EJPMR, 2026, 13(3), 52-54 **Review Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

A COMPREHENSIVE REVIEW ON KETOCONAZOLE-LOADED NANOSPONGES IN NANOEMULGEL FORMULATIONS FOR ENHANCED TOPICAL ANTIFUNGAL THERAPY

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DOI: https://doi.org/10.5281/zenodo.18796514

How to cite this Article: N. Arjun*, Deekshitha. (2026). A Comprehensive Review on Ketoconazole-Loaded Nanosponges In Nanoemulgel Formulations For Enhanced Topical Antifungal Therapy. European Journal of Biomedical and Pharmaceutical Sciences, 13(3), 52–54.

Article Received on 28/01/2026 **Article Revised on 18/02/2026** **Article Published on 01/03/2026**

ABSTRACT

Fungal infections pose a serious dermatologic problem, and cases of superficial and systemic mycoses are also increasing all over the world. Ketoconazole is a broad-spectrum imidazole antifungal agent that is commonly used in the treatment of fungus but has limited aqueous solubility, poor skin penetration and can cause irritation when applied in the classical topical preparations. To address these drawbacks, new innovations have used nanosponges which is a new polymeric delivery system in conjunction with nanoemulgel formulations to improve the solubility of drugs, penetration in the skin, and controlled release.[1,2] This review aims at the overall design of loading ketoconazole nanosponges into nanoemulgels, the formulation strategies, methods of preparation, the physicochemical characterization, antifungal activity and its clinical application in the future.[4,5] Research indicates an increase in bioavailability, prolonged drug release, antifungal activity and patient compliance than conventional formulations.[5,6] The combination of nanosponges and nanoemulgels have a great potential in dermatological treatment solutions.[2,7]

KEYWORDS: Ketoconazole; nanosponges; nanoemulgel; topical delivery; antifungal therapy; drug release; skin penetration.

INTRODUCTION

Millions of patients across the world are infected with superficial fungal infection, which causes them discomfort, disfigurement, and quality of life.[7] The skin, as it is a barrier agent, restricts the penetration capabilities of antifungal drugs applied to it.[2,7]

Ketoconazole is a strong antifungal that is available to treat dermatophyte, candidiasis and seborrheic dermatitis.[6] Although it has a wide spectrum of activity, traditional ketoconazole preparations such as creams and shampoos have low solubility in water and low skin penetration.[3,5] Also, these formulations may produce some irritants on the local site, and have to be used frequently which result in poor patient compliance.[3,6]

New development in nanotechnology has provided ways of overcoming these problems.[7] Owing to their porosity and capacity to entrap hydrophilic and lipophilic medicines, nanosponges have become the possible carriers of controlled drug delivery.[1,4] Together with nanoemulgels, nanoemulsions that are inserted into a gel base, the composite system has two advantages: its improved solubility and increased residence time on the skin.[2,5] This new method enhances the efficacy of ketoconazole therapeutically and reduces the side effects.[5,6]

This is a review of the formulation, evaluation, and therapeutic prospects of ketoconazole-loaded nanosponges entrusted into nanoemulgel systems. It shows the benefits of this mixed-delivery tool in comparison with traditional therapies and emphasizes the opportunities of its clinical implementation in the future.[2,7]

KETOCONAZOLE: PROFILE AND LIMITATIONS

Ketoconazole is an imidazole analog which blocks fungal cytochrome P450 enzymes, interfering with the production of ergosterol and hence breaking the cell membrane structure of fungal cells.[6] It has good activity against a great variety of fungi such as dermatophytes, yeasts, and systemic fungi.[6] Nevertheless, its low water solubility (0.05 mg/mL), absorbing with pH, and low permeability properties make it ineffective in topical delivery systems.[3,5] Topical ketoconazole preparations are likely to be quickly excreted through the skin surface and they are likely to require frequent applications.[5,6] In addition, the lipophilicity of the drug leads to unpredictable absorption and possible irritation.[3,6]

Therefore, there is an urgent necessity in the delivery systems that could increase the solubility, retention, and controlled release of ketoconazole at the location of infection.[2,5]

NANOSPONGES: DEFINITIONS, TYPES, AND MECHANISMS

Nanosponges are small hollows, porous materials that are usually created by the cross-linking of polymers like cyclodextrins with an appropriate cross-linker like diphenyl carbonate or carbonyldiimidazole.[1] The sponge-like structure enables them to entrap a range of drugs, which is a controlled and sustained release profile.[1,4] Nanosponges can be made out of cyclodextrin-based nanosponges[1], ethyl cellulose nanosponges[4] and with the hyper-crosslinked polymer nanosponges.[7] Other widespread preparation procedures are solvent evaporation, emulsion solvent diffusion, and ultrasonication.[4] Nanosponges are most often prepared through the solvent evaporation method of ketoconazole loading.[4] Under this technique, ketoconazole is added to an organic solvent with the polymer and the whole solution is emulsified into an aqueous phase that contains a stabilizer, such as polyvinyl alcohol (PVA). This is followed by the evaporation of the solvent on a lowered pressure, which leads to the development of nanosponges to entrap the drug.[4] Such advantages include; high drug loading, stability throughout a wide range of pH, controlled and sustained drug release, increase in skin permeability, and the decreased possibility of irritation.[1,2,4–6]

NANOEMULGEL: CONCEPT AND BENEFITS

Nanoemulgels Nanoemulgels consist of a biphase delivery system in which a nanoemulsion is entraped within a gel matrix.[2,5] Nanoemulsions are thermodynamic stable mixtures of two incompatible-liquids that have been stabilized by surfactants.[2] The topical delivery of hydrophobic drugs such as ketoconazole is preferably done using these systems because of their low drop size and increased permeation capability.[2,5] The gel base is usually a form of polymers such as Carbopol or hydroxypropyl methylcellulose (HPMC), which provides the formulation with viscosity and enhances its ability to remain on the skin surface.[2] Nano emulsion combined with a gel does not only increase the aesthetic appeal and spreadability but also increases the contact time with the skin and hence improves bioavailability.[2,5] Advantages of nanoemulgel are that the hydrophobic drugs are more soluble, the skin penetration because of the nanoscale droplets, the compound is non-greasy and easy to apply to patients, drug retention and regulated release, and reduced application frequency.[2,5,6]

FORMULATION STRATEGIES OF KETOCONAZOLE-LOADED NANOSPONGES IN NANOEMULGEL

The nanosponges that are loaded with ketoconazole are prepared by determining appropriate polymers, and balancing drug to polymer ratios to achieve maximum entrapment and release profile.[1,4] The polymers that are commonly used are beta-cyclodextrin and ethyl cellulose where stabilizers such as PVA are used in aqueous phases.[1,4]

After the preparation of nanosponges, the latter are placed in a nanoemulgel.[2,5] The drug-loaded nanosponges are then combined with oils (isopropyl myristate or caprylic/capric triglyceride), surfactants (Tween 80 or Span 20), and co-surfactants (propylene glycol or ethanol) and high-shear mixing or ultrasonication is used to form the nanoemulsion.[2,5] This emulsion is then inbedded into a gel base which results in the final nanoemulgel formulation.[2,5]

The important formulation factors are the choice of oils and surfactants to promote droplet compatibility with drugs, droplet size optimization as a skin penetration factor, pH and viscosity modification to promote skin-compatibility and finally testing the stability of the product to achieve a long shelf life.[2,5]

CHARACTERIZATION AND EVALUATION

The most important parameters of the evaluation are the analysis of the particle size and zeta potential, Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), in vitro drug release in Franz diffusion cells, and in vivo skin permeation.[1,2,4–6]

ANTIFUNGAL EFFICACY AND CLINICAL PROSPECTS

Research has indicated that nanoemulgel formulations which are loaded with ketoconazole offer better antifungal effects than traditional creams.[5,6] The increased permeability and prolonged release lead to the prolonged presence of the drug at the place of infection.[5,6] The higher efficacy is supported by zone of inhibition studies and determination of MIC.[6] The benefits of the clinical are reduced dose requirement, decreased side effects and irritation, as well as better patient compliance through less frequent use.[5,6]

CHALLENGES AND FUTURE PERSPECTIVES

Nanoemulgels have issues with scalability, stability in the long-run, regulatory obstacles, and high-cost production.[2,7] The way forward in future studies should be human clinical trials, standard regulatory frameworks and cost effective manufacturing.[7]

CONCLUSION

The Ketoconazole-impregnated nano sponges of nanoemulgel formulations are a new and efficient approach to treating the superficial fungal infections.[2,5] The combination has provided increased drug solubility and enhanced skin retention and duration of drug release which overcome the shortcomings of the traditional formulations.[3,5,6] Further development of formulation science and clinical validation can soon make nanoemulgel systems the topical antifungal treatment of choice.[2,7]

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