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Review Article

Review on Nanoemulsion Based Nanogel for Fungal Infection

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ABSTRACT

Nanoemulsion-based nanogels have emerged as a promising approach for treating fungal infections due to their unique properties. Nanoemulsions are fine oil-in-water or water-in-oil dispersions stabilized by surfactants, characterized by their small droplet size, which enhances the solubility and bioavailability of hydrophobic drugs. When integrated into nanogels, these nanoemulsions provide a stable, gel-like medium that ensures prolonged retention and controlled release of antifungal agents at the infection site. The nanogel matrix not only offers a localized treatment, reducing systemic side effects, but also protects the encapsulated drugs from degradation, enhancing their efficacy. Additionally, the high surface area and small size of nanoemulsion droplets facilitate better penetration into fungal biofilms and deeper layers of infected tissues, improving therapeutic outcomes. Recent studies have demonstrated the effectiveness of nanoemulsion-based nanogels in delivering antifungal agents like fluconazole, amphotericin B, and clotrimazole, showing enhanced antifungal activity compared to conventional formulations. These nanogels exhibit superior mucoadhesive properties, making them suitable for treating mucosal infections. In conclusion, nanoemulsion-based nanogels represent a significant advancement in antifungal therapy, offering improved drug delivery, enhanced antifungal efficacy, and reduced adverse effects, thus holding great potential for the effective management of fungal infections.

Keywords: Antifungal Agents, Hydrophobic Drugs, Mucoadhesive, Nanoemulsions.

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INTRODUCTION

Infections are increasing and are one of the most important factors in human health. The end of the last century and the beginning of the current one were marked by a decrease in the interest and number of new drugs resulting from their long development and high cost because many diseases had been eradicated anyway (Sousa *et al*., 2020). This changed in a dynamic and evolving way, with the resurgence of many viral, bacterial and especially fungal diseases, such as the well-known Acquired Immunodeficiency Syndrome (AIDS), by the Epstein-Barr virus, hepatitis, tuberculosis and others arose due to ura disease (Bongomin *et al*., 2022).

The return of fungal diseases on a large scale has brought difficulties and complications for medical treatment, since the agents causing these infections are difficult to treat. Advances in the development of new delivery systems aim to optimize therapy, focusing on targeting the therapeutic agent in infected areas, reducing dose intervals, side effects and improving bioavailability. Nanostructures, especially emulsions and hydrogels, are promising drug delivery systems and reduce the development time of the drug to market. In this manuscript, we developed and evaluated a nanoemulsion-based hydrogel for the treatment of fungal infections caused by the K. Sprengeri vegetable's essential oil (Rhijn and Bromley, 2021; Gupta *et al*., 2021; Wiederhold, 2022).

Background and Rationale

Hence, the survey and assessment of nanoemulsion and nanogel-loaded drugs as antimycotic agents for the treatment of deep-seated fungal infections are essential. The efficacy of Chloramphenicol (CA), Clotrimazole (CT) and Itraconazole (IT) loaded Poly D, L-Lactide-co-Glycolide (PLGA) based nanogel was evaluated in our previous work and it revealed a profound and controlled capacity of the nanogel to deliver gene drugs at the site of infection (Aderibigbe, 2024). However, the retention of mature fungal infection to exert sustained drug release of gene drugs is needed. The development of polymeric or lipid-based nanoemulsions is reported to enhance thermodynamic stability and establish promising physicochemical and colloidal properties, respectively, that help protect antibiotics, antiviral and antifungal agents for inherently increased shelf life and provide sustained

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action with improved antifungal efficacy in the target tissue than conventional aqueous delivery (Choi and McClements, 2020).

The nanoemulsions, having a droplet size in the range of 10-100 nm, which provides a high surface area for delivering water-insoluble drugs in a solubilized form within an oil-in-water pre-concentrate. This results in enhancing drug permeation and retention within deep-seated fungal infections. The nanoemulsions, with a droplet diameter below 200 nm, typically protects the incorporated drug from degradation, enhances its uptake into the cell, favors controlled and sustained drug release and likely potentiates its retention within the deep-seated target niche. The nanogel, having a spongy and porous system, allows drug content to be loaded within the nanogel core. The nanogel network swells and disassociates in the presence of body physiological vaginal (acidic pH, high viscosity, increased temperature) and rectal (neutral pH, low viscosity, decreased temperature) triggering factors, promoting highly localized sustained drug delivery without systemic toxic side effects in treating deep-seated vaginal and rectal fungal infections (Sadeq, 2020; Ma *et al*., 2021; Malode *et al*., 2021).

Scope and Objectives

The prepared nanoemulsions have been characterized and further developed into nanogel using a synthetic polymer. The formulation work encompasses tioconazole-loaded nanoemulsions preparation by ultrasonication method using soybean oil and cremophor ELP as oil and surfactant respectively.

Secondly, the existing work aims to evaluate the suitability of such optimized eudragit S100-based nanogel in a wound healing delivery strategy, using a standardized wound healing mouse model.

In this work, nanoemulsion-based nanogel systems are an attractive system for incorporating a drug, which can be used for treating various fungal skin infections, in a way facilitating the efficacy at affected sites, improving the localized sustained release of the drug, as well as reducing the side effects.

Nanoemulsions and Nanogels

A nanogel-based nanoemulsions technique using the self-gelation of carbopol 940 polymers was also mentioned in detail, in which the manipulated polymer microstructure could give the formulated nanogels a unique organization and properties. The focus is on the interfacial nanogel layer that determines its controlled drug release.

Nanogels and nanoemulsions are potential drug delivery systems used to improve the therapeutic or toxic effects of drugs by either selective targeting or imaging of the site in the body or by controlling an *in situ* release. In addition, nanogels and nanoemulsions have full function in the optical properties of contrast agents, making them applicable to multiple imaging technologies compatible.

Nanogels are extensively used in the delivery of both hydrophilic and hydrophobic drugs to the site of action and they possess excellent properties like ease of administration, enhanced bioavailability and prolonged release. Due to improvements in the drug delivery route, nanogels and nanoemulsions can be used for both lipophilic and hydrophilic drugs that can extend half-life, slow down the clearance of the active component in the body, reduce the adverse effects of the drug and achieve an easy therapeutic concentration (Garg *et al*., 2020; (Patil and Kontamwar, 2021; Carvalho *et al*., 2021; Sindhu *et al*., 2022).

Nanogels based nanoemulsions are a less explored drug delivery system for the efficient delivery of antifungal drugs. In this probable work, an attempt was made to fabricate and evaluate the nanogels based nanoemulsions for prolonged and efficient delivery of amphotericin B. The formulation was optimized and *in vitro* drug release and *in vivo* antifungal testing had shown promising results. Its significant use lies in the proper administration of amphotericin B with the required concentrations for its efficient antifungal effect and also decreases the toxic nature caused by IV injection of amphotericin B (Li *et al*., 2021).

Nanoemulsions have been used extensively in agricultural, pharmaceutical and food products due to their unique properties. Nanoemulsions are prepared through different methods like high-pressure homogenization, microfluidization, ultrasonication and phase inversion composition. Among them, phase inversion composition is a simple, easy method that offers high drug encapsulation along with uniform size distribution at low energy (Zhang and Zhang, 2020).

Nanoemulsions: Composition and Properties

The air-containing lipid droplets are coated with Polyethylene Glycol (PEG) and applicable targeting antibodies (e.g., transferrin), they can be precisely targeted to the vascular endothelia of the occlusion tissue. It could target the gas volume in the brain and diagnose brain lesions. PBio found that this type of nanoemulsions could be used in a mouse model of breast cancer. Animal experiments show that 5 to 20 min after the nanoemulsions containing macrophages that can bind to over expressed vascular endothelial cells accumulates in the mouse blood vessels, large embolisms are found in the corresponding opaque tissues. Such nanoemulsions provides a new possibility for the diagnosis, treatment and monitoring of vascular occlusion diseases (Zhang *et al*., 2021).

The nanostructure of emulsion is a novelty in emulsion droplets. The droplets in the emulsion could employ drug targeting to deliver hydrophobic drugs *in vivo*. We can obtain these favorable biological distribution characteristics by altering the hydrophobic structure of the nanoemulsions. Propranolol in nanoemulsions

was distributed in adipose tissue (rich in hydrophobic) more significantly than the conventional liquid particle emulsion. The size of the droplet is adjusted to the diameter of the capillary, thereby reducing non-specific drug deposition along the arteriole wall, thereby facilitating the targeted delivery of colloidal drug carriers to the hydrophobic site of action (Rajput *et al*., 2020).

Nanogels: Structure and Functionality

Nanogels are highly swollen cross-linked polymeric networks dispersed in water. They are structurally similar to hydrogels but with dimensional reduction to the nanoscale size. Hydrogels are physically or covalently cross-linked polymeric three-dimensional networks that are capable of imbibing large amounts of water or biological fluids. The crosslinked networks in hydrogels vary according to the nature of monomers, repeating units and usually undergo swelling. If crosslinked polymers swell in a dispersed aqueous medium, those nanoscale gel structures are termed as 'nanogels' (Mauri *et al*., 2021; Scotti *et al*., 2022; Yin *et al*., 2020). The network structure and dimensional reduction to nanoscale are unique to nanogels, leading to the intriguing properties of nanogel resulting in considerable attention from scientific and industrial research. Owing to their characteristic range of particle sizes, nanogel formulations typically have low viscous liquids or soft solids properties. The nanoscaled size allows nanogels to permeate into tissues or efficiently uptake by a majority of the cells, which enables efficient penetration against biological barriers, such as the blood or intestinal barriers and also leads to rapid cellular internalization via endocytosis-mediated pathway such as clathrin-mediated endocytosis. Thus, nanogels are widely viewed as prescient multifunctional materials for medical delivery. Currently, some nanogels have inspired significant interest and have been chosen in other industrial applications of medical imaging, tissue engineering and designing enzyme immobilized supports and so on. The unique feature of the nanogel is discussed in brief (Cao *et al*., 2020; Dos Santos Matos *et al*., 2020).

Fungal Infections

Researchers have encapsulated amphotericin B into a nanoemulsion which can be used orally. Especially in the Indian subcontinent, fungal infections are endemic and amphotericin B is the drug of choice for the treatment of visceral leishmaniasis. Treatment options include miltefosine, liposomal amphotericin B and combination therapy. After administration, amphotericin B is responsible for organ toxicity, producing both acute and chronic side effects. This is explained by the liposomal or lipid-related drug formulations available, including the high price of amphotericin B for the treatment of patients in developing countries. These formulations also appear to have some irreversible constructive effects (Fisher *et al*., 2022). Fungal infections are an emerging health problem and the increase in fungal infections is evident. The most commonly used antifungal drugs, azoles, mainly act on the cell membrane of fungi. The rise of resistance to these drugs has led to the urgent need for new therapeutic approaches. Recent conventional research has focused on the combination of two or more existing drugs with different mechanisms of action, instead of developing new molecules (Pathakumari *et al*., 2020). Alternative therapeutic approaches are being developed as well, in particular, the nanoencapsulation of existing antifungal drugs. Nanoscale technologies have enormous potential, particularly in offering an innovative approach for the formulation of poorly water-soluble drugs (Tirado-Sánchez *et al*., 2020).

Types and Common Pathogens

There are different classes. Superficial mycoses are local infections of tissue or organ surfaces, where the pathogen proliferates without invading the subdermal tissues. They may be endemic or epidemic, clinical configurations resembling many other dermatoses. Or they can be the expression of more complex systems, including functional or metabolic alterations within the host that yield to imbalance of the biological relationship with the saprophyte microorganisms, which normally populate the corresponding sites and changes of the pathosphere by the action of one or more factors of charge. Cutaneous mycoses are a group of diseases with distinct clinical configurations or auxologic patterns, activated by the penetration, saprophyte invasion and proliferation in the stratum compactum of pathogens of a widespread mycetes sociologic, as clinically observable, mainly directly, with the appearance of colored macules, generally exercised with tests of virofteal findings (Mlynarczyk *et al*., 2021). Systemic mycoses are systemic generalized infectious syndromes determined by dimorphic micelles. The deep mycoses are thermonuclear diseases, occurring with important invasions to certain regions of the human organism, frequently reaching internal organs, presenting geographical distribution. They include lymphadenitis, paracoccidomycosis, histoplasmosis, blastomycosis, cryptococcosis and sporotrichosis. Deep Scopularioposis of Lymphatic System is due to the invasion of the lymphatic chain by a saprophyte basidiomycosis, but thermos de simulation profile, which extends to the subcutaneous cellular tissue, involving one or more lymphatic chains of the lateral cervical region, with exertion of several consultations; the lymphatic involvement only appears on MRI. Superficial mycoses usually include Pityriasis Chiracrai, white rot and black nail ringworm, hair infection, feet hyphae and scrotal tinea with the main pathogen of *Malassezia* sp (Renzi *et al*., 2021; Tragiannidis *et al*., 2021; McCarty *et al*., 2021).

Current Treatment Challenges

Furthermore, the numbers of invasive fungal infections, along with the limited range of antifungal treatments available, make the development of new antifungal agents an essential part of the next phases of tackling these infections. Commercial antifungal drugs, although necessary for public health, have several issues, such as high cost, increasing resistance and limited range for

their use, being an impetus to develop new, effective and selective treatments for these agents.

In the last two decades, an exponentially increasing prevalence of invasive candidiasis and candidemia has been observed, indicating an urgent need for new and improved antifungal agents. Currently available drugs face serious challenges, such as the emergence of resistant strains caused by the widespread use of antifungal agents, high drug toxicity, limited spectrum of antimicrobial activity, insufficient solubility and tissue distribution, low selectivity toxicity to fungal cells and an increase in patients undergoing antitumor chemotherapy, organ transplants, or cardiac surgery. As a consequence, the treatment of fungal infections requires the patient to receive antifungals for an extended period of time, producing undesired side effects in patients and toxicity for the administration of antifungal treatment (Logan *et al*., 2020; Pandey *et al*., 2020).

Combination Therapy Approach

Another research study from the Department of Pharmaceutics Andhra University, India formulated novel nanoparticles loaded gel for the treatment of vaginal fungal infections with butenafine HCl as the model drug. The *in vitro* VS-64 efflux pump inhibition in Candida species reduction was experimentally evidence for the higher accumulation of butenafine in nanoparticles compared to conventional topical formulation. The developed novel gel formulations loaded surface-modified nanoparticles improved the bioavailability of butenafine and efficient VS-64 efflux pump inhibiting action. The present minoxidil-loaded nanoemulgels can be used as a better and effective dosage form in the treatment of vaginal fungal infections (Kurakula and Naveen, 2020; Rial-Hermida *et al*., 2021).

Researchers have been turning their attention to combining several antifungal agents to treat severe fungal infections. Several reports suggest that there is a probability of interactions or a synergistic effect, which could be attributed to the increased clinical cure of fungi as different antifungal drugs. Nanogel with antifungal drugs such as itraconazole has been reported. It showed lower MIC and significantly higher antifungal activity against medically important Candida species, including some azole-resistant clinical strains. Due to its small particle size and high saturation solubility, it can penetrate the biofilm, resulting in the effective treatment of candidiasis (Yang *et al*., 2022).

Rationale for Using Nanoemulsion-Based Nanogel

Hydrogels based on natural polysaccharides have become a versatile scaffold for therapeutic applications due to their nontoxic, biodegradable and biocompatible properties. However, to achieve the beneficial effects for topical or systemic drug delivery, nanogel formulations consisting of controllable nanoscale size and mechanical properties, high biocompatibility and loading efficiency, acceptable stability and desirable functions in release were widely studied and are still under development. Forming nanogels with nanoemulsions through physical or chemical cross-linking is one of the effective strategies for further obtaining hybrid materials with excellent characteristics and resolving the limitations that exist in nanoemulsions or nanogels, providing a promising prospect in therapeutic drug delivery (Manimaran *et al*., 2023; Golwala *et al*., 2020).

Nanogel is a combination of the nanosized materials of hydrogel and a nanoparticle, which has novel properties for various applications. Nanoemulsions are a thermodynamically stable and transparent dispersion of two immiscible liquids, typically water and oil (or any nonpolar liquid), stabilized by an interfacial film of surfactant molecules. They also satisfy the nanoscale structural criterion and usually possess some unique structural, optical and physicochemical properties. Modification in the conventional gels with nanoemulsions results in the formation of nanogels. Nanoemulsions can easily facilitate the formation of nanoemulsion-based nanogels. Furthermore, nanoemulsions refresh the polymer chain space, leading to the polymer chain conversion from hydrophobic to hydrophilic across the interface. It results in enhanced physical properties, i.e., elongation at break and tensile strength, due to covalent bonding between the gel and the nanoemulsions. Several studies utilizing emulsions with alginate and poly (N-isopropylacrylamide) (PNIPAAm) as a crosslinker to prepare alginate-based and PNIPAAM-based nanogels were reported (Rathod *et al*., 2024; Bhattacharya *et al*., 2020).

Design and Formulation of Nanoemulsion-Based Nanogel

Nanoemulsions, with average particle sizes less than 100 nm, were formed under optimized processing conditions. The volume fraction of surfactant and co-surfactant influenced the formulation more significantly than homogenization speed. A Schematic Diagram of preparation of nanoemulsions is shown in Figure 1. The viscosity of nanogels, whose morphological measurement was recorded as good, was found to be well fitted with the power law. The released data of 78% from the nanoemulsions was the most suitable kinetic model, which suggested Fickian (anomalous diffusion) transport. The DoE-RSM used for the development of nanoemulsions in nanogel for antifungals with crab oil was found to provide positive and promising effects. The prepared formulation possessed excellent characteristics and had shown great potential for treating fungal infections in the future (Ahmad *et al*., 2022; Roselan *et al*., 2020).

Fungal infection is hard to treat because there are few antifungal active pharmaceutical ingredients, which restricts formulation development. And most of the available antifungals have significant drawbacks such as low solubility, poor permeability, multidrug resistance and low oral bioavailability. The objectives of this study are to develop a novel antifungal formulation, optimize

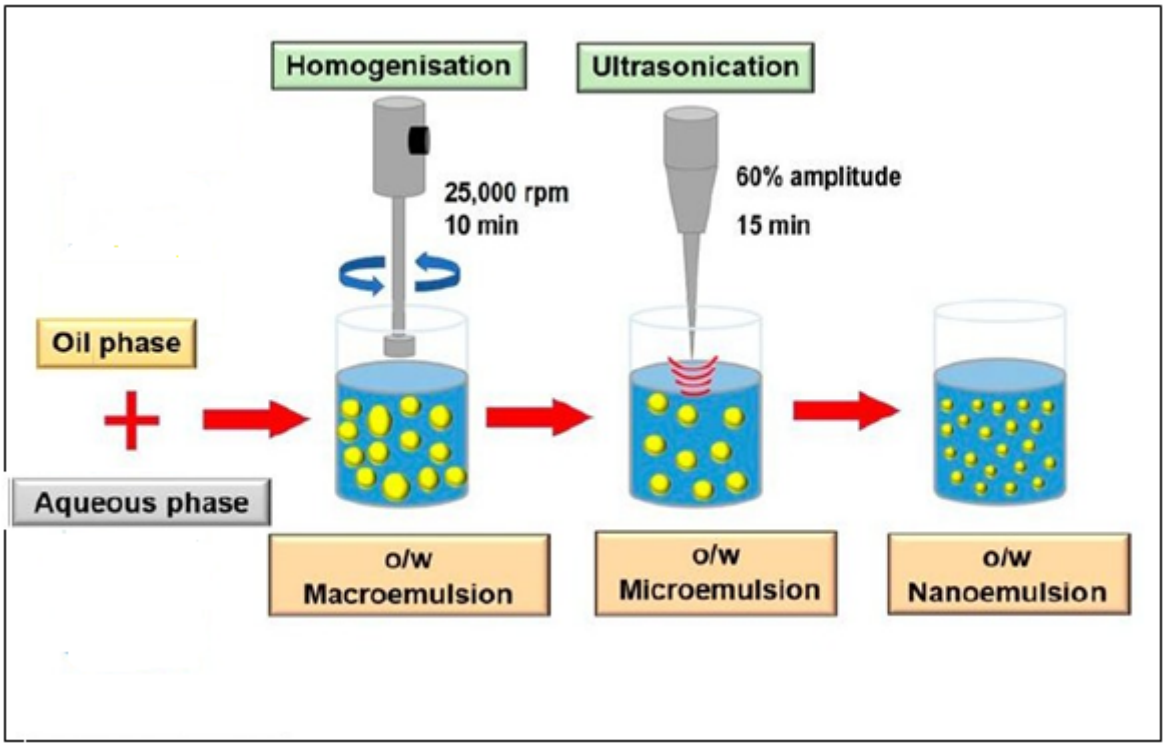

Figure 1: Schematic Diagram for the nanoemulsions preparation.

the preparation conditions and characterize the *in vitro* release behavior of the developed antifungals. The antifungal crab oil was taken as the oil phase for preparing nanoemulsions. Carbopol 940 was taken as the carrier for preparing nanogels and mixture design-response surface methodology was used to optimize the preparation conditions of nanoemulsion in nanogel (Roselan *et al*., 2020).

Selection of Ingredients

Currently, fluconazole resistance continues to be the main obstacle to successful use, limited application, very high and inconsistent oral bioavailability, poor and variable topical permeation and solubility problems. The optimized nanogel was able to increase the antifungal activity upon bacterial strain accumulation loaded with 150 ppm G26 broth filtrate as an antidermatophytic agent. The purpose of this study is to overcome the instability and low entrapment effectiveness of the optimized nanogel by formulating a nanoemulsions base for nanoparticle encapsulation. The optimized nanoemulsion was mixed with a selected single-stabilizer hydroxypropyl methylcellulose that contains the loaded antidermatophytic agent and converted into a stable and monodispersed nanogel structure. The work study included antidermatophytic activity, rheology, *in vitro* release, physical appearance, centric ability, skin drying time and antifungal efficacy on an antifungal-treated rat model (Kotta *et al*., 2021).

Among all topical formulations, emulgel is affected as it can overcome the pharmacokinetic limitation of conventional gel without losing characteristics of easy and non-greasy application, as well as patient compliance. Developing a nanogel emulgel has a safe and efficacious site-specific drug delivery system that promises the accurate release of the incorporated agent it is intended. It is increasing drug bioavailability, decreasing systemic toxicity, improving the stability of volatile and photosensitive compounds, improving drug stability, enhancing drug permeation, sustaining drug release and improving patient compliance. In this study, we are trying to optimize the formulation that was previously studied by our team, encapsulating antifungal fluconazole nanogel from a nanoemulsions base. In our previous work, we successfully selected and optimized Streptomyces spp. G26 against *Candida albicans* (Elsewedy *et al*., 2021).

Optimization of Formulation Parameters

In this approach, we studied the influence of independent formulation factors in nanoemulsions preparation and its effect on the dependent variables via response surface method. The experimental data were collected using a single-factor experimental procedure. Based on the preliminary experiments, the ranges and the levels for the three variables were selected. The design matrix was constructed based on the range of each factor and formulation runs were conducted according to the experimental design. After forming all the possible combinations of the formulation variables, the formulations of each combination were prepared according to the optimized method and the resultant nanogel was subjected to further investigations. As the factorial design matrix was created in order, a mathematical model was obtained and compatibility of the fitted model

was estimated in response Yates format. Finally, the resulting polynomial equations were expressed in mathematical mode and further analysis has been carried out in the form of 3D surface plots against the significant factors. The model was validated and the relationship between Z-potential versus different formulation parameters was established (Alam *et al*., 2022).

The 'Design of Experiments' is an appropriate tool to study and model the influence of formulation parameters used on the product quality. In the present research, we have used a 'Response Surface Methodology' in the form of a 'Central Composite Design' for the validation of the nanoemulsion-based nanogel. Three important factors including Na-caseinate, oil-surfactant and water ratios essential for the ocular nanogel have been studied. The influence of formulation parameters on the different responses has also been approached. A quadratic model was established within the ranges studied for analysis. To optimize the experimental conditions, constraint optimization method has also been applied. The compatibility of the fitted model has been evaluated by response Yates analysis (Gao *et al*., 2022).

Characterization Techniques

Design and synthesis of core-shell (nanoemulsions) are very important as they are responsible for the drug entrapment into the polymeric shell of nanogel and also respond to different stimuli. Normally, various characterization techniques such as TEM and CLSM are necessary for the characterization of the core-shell structure of the nanoemulsions. To study the nanogels, a number of methods are needed to characterize different properties of the nanogels. The characterization techniques, once developed, can be extended to different applications depending on the requirements.

Various characterization techniques, including particle size, polydispersity index, core-shell structure of nanogel, zeta potential, morphology, solid-state behavior, *in vitro* drug release, *in vitro* and *in vivo* antifungal activity and cytotoxic effect on phagocytic cells, need to be carried out.

Particle Size Analysis

The particle size distribution is important in the formulation of the nanogels, as it determines the physical properties of the nanogel. The size distribution of the nanogels was estimated using DLS. The selected nanogels were prepared and the particle sizes were calculated as a function of time. Initially, the nanogels were formed and the sizes were retarded. After a short incubation time, the size of the nanogels was increased and Z average of 594 nm was obtained. This effect signaled that the nanogels were swollen by the medium. With increased incubation time, aggregation was observed, due to the enhanced hydrophobic interaction driven by increased surfactant amounts. During the reaction, the distribution became broader, with the PDI higher than 0.5. This result indicates that the main part of the nanogels consisted of small-sized particles also produced with the light scattering effect and the aggregation degree was higher (He *et al*., 2023).

Zeta Potential Measurement

In our study, magnetic nanogels with different storage times were measured using Zeta potential. The theoretical value of Zeta potential for the excellent stability of nanoparticles in liquid is not less than -30 mV or higher than +30 mV. The results showed that there was no significant potential change in the following 28 days, which may depend on their relatively higher absolute Zeta potential. The absolute value of nanogel Zeta potential is determined by the difference in O-Fe bond. Before storage, the calculated absolute Zeta potential showed a maximum and the potential is close to -41 mV and the potential remained relatively constant for 28 days, which may depend on their relatively higher absolute Zeta potential. The absolute potential value of particles stabilizes, but changes rapidly when the threshold is exceeded. Then, the potential of Zeta was calculated as 28.7, approximately -30 mV and +30 mV (Keskin *et al*., 2021).

In vitro Evaluation

The nanogel was non-cytotoxic under an *in vitro* cytotoxicity study using Vero cells. Additionally, *in vitro* skin irritation studies demonstrated that the plain nanogel did not cause skin irritation, as evidenced by the histopathological evaluation after a 24 hr exposure time. Nanogels were prepared using carbopol 212 m (0.5% w/w) and hydroxypropyl methylcellulose (2% w/w) as the gelling agents. Clotrimazole was used as a model drug for minimum fungicidal concentration studies and was incorporated into the nanogel. The synthesized nanogels were characterized by the drug content, entrapment efficiency, pH, rheology, zeta potential, particle size distribution and polydispersity index. The physicochemical compatibility of the model drug with the components was evaluated by physical and chemical characterization. Cytotoxicity and skin irritation studies demonstrated that the developed clotrimazole-loaded HPMC K100 M nanogel was well tolerated. The present investigation was designed to develop clotrimazole nanogels and evaluate their suitability as a dermal nano-antifungal delivery system (Nnamani *et al*., 2021).

Nanogel prepared by the cold method was white and opaque with a smooth texture, whereas nanogel formulated by the hot method was transparent with a rubbery texture. The particle size and polydispersity index of carbopol 212 m/HPMC K100 M formulations were significantly affected by the selected gelling agent. The pH of the nanogel was within the acidic range, making it suitable for topical therapeutic application. Nanogels incorporating clotrimazole showed high drug entrapment efficiency in all formulations. Antifungal activity was evaluated against *Aspergillus flavus, Aspergillus niger, Penicillium chrysogenum* and *Candida albicans*. F1 4% HPMC K100 M nanogel formulated by the hot method was found to have a higher

antifungal effect against *A. niger* using an agar diffusion method (Arendrup *et al*., 2020).

Antifungal Activity Assays

Minimum Inhibitory Concentration tests were commonly carried out for susceptibility testing of Candida. The technique was easy to perform and was used when a stock of a limited number of drugs was available, avoiding the need to perform all individual antifungal drugs to check their effectiveness. Four miconazole solutions of known activity with the same quality control values but about 20% of the miconazole content were used (range of 0.015 to 8 µg/mL for *C. albicans*) and found to be acceptable (Medina-Alarcón *et al*., 2021).

Any formulation becomes meaningful if it accomplishes the intended therapeutic action in an organism. Nanoemulgel would be required to release drugs slowly, to provide uniform drug concentration, reduce frequency of the drug administration and to improve patient compliance and tolerability and to increase the duration of treatment with reduced systemic toxicity. Formulations can be screened either by screening of nanogels for particle size diameter, zeta potential, polydispersity index, drug content, encapsulation efficiency, transmission electron micrographs and drug release and stability studies. However, they need to be evaluated by *in vitro* studies and drug release patterns. Finally, their therapeutic efficacy can be tested in *in vivo* experiments on different animal disease model (Pereira and Cotas, 2024).

In vivo Studies

Antifungal LC2 NE2 treatment also did not promote any reduction in *C. gattii* CNS infection. However, NE3 antifungal therapy not only arrested the progression of the infection inhibiting main *C. gattii* interactions with the host but also reversed signs of illness and increased the activity of the infected animals.

The report of improved *in vitro* activity of NE3 against Cryptococcus spp. led to the necessity of examining whether it can also operate with the *in vitro* observed potential, in the *in vivo* model. Initially, a study was conducted involving both *in vivo* challenges using infected mice as well as antifungal treatment carried out using NE3. Overall, NE3 was found to be more efficacious in treating early-stage infections when testing against *C. gattii*, while having minimal toxicity toward mice. Interestingly, when tested against multidrug-resistant clinical *C. gattii* isolates, NE3 demonstrated a composition-dependent improved curative effect on infections caused by some Cryptococcus strains. After intranasal administration, NE3 performed well in both prophylactic and treatment experiments carried out using mice infected with *C. gattii*. When testing NE3 using a high mortality model, the average survival of the mice treated using NE3 was higher when compared with the mice treated with amphotericin B (Samson, 2020).

Animal Models and Ethics Considerations

After infection, the animals were divided into four groups, I, II, III and IV and treated with PBS, natamycin, NE and NE/NG, respectively. An equal concentration of clotrimazole was added in the NE and NE/NG groups. At the end of the study, 30% of the animals in the PBS group had to be sacrificed due to irreversible keratitis, while 10% of the animals in the NE group (only reducing inflammation), 10% of the animals in the natamycin group and 70% of the NE/NG group completed the study with significant improvement in infection. Our results revealed that NE/NG significantly improved the ocular retention time and the antifungal efficacy of NE, which can be attributed to the mucoadhesive property of the gellan gum used in the synthesis of the nanogel. These results support NE/NG as a promising nanomedicine for the efficient treatment of fungal infection.

Both *in vitro* and *in vivo* models are necessary to assess the antifungal efficacy of nanoemulsion-based nanogel. *In vitro* antifungal efficacy assessment is helpful in determining the minimum inhibitory concentration of the nanogel. The antifungal efficacy of NE/NG was assessed against *F. solani* in an animal model of fungal keratitis. A total of twenty animals were used for the *in vivo* study. The animals were administered local anesthesia. For induction of fungal keratitis, 0.0186 mol/L of *F. solani* suspension cultures were injected into the corneal stroma using a 30-gauge needle. The infection was confirmed by 1% calcofluor white staining (McAleenan *et al*., 2020; Pereira *et al*., 2022).

Pharmacokinetic and Pharmacodynamic Studies

PD efficacy is potent and critically dependent on the actual administered dose, such as the drug concentration at the site of infection. This drug concentration and the pharmacokinetic properties of a dosage regimen define the PK/PD index that correlates with drug efficacy. It is strictly applied for all known dosage forms. After collection of concentration-time data profiles, a calculation algorithm evaluates the PK-PD indices from temporal exposure-response dynamics (Pharmacobotanic bacterial killing of drug) required to produce selective endpoint action. Time-kill curve analysis is just one of several different *in vitro* exposure-response (time-kill-based) models used to define the relationship of drug concentration to inhibitory activity and a variety of alternate models (e.g., post-antibiotic, post-antifungal, post-antiviral, post-antimalarial and post-diagnosis effects) have been described to help explain the impact of chemotherapy on infecting microorganisms (Firacative, 2020; Jenks *et al*., 2020).

A limited number of reports are available on the pharmacokinetic and Pharmacokinetic-Pharmacodynamic (PK-PD) of NNGE and whether these dosage forms could offer healing with lower side effects remains unresolved. PK-PD is the scientific discipline involved in determining the relationships between drug dosage regimens and toxic effects. These studies have described the relationships of PK/PD index to the efficacy of NNGE. Usually,

determination of the standard PK/PD indices of NNGE is a crucial part of these studies.

Safety and Toxicity Assessment

Fungal infections continue to cause significant morbidity and mortality despite an increasing number of antifungal agents. In therapy, there are various limitations of traditional fungicides, such as poor bioavailability, drug resistance and systemic side effects. In the present study, a propiconazole Nanoemulsions (RTM-NE), Nanostructured Lipid Carrier loaded with propiconazole (RTM-NLC) anda propiconazole nanogel; hydrogel loaded with RTM-NLC (RTM-NG) were designed for the skin delivery of a hydrophobic fungicide. The differences between the particle sizes through communication, zeta potential, morphological, entrapment efficiency, drug release profile, antifungal activity and safety profiles were examined.[60,61] The Minimum Inhibitory Concentration (MIC) of RTM-NE, RTM-NLC and RTM-NG against *M. canis* was 62.5 µg/mL, 15.63 µg/mL and 7.82 µg/mL, which were reduced by more than two-fold at each sample when compared to the free drug. An *in vitro* cytotoxicity test revealed that fresh and storage samples showed a particle size range of approximately 193 nm, a zeta potential of -9.60 mV and an entrapment efficiency of 92.53%. RTM-NE, RTM-NLC and RTM-NG had a slow-release profile in the sink condition. The safety evaluation of the prepared formulations revealed the safe and non-toxic nature of the nanoemulsions.

The therapeutic efficacy of and systemic side effects resulting from the administration of an antimicrobial drug are both important. An *in vitro* cytotoxicity study was performed using Vero cells and *in vivo* acute oral toxicity was performed in Balb/c mice. The cell viability of Vero cells treated with fresh and aged RTM-NLC and RTM-NG was above 80% at all concentrations, demonstrating the safety of the nanocarriers. An *in vivo* acute oral toxicity study showed no abnormalities in behavior or histopathological changes in all examined organs compared to the control. The non-irritating and non-toxic effects of the prepared nanocarriers in the host system displayed their potential future use as antifungal agents (Yang *et al*., 2021).

In vitro Cytotoxicity Assays

Trypan Blue Exclusion Assay

Media for mammalian cell culture must provide a variety of *in vivo* services and be capable of supporting the growth and viability throughout the life cycle of a given cell. Generally, media formulations consist of a source of energy for cellular processes (sugars); material for nucleic acid and phospholipid synthesis; a buffering system to maintain the physiological pH of the medium, which can be affected by the production of carbon dioxide, a byproduct of cellular respiration; ions and vitamins that are usually also provided as a mixture of fatty acids and protein, sterilized to avoid contamination. The main objective of the culture medium for *in vitro* assays is cytoprotection, which means maintenance of cell viability and its normal behavior. This is paramount to obtain biologically relevant and meaningful results in any experiment that aims to evaluate cell performance, due to pharmacological or toxicological studies, for example. Cell viability should also be an important parameter to be controlled in cell culture studies, as it affects the reliability, reproducibility and acceptability of the results. A number of methods can determine the viability density of the cells. A simple technique is the trypan blue exclusion test, which stains non-viable cells blue, allowing visualization under a light microscope. 0.05% trypan blue in phosphate-buffered saline was used to exclude dead cells for statistical analysis (Kamiloglu *et al*., 2020; Pintor *et al*., 2020).

Chemicals and Reagents

All the chemicals, reagents and medium solutions used in the cytotoxic experiments were of analytical grade. They were purchased from closely located vendors. Their stock solutions were prepared in the laboratory and were kept in the dark at 4°C for a maximum of 8 weeks before use. In order to avoid evaporation of the solvents, the stock solutions were put in airtight vials. The contents of each vial were used only once. RPMI-1640 medium was supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL) and 10% heat-inactivated fetal bovine serum. The compound (10 mM) was dissolved in DMSO and 20 or 50 µg/mL stock solutions were made prior to starting the experiments.

In vivo Toxicity Studies

In vivo toxicity studies provide meaningful information regarding the hepatic and renal function of an organism. Evaluation of liver function was done by estimating the levels of liver enzymes like alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase synthesized in liver and clearance of total bilirubin and albumin from liver. The estimation of serum alkaline phosphatase forms an early and sensitive test for hepatic damage. The level of serum albumin indirectly reflects the function of the liver. Serum bilirubin level provides information regarding liver cell necrosis and is raised in patients with hepatic or cholestatic disease (Makhdoumi *et al*., 2020).

The influence of TO-NE-NG and NP-NE-NG on liver and kidney function of both healthy and infected mice was investigated. The investigation revealed that a significant increase in liver enzymes, alanine aminotransferase, alkaline phosphatase and levels of bilirubin from liver, albumin and creatinine clearance from kidney were found in infected mice and treated with posaconazole. Treatment with NP-NE-NG and TO-NE-NG resulted in non-significant changes in liver enzymes and markers of liver function. A similar trend was observed for renal function in both healthy and infected mice and treated with NP-NE-NG and TO-NE-NG.

Future Directions and Challenges

With respect to the evaluation of antifungal nanoemulsions, not many methods are available. The main problem lies in the growth of the fungi. Many antifungals are fungistatic, meaning they slow down or stop the growth of the fungal cells. This would lead to an inaccurate method being used. Currently, the half maximal Inhibitory Concentration (IC_{50}) is commonly used for the evaluation of antifungals. The time taken to reach the half maximal Inhibitory Concentration (IC_{50}) is assessed for each treatment and the faster the time required, the better the treatment. Is IC_{50} the best method? Else, can other better methods be used for the evaluation of nanoemulsions as antifungal agents? More effective and selective assessment of the method should be developed (Miri *et al*., 2020; Trefzger *et al*., 2020).

The studies (*in vivo*) are yet to be conducted to prove the synergistic effect of essential oils, particularly in resistant strains. The failure of the most resistant strains in the clinical environment might be one of the potential problems in clinical therapy with diffusion therapy. However, history has shown the potential of essential oils as antifungals. Unrigging the bell, will the effort succeed in controlling the resistant strains as fast as the evolution of resistance? The usage of a larger amount of essential oils in the antifungal nanoemulsions should also be considered because there are no reports regarding the essential oil in monotherapy (Ju *et al*., 2022; Sharma *et al*., 2020).

CONCLUSION

In summary, the results of the drug-gelatin combination mechanism study showed that there are good binding modes for the binding models in two nanogels, separated the different source of the drug particles in the nanogel and effectively increasing the probability of encouraging intermolecular interaction of Dexidin antifungal NAGs, revealing drug efficacy. The current comprehensive study highlighted the successful development of controlled drug delivery nanogel systems utilizing NAGs with Dexidin antifungal NAGs, which was fabricated by means of the nanoemulsions process by employing bio-ingredients-based biomaterial. Due to the small size and the oil-based membrane of the NAGs, these competitive drug-entrenched nanogels enhanced the local conditioning of the drugs. The drug-nanogel effectively controlled antifungal activity, as well as outstanding thermal stability. The biodegradation test recommends the potential application of the NAGs as a drug delivery agent. The *in vitro* and *in vivo* studies furnish drug efficacy and biocompatibility for further subungual delivery design preclinical and clinical studies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AIDS: Acquired Immunodeficiency Syndrome; **CA:** Chloramphenicol; **CT:** Clotrimazole; **PIT:** Itraconazolec; **PLGA:** Poly D, L-lactide-co-glycolide; **PEG:** Polyethylene glycol; **PNIPAAm:** Poly N-isopropylacrylamide; **PK-PD:** Pharmacokinetic-Pharmacodynamic; **MIC:** Minimum inhibitory concentration.

IMPLICATIONS

The Dexidin antifungal drug encapsulated oil-in-water nanoemulsions loaded nanogels have a particle size in the submicron range for fungal infection. The low concentration of efficient antifungal drug-loaded nanogels showed substantial mycological cure due to the direct application of the nanogel on subungual infection. The advantage of drug efficacy nanogel is beneficial for the treatment of subungual fungal infection, which contemplates developing a new drug delivery system for drug formulation with dexidin antifungal drug properties.

This delivery system also creates new dimensions for cosmetic application for nail care without the presence of harmful cocktail chemicals. The functional groups present in the drug-nanogels and drug-gelatin interactions in the biological/physiological medium were evaluated by ATR-FTIR and molecular docking. The results showed standard FT-IR results for the investigation of dexidin drug functional groups and docking outcomes were reflected for the drug-docking targets present in the nanogel. The docking analysis data has given an established structure of gelatin for NAGs. The average molecular distance between all possible pairs of the considered drug-nanogel was calculated and the dynamical behavior of the nanogel was studied using the radial distribution function.

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