifungal effectiveness against fungal pathogens when compared to traditional creams.

4.4 Mechanism of Enhanced Skin Permeation

Nanoemulsions enhance drug permeation through multiple mechanisms:

Nanoscale droplets lead to an expanded surface area.

The lipid structure of the stratum corneum is disrupted.

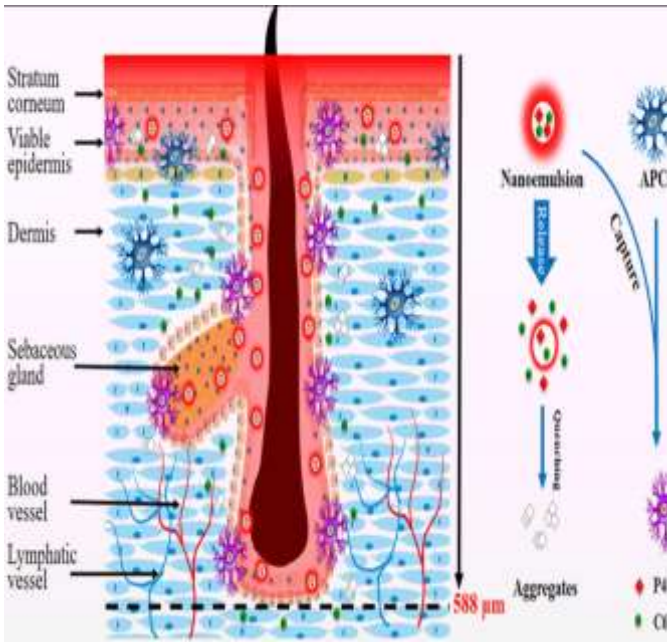
An occlusive effect enhances skin hydration.

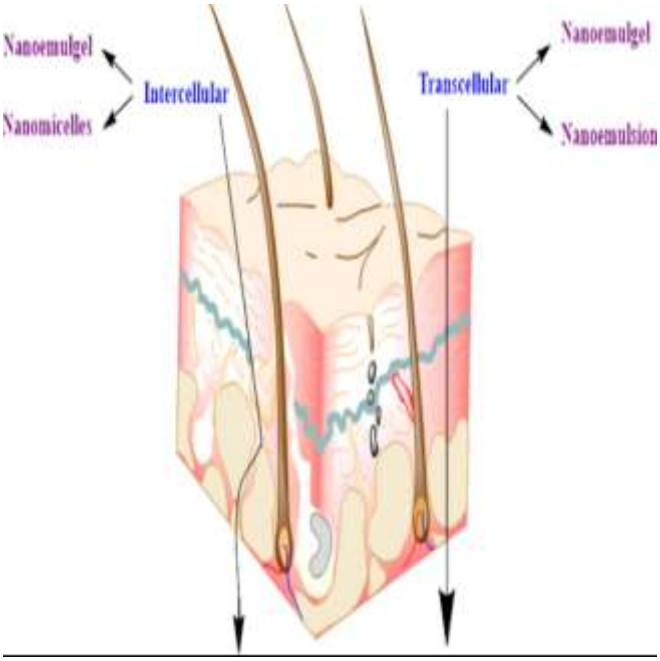
Surfactants aid in permeation enhancement.

Together, these mechanisms contribute to increased drug deposition within the skin layers.

Suggested Figure 1

"Mechanism of Enhanced Skin Penetration by Nanoemulsion-Based Topical Drug Delivery Systems"





4.5 Types of Nanoemulsions Used in Antifungal Delivery

Oil-in-Water (O/W) Nanoemulsion

Water-in-Oil (W/O) Nanoemulsion

Bicontinuous Nanoemulsion

O/W nanoemulsions are ideal for delivering antifungal treatments topically because they are not greasy and can release drugs effectively.

Table 1

Table 1: Summary of Recent Nanoemulsion-Based Antifungal Formulations

Drug	Type of Nanoemulsion	Droplet Size (nm)	Key Findings
Econazole nitrate	O/W NE	~100–200	Improved solubility and release

Drug	Type of Nanoemulsion	Droplet Size (nm)	Key Findings
Posaconazole	O/W NE	~78 nm	Enhanced stability and bioavailability
Luliconazole	Nanoemulgel	~86 nm	Increased skin permeation
Chrysophanol	NE & Nanogel	~231 nm	Sustained drug release

5. AIM AND OBJECTIVES

5.1 Aim

To create, refine, and assess drug delivery systems using nanoemulsions that include antifungal agents with low water solubility, aiming to enhance solubility, stability, and therapeutic effectiveness in topical uses.

5.2 Objectives

1. To choose the right antifungal medication and excipients for creating a nanoemulsion.

2. To create a nanoemulsion by employing suitable preparation methods.

3. To refine the formulation through the use of pseudo-ternary phase diagrams and statistical design techniques.

4. To analyze physicochemical characteristics such as droplet size, PDI, zeta potential, and stability.

5. To examine in vitro drug release and ex vivo skin permeation.

6. To test antifungal activity and therapeutic effectiveness.

6. MATERIALS AND METHODS

6.1 Materials

- Antifungal drugs with low water solubility (such as Ketoconazole, Terbinafine, Luliconazole)
- Oil components (Oleic acid, Capryol, Cinnamon oil)
- Surfactant agents (Tween 80, Poloxamer 188)
- Co-surfactants (Transcutol, PEG 400)
- Purified water
- Carbopol (used for converting to nanoemulgel)

6.2 Preformulation Studies

1. Investigations into solubility in different oils and surfactants

2. Compatibility analysis of drug and excipient using FTIR and DSC

3. Assessment of partition coefficient

6.3 Preparation of Nanoemulsion

The nanoemulsion was created through the following methods:

High-pressure homogenization

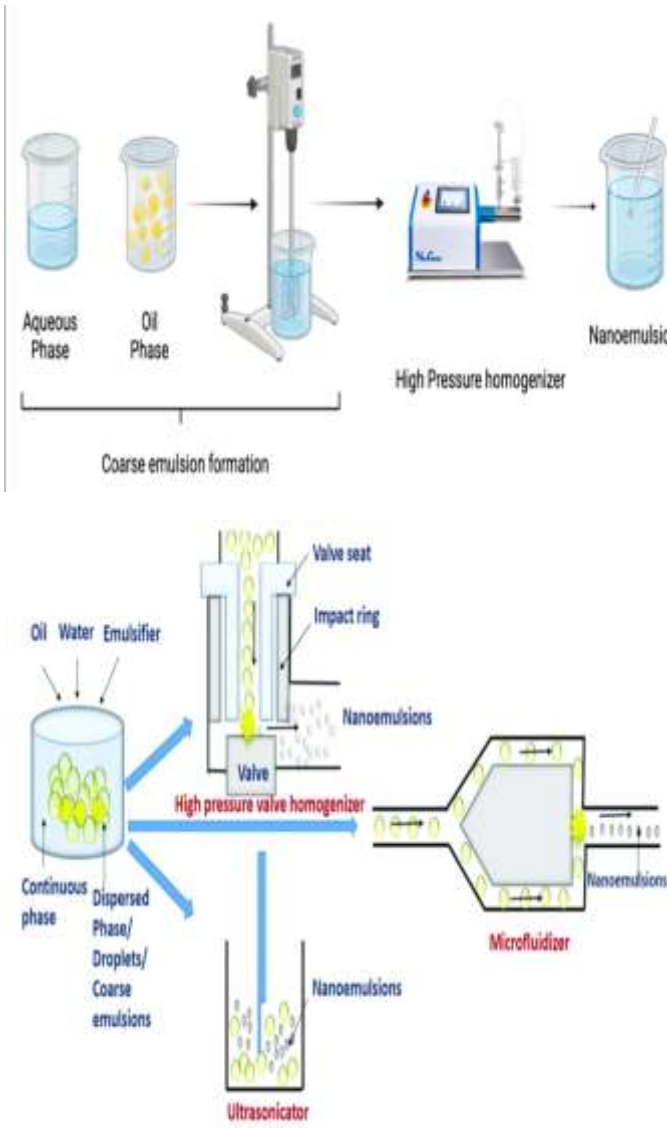
Ultrasonication

Spontaneous emulsification

These approaches facilitate the attainment of nanometer-scale droplet sizes and ensure a stable dispersion.

Figure 2

"Preparation Methods of Nanoemulsion"



6.4 Construction of Pseudo-Ternary Phase Diagram

Various ratios of oil, surfactant, co-surfactant, and water were combined and then visually assessed to determine the nanoemulsion region based on their transparency and stability.

Table 2: Composition Ratios Used in Pseudo-Ternary Phase Diagram

Oil (%)	Smix (%)	Water (%)	Observation
10	40	50	Transparent NE
20	30	50	Slightly turbid
30	50	20	Phase separation

6.5 Optimization Using Design of Experiments (DoE)

Optimized factors include:

- Concentration of oil
- Concentration of surfactant
- Ratio of Smix
- Speed of homogenization

Responses measured:

- Droplet size
- PDI
- Drug release

6.6 Evaluation Parameters

6.6.1 Physicochemical Characterization

- Size of droplets and PDI (Dynamic light scattering)
- Zeta potential
- Viscosity
- pH level
- Drug content and efficiency of entrapment

6.6.2 In Vitro Drug Release Study

The experiment utilized a Franz diffusion cell equipped with a dialysis membrane. To prevent any leakage, the membrane was meticulously positioned between the donor and receptor sections. The donor section was loaded with the test formulation, whereas the receptor section was filled with an appropriate dissolution medium kept at a temperature of 37 ± 0.5°C. At specified time points, samples were taken for analysis and replaced with fresh medium to sustain sink conditions.

6.6.3 Ex Vivo Skin Permeation Study

Utilizing removed animal or human skin, this model facilitates a controlled examination of skin permeability and drug diffusion in a standardized setting. It offers important understanding of how topical formulations interact with the skin barrier. Moreover, it aids in assessing the effectiveness and safety of new dermatological products prior to clinical testing.

6.6.4 Stability Study

Tests were conducted under accelerated conditions of 25°C/60% RH and 40°C/75% RH, which mimic common storage environments to evaluate the product's stability and shelf life. At set intervals, samples were examined to track any physical, chemical, or microbiological alterations. The resulting data offer essential information for determining suitable expiration dates and storage guidelines.

6.6.5 Antifungal Activity Study

Assessment of inhibition zones against fungal strains. The inhibition zone was assessed by gauging the clear region around fungal colonies on agar plates. Larger inhibition zones suggest stronger antifungal properties of the agents tested. This evaluation offers a quantitative measure of the substances' effectiveness against the fungal strains.

7. RESULTS

7.1 Optimization Results

The optimized nanoemulsion exhibited:

Droplet size is less than 100 nm

PDI is below 0.3

Zeta potential ranges from −20 to −30 mV

Drug entrapment is high, exceeding 90%

These characteristics suggest a stable nanoemulsion with consistent distribution.

Table 3: Physicochemical Evaluation of Optimized Nanoemulsion

Parameter	Result
Droplet size	92 ± 3 nm
PDI	0.25 ± 0.02
Zeta potential	−24 mV
Drug content	98.5%
Entrapment efficiency	94%

7.2 In Vitro Drug Release

The nanoemulsion demonstrated a prolonged release pattern in contrast to traditional cream, indicating improved drug dissolution. This enhancement in dissolution is due to the nanoemulsion's smaller droplet size and larger surface area, which promote superior drug solubility. Moreover, the nanoemulsion matrix offers a protective setting, minimizing drug degradation and boosting stability. Together, these elements lead to the sustained and controlled release seen in the formulation.

7.3 Ex Vivo Skin Permeation

There was a notable increase in drug permeation, suggesting improved penetration through the stratum corneum.

7.4 Antifungal Activity

The nanoemulsion showed a greater zone of inhibition than the marketed formulation, indicating superior therapeutic effectiveness. This increased activity is due to the nanoemulsion's smaller droplet size and larger surface area, which enhance penetration and allow for a sustained release of the active ingredient. Furthermore, the stability and even distribution of the nanoemulsion enhance its antimicrobial effectiveness. These results indicate that nanoemulsion formulations have considerable potential to enhance therapeutic outcomes over traditional marketed products.

8. DISCUSSION

Delivery systems utilizing nanoemulsions have effectively improved the solubility, stability, and therapeutic effectiveness of antifungal drugs with low solubility. By decreasing droplet size, the surface area was expanded, leading to an enhanced rate of drug dissolution. Surfactants and co-surfactants served as permeation enhancers, aiding in the transport of drugs across skin layers. The optimized formulation demonstrated outstanding physicochemical stability and a prolonged release of the drug. Enhanced antifungal activity indicated superior therapeutic performance when compared to traditional formulations. Additionally, nanoemulsions minimized irritation and boosted patient compliance due to their non-greasy texture and regulated drug delivery.

9. Conclusion

Drug delivery systems utilizing nanoemulsions offer a highly promising approach to improve the solubility, stability, and therapeutic effectiveness of antifungal agents with low water solubility in topical applications. By employing systematic design, optimization, and assessment, nanoemulsions can address significant formulation issues found in traditional topical dosage forms. The optimized nanoemulsion exhibited enhanced physicochemical properties, increased skin penetration, prolonged drug release, and superior antifungal efficacy. These results highlight the potential of nanoemulsion systems as advanced topical delivery platforms for antifungal treatments. Future studies should concentrate on large-scale production, clinical trials, and the integration of multifunctional excipients to further improve therapeutic results.

10. References

1. Shaikh NM et al. Formulation and Evaluation of Nanoemulsion for Topical Application. J Drug Delivery Ther.

2. Patel S et al. Nanoemulsion: Methods and application in drug delivery. Nat J Pharm Sci.

3. Gorle A et al. Design and Characterization of Posaconazole Nanoemulsion.

4. Kakade KS et al. Nanoemulsion-Based Gel for Topical Fungal Treatment.

5. Pontes CS et al. Improving Drug Delivery on Candida albicans Using Geraniol Nanoemulsion. Pharmaceutics.

6. Kaur M et al. Novel Nanoemulgel Formulation of Luliconazole.

7. Chaurasiya C et al. Herbal Nanoemulsion in Topical Drug Delivery.

8. ACS Omega. Natural Oils Enhance the Topical Delivery of Ketoconazole by Nanoemulgel.

9. Mahoto et al. Nanoemulsion Gel of Terbinafine for Treating Fungal Infections.

10. MDPI Review on Nanoemulgels as Advanced Topical Drug Delivery Systems.

11. Elmataeeshy, M. E., Sokar, M. S., Bahey-El-Din, M., & Shaker, D. S. (2018). Enhanced transdermal permeability of Terbinafine through novel nanoemulgel formulation; Development, in vitro and in vivo characterization. *Future Journal of Pharmaceutical Sciences*, *4*(1), 18–28. https://doi.org/10.1016/j.fjps.2017.07.003

12. Esson, M. M., & Mecozzi, S. (2020). Preparation, Characterization, and Formulation Optimization of Ionic-Liquid-in-Water Nanoemulsions toward Systemic Delivery of Amphotericin B. *Molecular Pharmaceutics*, *17*(6), 2221–2226. https://doi.org/10.1021/acs.molpharmaceut.9b00809

13. Yang, W., Wiederhold, N. P., & Williams, R. O. (2008). Drug delivery strategies for improved azole antifungal action. *Expert Opinion on Drug Delivery*, *5*(11), 1199–1216. https://doi.org/10.1517/17425240802457188

14. Rehman, F. U., Shah, K. U., Shah, S. U., Khan, I. U., Khan, G. M., & Khan, A. (2016). From nanoemulsions to self-nanoemulsions, with recent advances in self-nanoemulsifying drug delivery systems (SNEDDS). *Expert Opinion on Drug Delivery*, *14*(11), 1325–1340. https://doi.org/10.1080/17425247.2016.1218462

15. Eqbal, A., Ansari, V. A., Hafeez, A., Ahsan, F., Imran, M., & Tanweer, S. (2021). Recent Applications of Nanoemulsion Based Drug Delivery System: A Review. *Research Journal of Pharmacy and Technology*, 2852–2858. https://doi.org/10.52711/0974-360x.2021.00502

16. Tejashri, G., Amrita, B., & Darshana, J. (2013). Cyclodextrin based nanosponges for pharmaceutical use: A review. *Acta Pharmaceutica*, *63*(3), 335–358. https://doi.org/10.2478/acph-2013-0021

17. Chauhan, A., Kamal, R., Mishra, R., Shekho, D., & Awasthi, A. (2024). A Comprehensive Guide to the Development, Evaluation, and Future Prospects of Self-nanoemulsifying Drug Delivery Systems for Poorly Water-soluble Drugs. *Current Pharmaceutical Design*, *30*(16), 1211–1216. https://doi.org/10.2174/0113816128296705240327065131

18. Jacob, S., Nair, A. B., & Shah, J. (2020). Emerging role of nanosuspensions in drug delivery systems. *Biomaterials Research*, *24*(1). https://doi.org/10.1186/s40824-020-0184-8

19. Kim, C.-K., & Park, J.-S. (2004). Solubility Enhancers for Oral Drug Delivery. *American Journal of Drug Delivery*, *2*(2), 113–130. https://doi.org/10.2165/00137696-200402020-00004

20. Singh, B., Bandopadhyay, S., Kapil, R., Singh, R., & Katare, O. P. (2009). Self-Emulsifying Drug Delivery Systems (SEDDS): Formulation Development, Characterization, and Applications. *Critical Reviews in Therapeutic Drug Carrier Systems*, *26*(5), 427–451. https://doi.org/10.1615/critrevtherdrugcarriersyst.v26.i5.10