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REVIEW ARTICLE

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KETOCONAZOLE-LOADED NANOGELS FOR TOPICAL DRUG DELIVERY IN FUNGAL INFECTIONS: FORMULATION STRATEGIES, EVALUATION AND RECENT ADVANCES

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ABSTRACT: A significant issue in dermatological health is superficial fungal infections, and traditional topical antifungal formulations have drawbacks that might make it more difficult for the medication to reach the afflicted skin. However, the broad-spectrum imidazole antifungal drug ketoconazole (KTZ), which is often used to treat superficial fungal infections, may not dissolve, release, distribute, or be topically available in the targeted region due to its lipophilicity and poor water solubility. With its hydrated 3D polymeric network and nanoscopic carrier characteristics, nanogels have been identified as promising drug delivery nanostructured systems with the potential to improve drug loading capacity, controlled release, skin residency, and local drug deposition. A critical review and discussion are held regarding the formulation approach, physicochemical characterization, drug-release, skin permeation, deposition, antifungal activity, safety, stability, and recent developments of ketoconazole-loaded nanogels for topical treatment of fungal infections. Additionally discussed are polymer selection, cross-linking procedures, preparation methods, formulation parameters, and quality-by-design and design-of-experiments methodologies for nanogel optimization. A comparative discussion is given of recent developments in a range of nanoemulsions, nanoemulgels, liposomal systems, solid lipid nanoparticles, nanostructured lipid carriers, nanofibrous systems, and novel nanogels. The distinction between real nanogels and other nanostructured gel systems is highlighted, along with the reasons why surface infections need deposition in the skin rather than maximal penetration thru the epidermis. These nanogels have not yet been validated; evidence points to their potential, but they have not yet been compared to other medications and need more standardization, long-term stability, scaling up, *in vivo* performance, and clinical translation. Strong formulation optimization and comparison investigations with therapeutically relevant formulations are required for future study.

Keywords: Ketoconazole; Nanogels; Topical drug delivery; Fungal infections; Skin deposition; Antifungal therapy

I. INTRODUCTION

One kind of fungal infection that poses a significant threat to world health is superficial fungal infections. The quality of life is diminished due to the recurrence and prevalence of common skin diseases such as Candidal, Malassezia-associated, and dermatophytic infections caused by genera such as Trichophyton, Microsporum, and Epidermophyton. The significance of effective treatment methods and optimised delivery systems is further highlighted by the increasing emergence of antifungal resistance [1].

One advantage of using topical antifungal treatments is that they target the infection at its surface, reducing the risk of systemic exposure. However, the drug's solubility, release, skin penetration, and skin retention duration determine its efficacy. The stratum corneum, the main obstacle to cutaneous drug transport and a restrictor of therapeutic medication availability, may impair the efficacy of conventional topical dose forms. Nanoemulsions, liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nanogels are some of the nanostructured delivery methods that have recently attracted a lot of attention for improving the administration of drugs topically [2].

For the majority of superficial fungal infections, including dermatophytosis, pityriasis versicolor, cytotoxic candidiasis, and seborrhoeic dermatitis, the medicine of choice is ketoconazole (KTZ), a broad-spectrum imidazole antifungal agent. Inhibiting fungal ergosterol production is the fundamental mechanism of its antifungal action. Ketoconazole has shown therapeutic benefit; nevertheless, it may be difficult to dissolve, distribute uniformly, release, or administer topically due to its high lipophilicity and poor water solubility [3]. Consequently, several nanostructured delivery strategies have been investigated to improve the topical administration of ketoconazole. Antifungal activity and drug release, penetration, and deposition are all improved over traditional formulations by using nanocarriers such as nanoemulgels, nanoemulsions, and others. The findings point to the need for

nanoscale tactics to address significant issues with conventional ketoconazole formulations [4]. Nanogels' combination of 3D polymeric gel network with nanoscale carrier characteristics is one of its main selling points. Improved skin contact and residence duration, regulated medication release, and the incorporation of pharmaceuticals that are poorly water-soluble are all possible outcomes of this design. It is compatible with any other potential use of nanogels in topical treatment; recent studies using antifungal nanogels containing miconazole and terbinafine have shown favourable drug-retention, penetration, release, and antifungal characteristics [5].

Nanogel composition, production, drug-loading, characterisation, skin penetration models, and biological assessment are all areas where the literature is inconsistent. In addition, most of the recent studies have focused on the delivery of different types of nanostructured antifungals, but they haven't really examined the connections between ketoconazole's physicochemical properties, the factors in nanogel formulation, skin distribution, and therapeutic impact. Accordingly, ketoconazole-loaded nanogels should be thoroughly investigated [6].

This study takes a close look at nanogels loaded with ketoconazole and discusses their new developments, formulation techniques, physicochemical characterisation, drug release behaviour, skin penetration and deposition, antifungal activity, stability, and safety. The paper goes on to compare nanogels to other state-of-the-art topical administration systems and brings attention to the difficulties in optimising, scaling up, translating regulations into practice, and developing them for clinical use. Finally, we talk about some exciting new prospects for ketoconazole nanogel development, such as design-of-experiments, stimuli-responsive nanogels, and quality-by-design [7].

2. Ketoconazole: Pharmacological, Physicochemical and Biopharmaceutical Considerations

2.1 Pharmacological profile and mechanism of action

Dermatophytosis, pityriasis versicolor, cutaneous candidiasis, and seborrhoeic dermatitis are all examples of superficial fungal infections that may be treated with ketoconazole (KTZ), a broad-spectrum imidazoles antifungal medication. The major reason it has antifungal properties is that it may hinder the enzyme CYP51, which is involved in the manufacture of ergosterol, which is produced by fungal lanosterol 14α-demethylase. Fungi development and fungal membrane structure are both impacted by this pathway's inhibition.When treating superficial fungal infections, it is best to apply the medication topically so that it may reach the infection site and avoid systemic exposure [8].

2.2 Physicochemical characteristics

With a high logP value of around 4.3, ketoconazole has a molecular weight of approximately 531.4 g/mol. A major hurdle in its formulation is its poor water solubility, which might reduce the drug's efficacy and accessibility when applied topically using conventional methods. How well ketoconazole dissolves and disperses in a solution may also depend on the pH of the formulation and whether or not surfactants, solubilizers, or other excipients are included. Consequently, it is important to strike a balance during formulation development between drug solubilization, stability, and skin compatibility (Table 1) [9].

Table 1: Key physicochemical and biopharmaceutical characteristics of ketoconazole [12]

S. No.	*Characteristic*	*Ketoconazole*	*Relevance to topical nanogel formulation*
1	Drug class	Imidazole antifungal	Determines antifungal therapeutic role
2	Therapeutic category	Broad-spectrum antifungal	Suitable for treatment of superficial fungal infections
3	Molecular formula	$C_{26}H_{28}Cl_2N_4O_4$	Useful for structural and analytical characterization
4	Molecular weight	~531.4 g/mol	Influences diffusion, loading and skin transport
5	Chemical nature	Synthetic imidazole derivative	Determines drug–excipient compatibility
6	Lipophilicity	High	Promotes interaction with lipid-rich skin domains
7	XlogP	~4.3	Indicates strong lipophilic character
8	Aqueous solubility	Poor	Major limitation for conventional topical formulations
9	Biopharmaceutic challenge	Low aqueous solubility	May restrict dissolution and drug availability
10	Ionization behavior	pH-dependent	Influences solubility and drug–polymer interactions
11	Primary molecular target	Fungal CYP51/lanosterol 14α-demethylase	Determines mechanism of antifungal action
12	Mechanism of action	Inhibition of ergosterol biosynthesis	Disrupts fungal membrane structure and function
13	Major therapeutic target	Superficial fungal infection sites	Supports localized topical delivery
14	Stratum-corneum interaction	Significant	May promote local skin retention
15	Skin-delivery challenge	Balance between retention and penetration	Excessive retention or permeation may reduce therapeutic efficiency
16	Drug-loading requirement	High incorporation desirable	Supports adequate dose within nanogel
17	Release requirement	Controlled/sustained release desirable	Can maintain local drug availability
18	Suitable delivery strategy	Nanoscale polymeric carrier	May improve dispersion and regulate drug release
19	Important formulation attributes	Particle size, PDI, zeta potential, EE%, rheology	Determine stability and topical performance
20	Overall nanogel rationale	Poor solubility + high lipophilicity + need for local delivery	Provides a strong rationale for ketoconazole-loaded nanogel development

2.3 Biopharmaceutical limitations in topical delivery

Although ketoconazole's lipophilicity helps it reach the lipid-rich stratum corneum, it also causes it to stay in the outer skin layers for too long, which may prevent it from penetrating deeper into the skin. There may be a cap on the quantity of free drug at the formulation-skin contact due to the medication's restricted water solubility. Thus, for the substance

to be effectively delivered topically, there must be a balance between its solubilization, partitioning, diffusion, skin retention, and controlled release [10].

2.4 Rationale for nanogel-based delivery

Ketoconazole seems to be a good candidate for nanogel delivery based on its physicochemical properties. Incorporating pharmaceuticals into a nanoscale environment is possible with nanogels, and improving skin contact, residence duration, and release control is possible with a hydrated polymeric network. Thus, in creating ketoconazole nanogels, it is important to consider the following formulation attributes: drug-loading efficiency, particle size, crosslinking density, pH, rheology, drug release, skin deposition, stability, and safety [11].

3. Skin as a Biological Barrier to Topical Ketoconazole Delivery

3.1 Skin structure and drug-delivery barrier

The epidermis, dermis, and subcutaneous tissue make up the majority of the skin. The primary obstacle to drug transport in topical drug administration is the stratum corneum, the uppermost layer of the epidermis. This greatly hinders the transfer of several therapeutic compounds and is made up of corneocytes incased in a structured lipid matrix [13]. The goal of topical therapy for superficial fungal infections is to reach sufficient medication levels in the afflicted skin layers rather than necessary penetrating the skin systemically. Therefore, it is important to create a ketoconazole formulation that would allow for its deposition and retention at the application site while preventing any undesirable systemic transport [14].

3.2 Skin-penetration pathways

There are three primary ways that medications applied topically might enter the skin: intercellular, transcellular, and follicular. The transcellular route passes via the corneocytes and the intercellular lipids, whereas the intercellular route passes through the lipid domains that surround the corneocytes. The follicular route is a different channel that passes via the hair follicles and related tissues. The degree to which these routes contribute depends on the physicochemical characteristics of the medication as well as formulation characteristics such molecular size, lipophilicity, ionisation, surface charge, and carrier composition [15].

3.3 Barriers to ketoconazole delivery

However, ketoconazole's poor water solubility may limit the amount of medication that is easily accessible at the formulation-skin interface, while its high lipophilicity may aid partitioning into the lipid-rich stratum corneum. If there is too much retention in the outer layers of the skin, the swelling may also hinder some migration to deeper target locations. Therefore, maximising transdermal permeability is not as crucial for good topical distribution as the appropriate sol-sol, part-part, diff-part, and skin-retain components of the topical delivery system (Fig. 1) [16].

3.4 Role of nanogels in skin delivery

With nanogels, the hydrated polymeric network and nanoscale size may change how ketoconazole interacts with the skin at the cellular level. Their huge surface area may improve skin contact, and the gel matrix may delay a drug's release and give it a longer-lasting effect. Additionally, the barrier function of the stratum corneum, the skin's outer layer, may be impacted by the moisture and occlusive action [17]. However, an increase in penetration may not always translate into a therapeutic benefit. For superficial fungal infections, skin deposition and retention may be more significant goals than maximal receptor-phase transport [18].

3.5 Factors affecting nanogel-mediated delivery

Nanogel performance is influenced by a number of variables, including drug loading, penetration enhancers, pH, viscosity, cross linking density, polymer composition, surface charge, PDI, and particle size. Drug distribution may also be altered by other biological variables, including skin moisture, inflammation, and barrier integrity [19].

Therefore, rather than taking into account each formulation parameter separately, optimisation of ketoconazole nanogels should be carried out by linking the physiochemical characteristics with the skin deposition, antifungal efficacy, safety, and stability of the formulation [20].

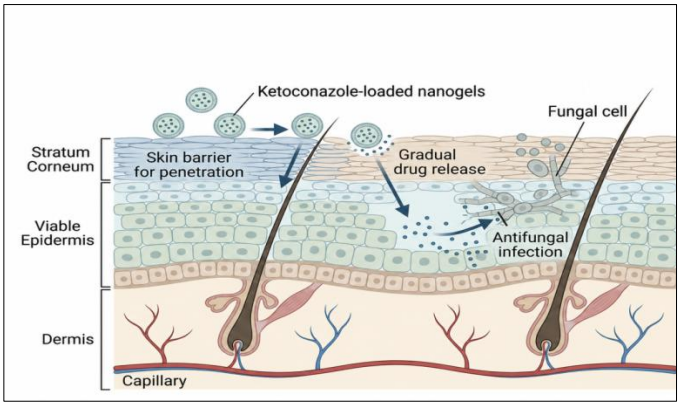


Figure 1: Skin barrier and proposed delivery mechanism of ketoconazole-loaded nanogel

4. Nanogels as Advanced Topical Drug-Delivery Systems

4.1 Definition and characteristics

Nanogels are three-dimensional, crosslinked polymeric networks that are nanoscopic and capable of preventing large volumes of water from penetrating the structure. They combine the swelling, residence, and drug-retention of hydrogels with the large surface area and adjustable characteristics of nanocarriers. By altering the polymer composition, crosslinking density, particle size, and surface characteristics, their characteristics may be modified. This design may provide a suitable environment for drug integration in topical applications, improve skin contact, and regulate drug release [21].

4.2 Classification and composition

Nanogels may be categorised as natural, synthetic, or hybrid systems based on their polymeric makeup. While synthetic polymers provide more control over network form and characteristics, natural polymers such as chitosan, alginate, gelatine, and hyaluronic acid are biocompatible. The advantages of both may be found in hybrid systems [22]**.** The drug, the polymeric matrix, the cross-linker, the aqueous phase, and functional excipients such as surfactants, solubilizers, stabilisers, or penetration enhancers can all be considered the active components of a ketoconazole nanogel. Particle size, drug loading, swelling and release, stability, and skin compatibility may all be influenced by the selection and concentration of these elements [23].

4.3 Drug-loading mechanisms

Depending on the drug–polymer combination, ketoconazole may be physically confined in the nanogels or *via* hydrophobic, electrostatic, or hydrogen bonding with the polymer. Since ketoconazole is highly lipophilic, medication incorporation may be significantly impacted by hydrophobic interactions [24]**.** However, when a drug-polymer interaction is too strong, it might restrict drug release. Therefore, a high drug loading, adequate drug availability, and controlled release must be ensured during formulation development [25].

4.4 Advantages and limitations

The use of nanogels for topical delivery of antifungal agents has several potential benefits, such as:

- Adhesion to the wall; and
- High surface area for skin interaction, and
- Delayed drug release; or
- Exposure to the applicational environment for a long duration;
- Adjustable particle size and surface properties; and
- Potential improvement in local drug deposition.

However, the nanogels have some disadvantages, including polymer variability, crosslinking control, aggregation, drug leakage, long-term stability, manufacturing repeatability, and scale-up. Controlling leftover solvents or crosslinking agents could also be essential [26]**.**

4.5 Relevance to ketoconazole delivery

Because of the compound's high lipophilicity, the use of nanogels to increase ketoconazole's water solubility and, therefore, topical distribution, is attractive. The polymeric network may assist extend the drug's residence duration in the skin and regulate its release, while the nanoscale carrier may aid in the drug's dispersion throughout the skin [27]. Most notably, the use of larger drug loading or lower particle sizes to improve nanogels does not justify their selection. In an integrated evaluation of drug release, skin deposition, antifungal activity, safety, and stability, their worth should be ascertained. When comparing nanogels to other comparable nanoformulations like liposomes, SLNs, NLCs, nanoemulsions, and nanoemulgels, there is a noticeable difference (Fig. 2) [28]**.**

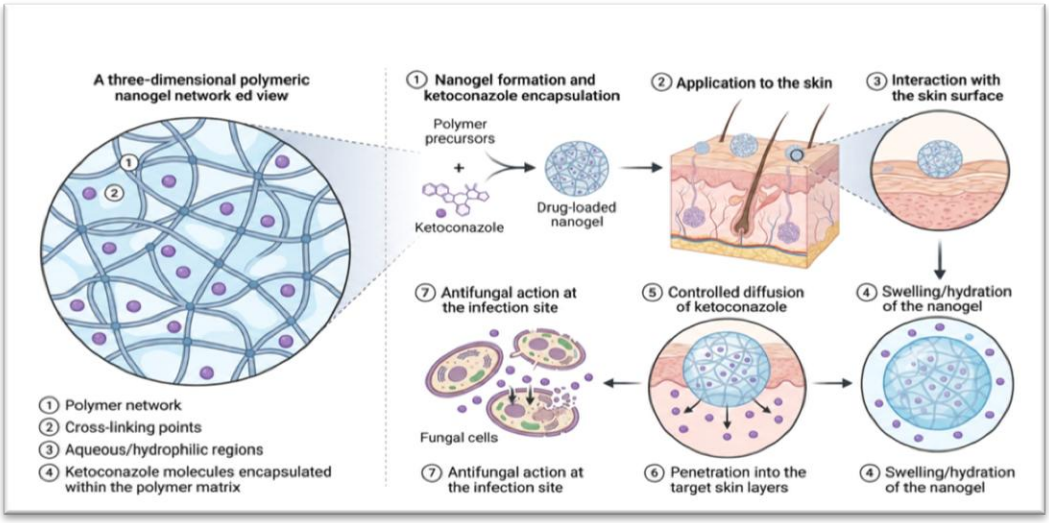


Figure 2: Architecture and drug-delivery mechanism of ketoconazole-loaded nanogels

5. Formulation Strategies for Ketoconazole-Loaded Nanogels

The performance of the ketoconazole-containing nanogels is influenced by the kind of polymer, crosslinking of polymers, drug-loading technique, excipients, and processing conditions. Particle size, medication loading, release, skin contact, stability, and antifungal efficacy are all impacted by these variables. Therefore, if formulation development is to be undertaken, there should be a link between the formulation variables, important quality features, and topical performance [29]**.**

5.1 Polymer selection

Polymers that control swelling, mechanical properties, drug loading, degradation, and release size make up the structure of nanogels. In contrast to synthetic polymers, which provide greater control over network structure and physicochemical properties, natural polymers, such as chitosan, alginate, gelatine, and hyaluronic acid, are biocompatible, have functional groups for drug incorporation, and are less controlled [30]**.** The fact that ketoconazole is extremely lipophilic and weakly soluble in water should be taken into consideration while choosing polymers for it. The medication should be able to be incorporated into the polymeric environment without significantly impeding drug diffusion. As a result, the ideal polymer should strike a compromise between drug loading, release, stability, and skin compatibility [31].

5.2 Cross-linking strategies

Crosslinking refers to a nanogel's three-dimensional polymeric network. This might be accomplished physically or covalently. Covalent methods often provide more structural stability, but they may also need purification, careful assessment of leftover chemicals, and chemical or cleavable cross-linkers. Physical crosslinking is a reversible contact that may be simpler to construct and may manifest as hydrophobic, electrostatic, or hydrogen bonding interactions. Cross linking density may be directly linked to oedema and medication release. Too few networks may result in poor structural stability, whereas too many networks might hinder ketoconazole's dissemination. Therefore, in order to get the intended release and stability profile, the crosslinking must be optimized [32].

5.3 Nanogel preparation methods

Common preparation techniques include emulsion/cross-linking, precipitation, polymerisation, self-assembly, and solvent-diffusion. The required particle size, drug loading mechanism, drug solubility, and polymer characteristics all play a role in the method selection process. Emulsion-based methods may be used to create nanoscale polymeric domains, however they may necessitate the use of organic solvents and surfactants, which calls for organic solvent management and purification. Both the solvent-diffusion approach and the precipitation method provide controlled nanosizing, but they need optimisation of the solvent composition, polymer content, mixing intensity, and surfactant concentration. Non-covalent interactions are used in self-assembly techniques, which may reduce the need for chemical cross-linkers but may need careful assessment of physical stability [33]**.**

It has been demonstrated in recent years that nanogel research with antifungal agents can create nanoscale antifungal nanogel systems using solvent-diffusion and high-speed homogenization techniques, as well as evaluate the properties of the particles, their release from the nanogel, skin penetration, and irritation caused by the nanogel [34].

5.4 Surfactants, solubilizers and penetration enhancers

Stabilisers and surfactants may aid in medication dispersion, reduce interfacial tension, and stop aggregation. Additionally, any co-solvents or solubilizers used for medications that are weakly soluble in water, such ketoconazole, may be suitable for increasing the apparent drug solubility. Penetration enhancers may boost drug deposition or penetration by interfering with the stratum corneum's barrier function. However, full transdermal penetration is not suitable for superficial fungal infections. Increased discomfort or systemic exposure may result from excessive amplification. Therefore, the drug's skin compatibility, local retention, release, and stability should all be considered when choosing excipients [35]**.**

5.5 Critical formulation variables

Some of the significant formulation and process parameters are:

- Processing temperature; and
- Drug-to-polymer ratio;
- Cross-linker concentration;
- Surfactant concentration;
- Solvent composition;
- Phase ratio;
- Homogenization/sonication conditions;
- Processing temperature/pH; and
- Penetration-enhancer concentration.

Particle size, PDI, zeta potential, entrapment efficiency, viscosity, swelling, drug release, and stability may all be affected by these factors. Above all, the effects are interrelated; for example, increased concentrations of polymers or cross-linkers may improve structural stability while simultaneously impeding drug diffusion [36]**.**

5.6 Quality-by-design and DoE-based optimization

A methodical approach to the creation of ketoconazole nanogels may be provided via quality by design (QbD). The evaluation of critical material characteristics and critical process parameters comes after the establishment of the Quality Target Product Profile (QTPP) and the identification of key quality attributes (CQAs).The pertinent CQAs include particle size, PDI, zeta potential, drug content, entrapment efficiency, pH, rheologic characteristics, drug release, skin deposition, antifungal action, safety, and stability [37]**.**

Factorial designs, Box-Behnken designs, and central composite designs are examples of design of experiments (DoE) approaches that may be used to create an optimal design space and identify interactions between formulation variables. Compared to a one factor-at-a-time experiment, DoE may be utilised more effectively to find the important factors and interactions in an experiment [38]**.**

5.7 Formulation optimization strategy

Obtaining the finest particles or the highest trapping efficiency should not be the main goals. A well-made ketoconazole nanogel should have excellent drug loading, controlled release, suitable rheology, physical stability, skin compatibility, efficient local drug deposition, and antifungal efficacy [39]. Therefore, the development of a formulation should begin with the drug's compatibility and solubilization with the polymer, followed by the preparation of nanogel, optimisation of its physical and chemical properties, and finally correlation with the drug's delivery to the skin and biologic activity.

This combination strategy may provide a stronger basis for future scale-up and the creation of repeatable formulations [40].

6. Evaluation and Characterization of Ketoconazole-Loaded Nanogels

To ensure quality, consistency, and therapeutic effectiveness, ketoconazole-containing nanogels should be well characterised. Instead of concentrating on just one of these characteristics, it is crucial to assess physicochemical features in conjunction to drug release, skin delivery, antifungal action, toxicity, and stability [41].

6.1 Particle size, PDI and zeta potential

Particle size and polydispersity index (PDI) are often measured using dynamic light scattering (DLS). The PDI shows the degree of homogeneity of the particle population, while the particle size influences surface area, drug release, colloidal stability, and skin interface. Although a reasonably narrow distribution is preferred for consistency, topical performance is not always improved by smaller particles [42]. The surface charge and potential stability of the colloids are revealed by the zeta potential. Instead of using a universal numerical threshold, the interpretation should consider the different types of polymers, stabilisers, and particle sizes in addition to the storage circumstances. Surface charge may potentially have an impact on how nanogels interact with skin components [43].

6.2 Morphology and structural characterization

TEM, SEM, or AFM may be used to evaluate the morphology, form, surface, and aggregation of nanogel. Because DLS provides measurements for hydrated particles whereas microscope measurements are often performed on dried or immobilised particles, the dimensions acquired by microscopy are frequently lower than those obtained by DLS [44]. A validated analysis, such as HPLC or any other spectrophotometric technique, should be used to determine drug content and drug entrapment efficiency (EE%). Because excessive drug-polymer interaction may impede drug release, high EE% may indicate excellent drug incorporation efficiency but may not necessarily indicate good therapeutic performance [45].

6.3 Drug-excipient compatibility and solid-state properties

DSC and XRD may provide information on the thermal behaviour and crystallinity, while FTIR can help investigate potential drug/excipient interactions. The methods are particularly useful for the medicine ketoconazole, which is weakly soluble in water, as a change in crystallinity may affect the drug's apparent solubility and dissolution. However, in order to prevent recrystallization, the amorphous state should not be physically unstable while being stored [46].

6.4 pH and rheological properties

The topical nanogel's pH should be suitable with the skin and shouldn't irritate it needlessly. Additionally, swelling, drug solubility, ionisation of the polymers, and formulation stability may all be impacted. Viscosity and rheological behaviour affect spreadability, extrudability, residence duration, and drug release. Low viscosity may reduce skin residence, whereas high viscosity can reduce application and patient tolerance. Since the viscosity decreases when applied and then rises again after application, shear-thinning behaviour could be advantageous [47].

6.5 In-vitro drug release

The rate and quantity of ketoconazole released from the nanogel are measured by in-vitro release studies, which may be carried out using membrane-diffusion or dialysis techniques. Release profiles may be compared with those of standard ketoconazole or free medication. Kinetic (zeroth order, first order, Higuchi, and Korsmeyer–Peppas) models are recommended where appropriate. The process of release should be considered while selecting a model rather than just the model with the best correlation coefficient [48].

6.6 Ex-vivo skin permeation and deposition

Ex-vivo skin delivery is often studied using Franz diffusion cells. It is necessary to separate two crucial endpoints:

A. Drug transportation through the skin to the receptor phase is known as penetration.

B. Drug presence in the skin is known as skin deposition or retention.

Since the goal is mostly in the skin's surface layers, greater skin deposition may be more clinically significant for superficial fungal infections than maximal flow across the skin. As a result, an optimised nanogel should have little systemic transit and strong local retention [49].

6.7 Antifungal efficacy

Agar diffusion assays, Microdilution and Microfiltration Concentration (MIC and MFC) assays, and other recognised microbiological tests using clinically significant fungal species may all be used to evaluate antifungal efficacy. To evaluate the impact of the nanogel system, comparison studies between

free ketoconazole, blank nanogel, standard ketoconazole formulation, and the optimised nanogel are required. Zone of inhibition results should be taken cautiously since the measured zone of inhibition may be impacted by the viscosity of the formulations and drug diffusion. Ex vivo or in vivo research, as well as quantitative microbiological testing, would be more persuasive [50].

6.8 Safety and stability

It should be possible to endure repeated topical application. use suitable, verified models to assess barrier effects, cytotoxicity, and irritation. Surfactants, penetration enhancers, crosslinking agents, and leftover solvents need special consideration.Important factors to keep an eye on in stability tests include particle size, PDI, Zeta potential, drug content, pH, viscosity, appearance, aggregation, drug leakage, and release behaviour. Establishing formulation robustness and shelf life requires both accelerated and long-term testing [51].

6.9 Integrated evaluation strategy

The ketoconazole-containing nanogels should be evaluated in the following order: Physicochemical characteristics → formulation characteristics → skin penetration → antifungal activity → stability → safety One parameter cannot be used to determine therapeutic superiority. For example, skin deposition or antifungal action are not usually directly correlated with particle size or EE%. Similarly, if an increase in penetration results in a loss in local retention or an increase in systemic exposure, it may not be desired. Therefore, therapeutically important performance variables, including crucial quality features, should be connected to formulation optimization (Fig. 3) [52].

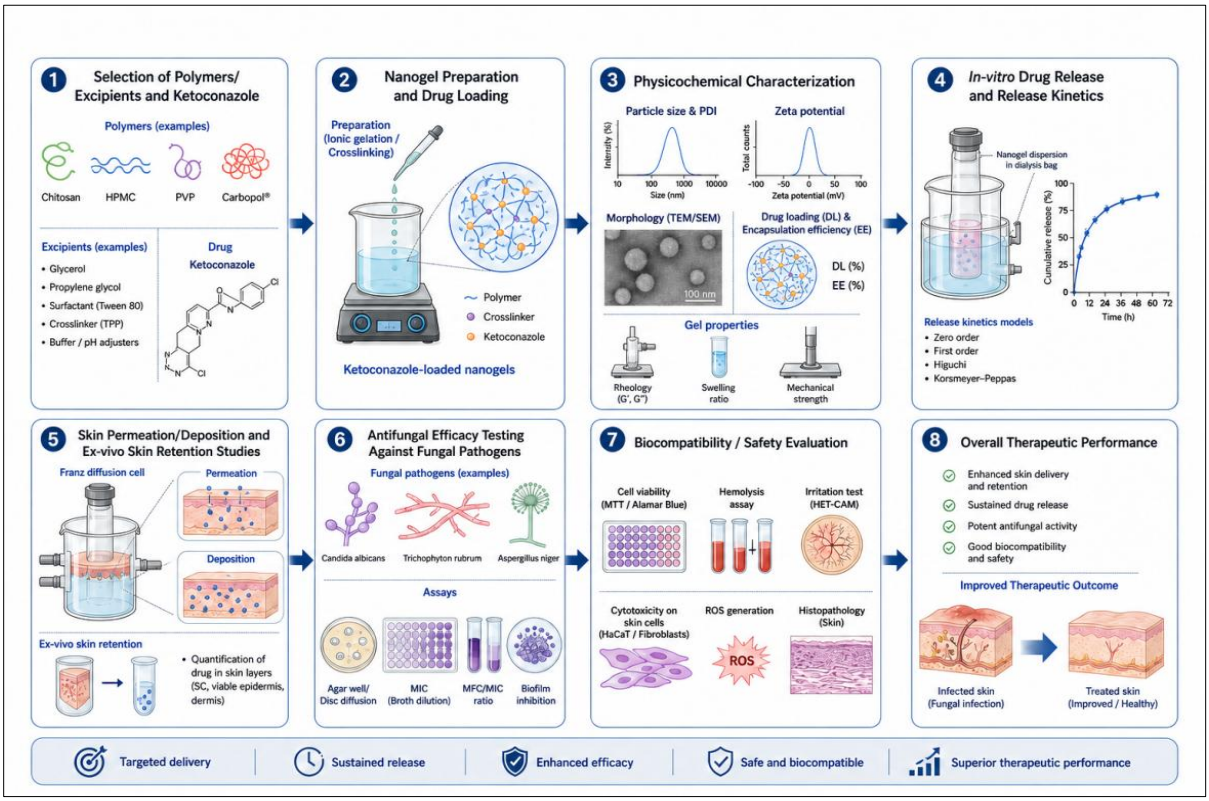


Figure 3: Formulation-to-therapeutic evaluation workflow for ketoconazole-loaded nanogels

7. Recent Advances in Ketoconazole-Loaded Nanostructured Topical Delivery Systems

Many innovative platforms, including liposomal systems, nanostructured lipid carriers (NLCs), nanoemulgels, nanofibers, and nanogels, have been developed in recent years to improve topical administration of ketoconazole. These systems are primarily intended to address the issue of low water solubility, improve skin penetration, administer the medication from the system over an extended period of time, and boost antifungal effectiveness. However, compared to similar nanostructured systems, true ketoconazole loaded nanogels have received comparatively little research [53].

7.1 Lipid-based and vesicular systems

Ketoconazole might be included into SLNs and NLCs, according to preliminary study. In addition to providing better chemical stabilisation of ketoconazole, NLCs also shown some particle size changes during storage. More recent investigations have shown that mucoadhesive ketoconazole-NLCs exhibit sustained-release, ex vivo penetration, and acceptable irritation qualities. However, as superficial fungal treatment primarily requires a localisation of the transport on the skin, the application of greater transdermal flux should be interpreted cautiously [54].

Studies have also been conducted on gels based on transfersomes (transfersomal gels) and liposomes (liposomal gels). It has been discovered that transfersomal Carbopol gels and liposomal gels containing ketoconazole exhibit superior drug release, penetration, and antifungal efficacy. These systems represent the broad notion that a nanoscale carrier combined with a gel matrix may improve drug residence and distribution, even if they are not nanogels in and of themselves. Due to variations in the barriers and treatment goals, the outcomes of vaginal delivery methods cannot be directly applicable to cutaneous fungal diseases [55].

7.2 Nanoemulsion and nanoemulgel systems

Using a nanoemulsion-based technology is one of the most researched approaches for topical ketoconazole administration. In this sense, compared to traditional formulations, ketoconazole nanoemulgels containing clove or eucalyptus oil have been shown to exhibit nanoscale droplets, longer drug release, enhanced epidermal penetration, and an antifungal impact [56].

A poly-δ-decalactone-based ketoconazole nanoemulgel containing eugenol was optimised using the design of experiments method. Sustained release, skin buildup, favourable rheological characteristics, little cytotoxicity, and strong antifungal action were all shown by the formulation. However, because ketoconazole's contribution to antifungal action is unique, the contribution of eugenol should be read cautiously [57]. More recently, the nanoemulsion formulation of the mucoadhesive drug ketoconazole has shown the capacity to induce sustained release and dramatically improve ex vivo permeability over commercial cream. However, as higher transdermal flux is not regarded as superior topical treatment, enhanced permeability must be taken into account in addition to other factors such skin retention, systemic exposure, and irritation [58].

7.3 Nanofibers and nanofibrous systems

It has been shown that ketoconazole nanofibers produced by the electrospinning method are antifungal against a number of filamentous fungi and serve as a high surface area drug delivery platform for regulated drug delivery. The use of ketoconazole nanofibrous patches using polymer blends and experimental design techniques has been investigated in recent works [59]. The recent creation of a nanofibrous gel based on cellulose nanofiber (CNF) extracted from the biomass of banana pseudostems is worth mentioning because it shows high drug release with improved ex vivo skin diffusion, antifungal efficacy against Candida albicans, and biocompatibility. This is particularly intriguing since it combines a potentially sustainable biomaterial platform with nanoscale delivery [60].

7.4 Emerging ketoconazole nanogels

Nevertheless, there were few publications that explicitly described ketoconazole-containing nanogels, despite the increased interest in topical distribution of nanostructures. With around 83.9% drug release after 12 hours, a new formulation of ketoconazole as nanoparticles contained in Carbopol-based gel showed satisfactory particle properties, rheology, drug content, and stability [61]. The fact that the book uses non-standard language is crucial. There are differences between nanogel, nanoemulgel, nanoparticle gel, and nanofibrous gel. The nanoemulgel is a dispersion of a nanoemulsion in a conventional gel matrix, while the genuine nanogel is a nanoscale cross-linked polymeric network. Another structure is seen in nanofibrous gels. Therefore, uniform language and accurate reporting on the carrier's architecture, particle/fiber size, polymer composition, and fabrication procedure are necessary for meaningful comparisons [62].

7.5 Critical synthesis of recent evidence

According to recent studies, ketoconazole nanostructured systems may improve skin deposition, antifungal efficacy, drug dispersion, prolonged release, and formulation stability. However, performance varied greatly based on the carrier design and experimental technique [63]. Maximum transdermal penetration should not be prioritised above skin deposition and retention in superficial fungal infections. The drug's skin-layer-specific distribution, antifungal action, irritation, systemic exposure, and stability should all be covered in further research. Furthermore, there aren't many research that use a standardised model to directly compare the impact of ketoconazole nanogels to commercial formulations. Most of the research to far has been conducted *in vitro* or *ex vivo*, and more conventional *in vivo* investigations as well as clinical validation are required (Table 2) [64].

Table 2: Reported ketoconazole-loaded nanostructured topical delivery systems [**65**]

Year	*Delivery system*	*Key formulation*	*Major findings*	*Principal limitation*
2005	SLN/NLC	Compritol-based lipid systems	NLC improved chemical stabilization	Particle-size increase during storage
2016	Electrospun nanofibers	PCL + ketoconazole	Antifungal activity demonstrated	Limited skin-delivery evidence
2017	Liposomal gel	KTZ + neem extract	Feasible vesicular topical delivery	Combination effects complicate interpretation
2017	Transfersomal gel	KTZ-transfersomes + Carbopol	Improved release and permeation	Vaginal rather than dermal application
2023	Nanoemulgel	KTZ + clove/eucalyptus oils	Enhanced release, permeation and antifungal activity	Contribution of oils requires consideration
2024	PDL-based nanoemulgel	KTZ + eugenol + Carbopol	Sustained release and enhanced skin accumulation	Combination formulation
2025	KTZ nanogel	KTZ nanoparticles + Carbopol	~83.9% release at 12 h	Limited skin-deposition/in vivo evidence
2026	Mucoadhesive NLC	Optimized KTZ-NLC	Sustained release and enhanced ex vivo delivery	Increased flux may not equal superior local retention
2026	Nanofibrous gel	Cellulose nanofibers + Carbopol + KTZ	High release, skin diffusion and antifungal activity	Early-stage evidence; clinical validation lacking

8. Critical Comparison of Topical Ketoconazole Delivery Platforms

Through the creation of nanostructured systems, a number of strategies have been presented to improve the topical distribution of ketoconazole. Drug solubilization, skin penetration, controlled release, stability, manufacturing complexity, and clinical translation are just a few of the advantages and disadvantages that each platform has to offer. Therefore, the therapeutic objective should guide the delivery method selection rather than the nanoscale size [66].

8.1 Conventional formulations

Conventional creams and gels are still widely used because they are simple to make, have established manufacturing processes, are easy to administer, and have a straightforward regulatory approval procedure. They may, however, provide less precise control over drug release and residence duration, particularly in cases when the medication is poorly soluble in water. The limitations make the development of more sophisticated delivery methods necessary [67].

8.2 Nanoemulsions and nanoemulgels

Drug release and transport to the skin may be enhanced by using nanoemulsions to promote the dispersion of weakly water-soluble ketoconazole. The viscosity, spreadability, and residence duration of a gel matrix may all be enhanced by gelatinization. However, with nanoemulgels, the concentration of surfactants, physical stability, and potential irritation must be regulated [68].

8.3 Liposomes, SLNs and NLCs

While the use of SLNs and NLCs offers lipid-based habitats appropriate for lipophilic ketoconazole, the use of liposomal and vesicular systems may result in the creation of controlled release products and promote contact with the skin. Compared to other SLN systems, NLCs may provide superior drug incorporation and chemical stabilisation. However, they may have issues with lipid crystallinity, physical stability, particle size variations, and manufacturing complexity [69].

8.4 Nanogels

While liposomal and vesicular systems may provide controlled release products and encourage skin contact, SLNs and NLCs provide lipid-based habitats suitable for lipophilic ketoconazole. NLCs may provide better medication integration and chemical stability than existing SLN systems. However, they could have problems with manufacturing complexity, particle size fluctuations, physical stability, and lipid crystallinity [70]. Compared to nanoemulsions, nanoemulgels, and lipid-based nanocarriers, the data base for ketoconazole in the usage of nanogels is rather small. As a result, the potential advantages of nanogels are now thot to be intriguing but unproven (Table 3) [71].

8.5 Comparative assessment

In the case of superficial fungal infections, the best delivery system of ketoconazole should ensure:

- Adequate drug solubilization;
- Reproducible and controlled release;
- High local skin deposition;
- Prolonged residence;
- Effective antifungal activity;
- Low systemic absorption; and
- Good physical and chemical stability; and
- Scalable manufacturing [72].

Table 3: Critical comparison of topical ketoconazole delivery platforms [73]

Parameter	*Conventional cream/gel*	*Nanoemulsion/Nanoemulgel*	*Liposomal/Vesicular*	*SLN/NLC*	*Nanogel*
Structure	Semisolid base	Nanoemulsion + gel	Lipid vesicles	Lipid nanoparticles	Cross-linked polymeric network
KTZ solubilization	Low–moderate	High	Moderate–high	High	High
Drug release control	Low	Moderate–high	High	High	High
Skin deposition	Moderate	High	High	High	Potentially high
Skin residence	Moderate	High	High	High	High
Stability	Generally high	Moderate–high	Moderate	Moderate–high	Formulation-dependent
Manufacturing complexity	Low	Moderate	High	Moderate–high	Moderate–high
KTZ-specific evidence	Extensive	Relatively strong	Moderate	Moderate	Limited/emerging
Major advantage	Simple and established	Solubilization + enhanced delivery	Controlled delivery	Suitable for lipophilic drug	Nanoscale carrier + gel properties
Major limitation	Limited release control	Surfactant/stability concerns	Vesicle instability	Lipid-related stability issues	Limited clinical validation
Overall potential	Established standard	Strong	Promising	Strong	Promising, requires validation

In general, the utilisation of nanogels should be seen as an emergent platform rather than a ready and accessible better option. Their capacity to concurrently tailor the macroscopic characteristics required for topical administration and the nanocarriers' microenvironment is their greatest scientific benefit. Therefore, future comparison studies should concentrate on skin-layer-specific drug deposition, antifungal efficacy, toxicity, stability, and therapeutically relevant outcomes rather than just particle size or particle release [74].

9. Challenges and Translational Considerations

Although there is a lot of promise for topical administration of ketoconazole using nanogels [75], many obstacles must be overcome before nanogels may be used in clinical settings.

9.1 Formulation and reproducibility

The characteristics of the polymers utilised, the crosslinking density, the particle size, the quantity of drug loaded, and the processing parameter all have a significant impact on how well nanogels work. Drug release, stability, and skin deposition may all be significantly impacted by changes to these factors. To guaranty repeated performance, the preparation techniques must be standardised and the essential quality criteria must be well specified [76].

9.2 Physical and chemical stability

Aggregation, particle size changes, drug leakage, polymer breakdown, and recrystallization of ketoconazole are all conceivable during storage. Therefore, during long-term stability investigations, the physicochemical and medication potency should be assessed. Stability tests under appropriate storage settings should be carried out before determining shelf life [77].

9.3 Safety and skin compatibility

The skin's tolerability may be impacted by the surfactants, penetration enhancers, crosslinking agents, or other excipients employed in topically produced nanogels. Thus, irritation, sensitisation, cytotoxicity, and impacts on the skin barrier should all be considered. Crucially, local safety shouldn't be sacrificed in the sake of better medicine delivery [78].

9.4 Scale-up and manufacturing

It's possible that industrial preparation differs from laboratory size preparation. Maintaining the same rheology, drug loading, polymer-network properties, and particle size while scaling up may sometimes be challenging. Therefore, it is important to design the production process with scalability, batch-to-batch consistency, purifiability, and quality control [79].

9.5 Regulatory and clinical translation

For regulatory approval, both the active ingredient and the nanoscale delivery method of nanogels must be evaluated. It is necessary to use standardised analytical techniques for particle stability, contaminants, drug release, composition, and characterisation.Furthermore, there is currently little clinical evidence of ketoconazole-loaded nanogel, and the bulk of the data that has been discovered so far has been in vitro and ex vivo. Therefore, future research should proceed with carefully planned in vivo experiments followed by carefully monitored clinical trials [80].

CONCLUSION

Despite being a significant topical antifungal agent, ketoconazole's lipophilicity and poor water solubility may cause topical formulations to release and localise drugs less effectively at the skin level. By improving medication dispersion, controlled release, and skin contact, nanostructured delivery devices provide viable answers to these problems. With a hydrated polymeric network and a nanoscale drug delivery environment, nanogels are a specific type of these systems that may provide chances to improve drug loading and skin residency, local drug deposition, and controlled release. The potential use of nanotechnology in topical antifungal medication delivery is shown by the use of lipid nanoparticles, vesicular systems, nanofibers, nanoemulsions, nanoemulgels, and novel nanogel formulations. Nevertheless, there is little concrete proof that "true nanogels" containing ketoconazole exist, and it is still unclear if these nanogels are better than other nanocarriers or traditional formulations. Future research should thus concentrate on standardised characterisation, skin-layer specific deposition, antifungal efficacy, safety, long-term stability, scalable production, and well planned comparative and clinical investigations.

In conclusion, the use of ketoconazole-loaded nanogels is an emerging platform that may be successfully applied in clinical settings if effective formulation quality is attained, localised antifungal delivery is enhanced, safety is guaranteed, and there is a therapeutic advantage over the current topical antifungal medications.

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