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Current Review On Nanosponges Gel For Effective Treatment Of Fungal Disease

[1]Aagre Diksha Virbhadra, [2]Dr. J. P. Rai

[1,2]School of Pharmacy LNCT University, Bhopal (M.P.)

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Abstract

Fungal infections represent a significant global health challenge, with more than 600 fungal species associated with humans as either commensals or pathogens. Environmental changes and modern lifestyle factors have facilitated the emergence and spread of fungal diseases, making effective prevention and treatment strategies crucial. Topical therapy remains a preferred approach for treating skin infections due to its direct action and reduced systemic side effects. Econazole nitrate, an imidazole antifungal, is commonly used in various topical formulations. Recent advances in drug delivery have introduced nanosponges innovative carriers that enhance drug solubility, stability, and bioavailability. This review focuses on the development and application of nanosponges for the delivery of antifungal drugs, highlighting their advantages in treating fungal infections. By encapsulating drugs in nanosponges, sustained release and targeted delivery can be achieved, improving therapeutic efficacy and patient compliance.

Keywords: Fungal infections, Topical therapy, Econazole nitrate, Nanosponges, Drug delivery systems, Antifungal treatment, Sustained release, Drug solubility, Drug stability, Targeted delivery.

Introduction

More than 600 fungal species are associated with humans, either as commensals and members of our microbiome or as pathogens that cause some of the most lethal infectious diseases (Fisher *et al*., 2016; Fisher *et al*., 2012). Understanding the factors that contribute to the emergence and spread of fungal diseases is crucial for effective preparedness and prevention strategies. Environmental changes, such as climate change, deforestation, increased population density and urbanization as well as global travel and migration can create favorable conditions for fungal growth and transmission. Climate change, on the other hand, can alter the geographical distribution of fungal pathogens, enabling them to establish themselves in new regions (Nnadi and Carter, 2021).

Fungal infections of the skin are one of the dangerous diseases in worldwide (Trotta, 2011). Topical therapy is an attractive choice for the treatment of the coetaneous infections due to various advantages such as targeting of drugs to the direct site of infection and reduction of systemic side effects. Econazole nitrate (imidazole) is an antifungal or pharmaceutical fungicide used topically to cure athlete's foot, ringworm, tineapityriasis versicolor, jock itch and vaginal thrush. The available products of econazole nitrate present in the market are cream, ointment, lotion, and solution. Adsorption of econazole nitrate is not significant when it is applied to the skin and effective therapy; need a high concentration of active agents to be combined. For this reason, econazole nitrate nanosponges were fabricated by emulsion solvent method and these econazole nitrate nanosponges were loaded in a hydrogel as a topical delivery for sustained release of the drug (Kaur *et al*., 2015; Renu, 2018).

Some of important fungal infections in humans, include Candidiasis, which is caused by Candida species and commonly affects the skin, nails, and mucous membranes. Aspergillosis is another fungal infection in humans caused by Aspergillus species, primarily affecting the respiratory system. Cryptococcosis is caused by *Cryptococcus neoformans* and *Cryptococcus gattii*, and it can lead to severe lung and central nervous system infections. Histoplasmosis is caused by the fungus *Histoplasma capsulatum* and primarily affects the lungs, but it can also spread to other organs. *Pneumocystis pneumonia* is a serious fungal infection caused by the fungus *Pneumocystis jirovecii*. It primarily affects individuals with weakened immune systems, such as those with HIV/AIDS. It can cause severe respiratory symptoms, including coughing,

shortness of breath, and fever (Rajendra *et al*., 2021), and Mucoromycosis, also known as zygomycosis, is a rare but serious fungal infection caused by fungi of the order Mucorales (Jafarlou, 2024).

Fungal diseases

Fungal infections are a growing public health problem, mainly related to the advances of modern medicine in prolonging the lifespan and the quality of life of patients under severe clinical conditions (Perlroth *et al*., 2007). A range of new broad-spectrum antibiotics made it possible to successfully treat infections of many microorganisms, which had previously been fatal. This resulted in prolonged survival of patients highly susceptible to infection. Thus, fungal infections emerge as leading causes of morbidity and mortality in immunocompromised and intensive care unit patients (Alangaden, 2011).

Pathogenic fungus diseases

Aspergillosis: The causative agent of aspergillosis is *Aspergillus fumigates*. It is a saprophytic fungus, consists of vegetative mycelium present in soil and produce asexual spores (Tekaia and Latge, 2005). Lung infection is caused due to the inhalation of conidia of *A. fumigates* (Wery, 2014). Although there are more than 300 known species within the genus, aspergillosis are mainly caused by *A. fumigatus* and only rarely by a few other species, i.e. *A. flavus*, *A. terreus*, and *A. niger* (Pitt 1994; Meersseman *et al*., 2004).

Blastomycosis: The causative agent of this infection is *Blastomyces dermatitidis*. *Blastomyces dermatitidis* cause subclinical infection. But it can also cause serious complications which can be fatal. The symptoms include fever, influenza, cough, pleurisy and may also cause myalgia arthralgia. This infection causes weight loss and fatigue which are the most common symptoms. In pulmonary blastomycosis patients have alveolar infiltrate. However, it is not advantageous for diagnostic purposes (Patel *et al*., 1999).

Cryptococcosis: Cryptococcosis is a potentially fatal mycosis. However, the anamorphic genus Cryptococcus comprises basidiomycetous yeasts, most of which are environmental saprophytes that do not cause infections in humans or animals (Kwon *et al*., 2017). *C. neoformans* is a fungus which causes cryptococcosis. It is a facultative intracellular, opportunistic and encapsulated pathogen. It causes disease in immunocompromised and T-cell deficient patients (Kwon, 1992).

Candidiasis: The genus Candida comprises over 200 species, with 15 isolated from infections in humans and animals (Pal *et al*., 2015). Around 80% of infections are caused by *Candida albicans*, although the incidence of candidiasis due to non-albicans Candida (NAC) sp. is increasing. *C. albicans* is dimorphic fungal specie. It is present in gastrointestinal and reproductive tract. Approximately 75% women in their reproductive ages are affected due to this infection (Fidel, 2005).

Histoplasmosis: *Histoplasma capsulatum* is a dimorphic fungus found in soil contaminated with bird or bat droppings. It causes histoplasmosis, a respiratory infection that can progress to disseminated disease in immunocompromised individuals (Mittal *et al*., 2019). *H. capsulatum* possesses the ability to evade immune responses. The fungus can modulate the host immune system by interfering with the activation of immune cells and suppressing the production of pro-inflammatory cytokines. This allows the fungus to establish a chronic infection and avoid clearance by the immune system (Valdez *et al*., 2012).

Diagnosis of fungal infections

Diagnosis of fungal infections is problematical and many infections are confirmed only at autopsy. In addition, the isolation of fungi from clinical samples is unreliable and may be complicated by the presence of a colonizing commensal organism, or ubiquitous fungi in the environment, causing false-positive results. Serological tests that detect antibodies are low in sensitivity and specificity because many patients with systemic fungal infections are immunocompromised and, therefore, have an impaired antibody response. The diagnosis of aspergillosis include the greater use of routine highresolution computed tomography (CT) scanning, PCR for the detection of RNA or DNA, and ELISA testing for circulating galactomannan, a component of the fungal cell wall in Aspergillus (Tyagi, 2016).

Antifungal drugs

Clotrimazole: Clotrimazole is used for the treatment of topical infections like tinea, mucocutaneous candidiasis, and vaginal candidiasis. It is not used orally for treatment of systemic infections as it causes severe GIT disturbances (Crowley and Gallagher, 2014).

Miconazole: Miconazole base can be used intravenously in the treatment of systemic fungal infections. Topically miconazole nitrate can be used in the treatment of tinea versicolor, mucocutaneous candidiasis, and of corneal infection caused by candida and aspergillus (Fothergill, 2006).

Ketoconazole: It is topically in treatment of many fungal infections and orally it is effective in many mucocutaneous and systemic mycoses, or to treat severe cutaneous dermatophytic infections, which do not respond to topical therapy or oral griseofulvin (Van, 1983).

Bifonazole: Bifonazole is an imidazole antifungal drug used in form of ointments.The most common side effectis a burning sensation at the application site. Other reactions, such as itching, eczema or skin dryness, are rare (Hage *et al*., 2011).

Econazole: Econazole is used as a cream to treat skin infections such as athlete's foot, tinea, pityriasis versicolor, ringworm, and jock itch. It is also sold in Canada under the brand name Ecostatin as vaginal ovules to treat vaginal thrush. Econazole nitrate exhibits strong anti-feeding properties against the keratin-digesting common clothes moth *Tineola bisselliella* (Jana *et al*., 2021).

Nanosponges

Nanosponges are the versatile drug delivery systems developed for targeted drug delivery. These are nanoporous tiny mesh particular structure in which a large variety of drug substances can be suspended, and then incorporated into a specific dosage form. Nanosponges are more like a threedimensional network in which the backbone is a long length of polyester which is mixed in solution containing crosslinking agent. These crosslinking agents link different parts of polymer by acting as mini hooks. They have spherical colloidal nature and reported to have high solubilization capacity of poorly water soluble drug which provide sustained release as well as improving drug bioavailability. Because of their inner hydrophobic and outer hydrophilic branching, they are able to load both hydrophilic and hydrophobic drug molecules offering unparalleled flexibility (Ujjwalnautiya *et al*., 2015).

Advantages

Nanosponge molecules are soluble in water and can be enclosed within the sponge. Drug irritability can be significantly reduced with nanosponges without compromising efficacy. By prolonging the time between doses, nanosponges improve patient compliance. A targeted, site-specific medication delivery method is provided by nanosponge. Better stability, enhanced elegance, and greater formulation flexibility are all advantages of nanosponges. Nanosponges are non-toxic, non-allergenic, nonmutagenic, and non-irritating. These are selfsterilizing as their average pore size is 0.25µm, where bacteria cannot penetrate (Uday *et al*., 2013; Vishwakarma and Choudhary, 2019).

Disadvantages

Nanosponges incorporate only tiny molecules. Nanosponges are dependent on loading capacities (Kaivalya *et al*., 2020). Dose dumping may take place in nanosponges (Bhowmik *et al*., 2018).

Mechanism of drug release from nanosponges

The sponge particles have an open structure and the active drug moiety moves in and out from the sponge particles into the vehicle until equilibrium is retained. In case of topical delivery, once the finished dosage form is applied on to the skin, the active drug which is already present in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated hence disturbing the equilibrium. This will start a flow of the active drug from the sponge particles into the vehicle and from it into the skin until the vehicle is either dried or absorbed. Even after that the sponge particles will get retained on the surface of stratum corneum which will continue to gradually release the active to the skin, providing sustained release of the drug overtime (Harsha and Naseeb, 2021).

Chemicals used for the synthesis of nanosponges

Polymers: Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl βCyclodextrins and Copolymers like Poly(valerolactone-allylvalerolactone)

Crosslinkers: Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride, Carbonyldiimidazoles, Epichloridrine, Glutarldehyde, Carboxylic acid dianhydrides, 2,2- bis(acrylamido) Acetic acid and Dichloromethane.

Apolar solvent: Ethanol, Dimethylacetamide, Dimethyl formamide (Kumar, 2017)

Method of preparation

Ultra-sound-assisted synthesis: Nanosponges can be made using this process, which involves reacting polymers with cross-linkers in the absence of a solvent and sonication. The nanosponges produced will be spherical, homogenous in size, and less than 5 microns in diameter. The cross-linker in this approach is di-phenyl carbonate (or) pyromelitic anhydride. Place the flask in a water-filled ultrasonic bath and heat it to 90°C. For 5 hours, sonicate the mixture (Ajinkya *et al*., 2015).

Emulsion-solvent diffusion method (ESDM): This approach creates nanosponges by mixing ethyl cellulose and polyvinyl alcohol in various ratios or amounts. This approach employs both dispersed and continuous phases. Ethyl cellulose and the drug collectively forms the dispersed phase, which is then combined with 20 ml of dichloromethane and some polyvinyl alcohol (PVA) to create the continuous phase (aqueous). The mixture is then agitated for around 2 h at a speed of 1000 rpm. The finished product, or nanosponges, is obtained by filtration. The product is dried in the oven at a final temperature of 400° (Surushe *et al*., 2023).

Solvent method: Using solvent method, Nano sponges are prepared by mixing polar aprotic solvents like Dimethyl sulfoxide (DMSO), Dimethylformamide (DMF) with the polymer. A crosslinker is then added to this mixture in the ratio of 1:4. The above reaction should be proceeded at temperature 10˚C to reflux the temperature of the solvent for the time ranging from 1 to 48 h. Once the reaction has completed, the solution is cooled down at room temperature and then obtained a product is added to bi-distilled water. The product is recovered by filtering the product under vacuum and refining by soxhlet extraction with ethanol followed by drying (Bezawada *et al*., 2014; Pandey, 2019).

Melt method: During the melting process, the crosslinker and the polymer are combined. Nanosponges were collected by periodically washing them with a suitable liquid (Tiwari and Bhattacharya, 2022). Nanosponges are obtained after product cleaning, removing the waste polymer and unreacted chemicals (Tarannum *et al*., 2020).

Bubble electrospinning: A syringe, syringe pump, grounded collector, and high-voltage power are the key components of a standard electro-spinning setup, as defined in several kinds of literature. The amount of production of nano-fibers, however, is one of the major restrictions that limit their applicability. Polyvinyl alcohol (PVA) can also be utilized as a polymer in bubble electro-spinning (Shrestha and Bhattacharya, 2020).

Quasi-emulsion solvent method: The polymer was used to assemble the nanosponges in various quantities. The inner stage is produced and added to a reasonable dissolvable stage using Eudragit RS 100. Under ultrasonication, the medication employed elicited a response and broke down at 35 °C (Zhang *et al*., 2017). This internal procedure utilized in the exterior phase containing PVA goes around as an emulsifying operator. The mix is blended for 3 h at room temperature at 1000-2000 rpm, then dried (12 h) in an oven (40 °C) (Mahmoudi *et al*., 2009).

Evaluation of Nanosponge

Particle size determination: Free-flowing powders with fine aesthetic qualities can be obtained by controlling the size of particles during polymerization. The particle size study of loaded and unloaded nanosponge and microsponges can be done by laser light diffractometry or Malvern Zeta sizer (Reddy *et al*., 2019; Subramanian *et al*., 2012).

Drug Content or Entrapment Efficiency (%): 50 mg of the prepared drug Nanosponges were suspended in 50 ml of methanol using the emulsion solvent diffusion method using the required polymer and subjected to ultracentrifugation for 40 minutes. The spectrophotometric percentage of the integrated drug was calculated at precise nm. The number of the free drug was detected after centrifugation in the supernatant and the aqueous suspension. Then formula,

Entrapment efficiency = Total drug (assay) – Free drug / Total drug ×100

Scanning Electron Microscopy (SEM) analysis: For the determination of particle surface features and size, SEM analysis is important. The scanning electron microscopy was conducted at an acceleration voltage of 15KV.

Zeta potential: Zeta potential of any system under investigation is a measured of the surface charge (Sri *et al*., 2018).

Loading efficiency: The loading efficiency of nanosponges can be determined by the quantitative estimation of drug loaded into nanosponges by UV spectrophotometer and HPLC methods (Simranjot and Sandeep, 2018).

Solubility studies: The phase solubility method defined by Higuchi and Connors, which explores the effect of a nanosponge on drug solubility, is the most commonly used approach to studying inclusion complexation.

Fourier Transform Infrared (FTIR): Fourier transform infrared analysis was performed to verify the possibility of the interaction of chemical bonds between drugs and polymers. Samples were scanned within the 400-4000 cm-1 and carbon black reference range (Ghurghure *et al*., 2018).

Drug release kinetics: In order to investigate the mechanism of drug release from the Nanosponge and release data was analyzed using the Zero Order, First Order, Higuchi, Korsemeyer Peppas, Hixon Crowell, Kopcha and Makoid-Banakar models. The data could be analysed using graph pad prism methods (Subhash and Mohite, 2016).

Porosity: Porosity analysis has been performed to check the extent of nanochannels and nanocavities generated. As Helium gas is capable of penetrating inter- and intra-specific material channels, the helium pycnometer is used to measure the porosity of nanosponges (Jilsha and Viswanand, 2013). By equation, percent porosity is given:

Porosity = Void volume (Vv) / total volume (VT)

Challenges in nanosponges development

Increase in polymer concentration decreases percentage of drug release and rate of permeation. Increase in drug and polymer ratio decreases particle size of nanosponges upto some extent, there after particle size will be increased due to polymer – polymer interaction overruling drug polymer interaction. High stirring rate effects practical yield and swelling ratio of nanosponges. By increasing the amount of cross linking agent, viscosity and porosity of formulation will be increased further leading to less entrapment efficiency.Increase in surfactant concentration decreases entrapment efficiency of the formulation due to insufficient polymer concentration (Prathima and Sreeja, 2013).

Application of nanosponges

Nanosponges have a wide range of application in the pharmaceutical field, because of its biocompatibility and versatility. In the pharmaceutical industry, nanosponges can be used as an excipient for the formulation of tablets, capsules, granules, pallets, suspensions, solid dispersions and topical dosage forms. Nanosponges can accommodate both lipophilic and hydrophilic drug molecules, basically, those drugs substances which belong to the biopharmaceutical classification system (BCS-class II) as well as the poorly water-soluble drug (Trotta *et al*., 2014).

Nanosponges for drug delivery: Nanosponges can carry the water-insoluble drug because of their tiny porous structure. To increase the dissolution rate, solubility and permeability of drug nanosponges complexes play a major role.

Nanosponges for cancer therapy: Most challenging works nowadays in the pharmaceutical field is the delivery of anticancer drug because of their low solubility. When nanosponges confront the tumor cell they stuck on the surface of tumor cell and start to release the drug molecules. The advantage of targeting drug delivery is to get a more effective therapeutic effect at the same dose and with minimized side effect (Naga *et al*., 2013).

Conclusion

Novel drug delivery systems are being researched extensively, with nanosponges being one of the most successful, as they may carry either lipophilic or hydrophilic drugs and release them at the target location in a controlled and predictable manner.Nanosponges have been proved to be a safe and efficient delivery mechanism for pharmaceuticals and other applications in addition to medication delivery.These systems mainly help in reducing the toxicity and increasing the efficacy of antifungal drugs, thus increasing the therapeutic effect of antifungal drug treatment.

Table 1: List of marketed formulation of antifungal drugs given as nanosponges gel

S.no	Antifungal drug	Method	Author and year of study
1	Butenafine Hydrochloride	Emulsion solvent evaporation	Ahmed *et al*., 2021
2	Luliconazole	Emulsion solvent evaporation technique	Malothu *et al*., 2024
3	Voriconazole	Solvent evaporation process	Kirankumar and Ganeshkumar, 2024
4	Clotrimazole	Emulsion solvent diffusion method	Charan *et al*., 2023
5	Fluconazole	Emulsion solvent diffusion method	Abbas *et al*., 2019

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