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Nanoparticles: A Novel Antifungal Drug Delivery System †

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Abstract: Innovative drug delivery systems show how pharmaceuticals are administered to the site of action in order to produce the therapeutic effect. Fungal infections are a problem today on a global scale. There is no medical cover-up in the world regarding the significance of fungi as a human pathogen. According to recent developments, the accurate diagnosis and treatment of these infections are crucial and required. Numerous factors influence the development of modern pharmaceutical products and their methods of administration. For the development of a successful novel antifungal drug delivery system, it is essential to thoroughly investigate the relationships between the formulations, the mode of administration, pharmacological properties, pharmacokinetics, pharmacodynamics, stability, efficacy, safety, and clinical indications. This review article discusses various types of nano techniques used in the delivery of antifungal drugs, including dendrimers, polymeric nanoparticles, inorganic nanoparticles, and nanoparticles based on phospholipids (nano-vesicles). Due to their unique properties, nanoparticles can exert more inhibitory power through lower concentrations than conventional dosages when used in the treatment of fungal infections. Reduced drug efficacy, limited penetration through tissue, poor aqueous solubility, decreased bioavailability, and poor drug pharmacokinetics are among the drawbacks to using antifungal medications in delivery systems. Therefore, the incorporation of antifungal medications through the nanoparticles' drug delivery systems can reduce these undesirable properties.

Keywords: novel drug delivery; antifungal; nanoparticles; nano-vesicles

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1. Introduction

Fungal infections are infections that affect the skin and mucous membranes, or cause more severe, invasive, and systemic diseases of the internal organs. Fungal infections can also affect the lungs and heart [1]. People who have a weak or imbalanced immune system are more likely to get airborne fungal infections. Nanoparticle-based alternative therapies have received significant scientific attention in recent years. By adhering to the fungal cell wall and thereby increasing the drug concentration close to fungi, nano-carriers have the potential to enhance the efficacy of antifungals [2]. Systemic mycosis, superficial mycosis, cutaneous mycosis, and subcutaneous mycosis are the four types of these infections. According to researchers, treating these mycoses would not be possible by relying solely on the antifungal compounds that are currently available. A brand-new antifungal drug that works at the target sites needs to go through a long discovery phase, several clinical trials on humans and animals, development, and regulatory approval before it can be sold [3]. Due to their distinct structural and functional characteristics, advanced topical carriers overcome biopharmaceutical issues such as low bioavailability and poor retention that are associated with conventional drug delivery systems. According to the literature,

topical nano-carriers containing antifungal agents have a superior therapeutic response, while being the least toxic [4]. In recent years, alternative therapies based on nanoparticles have received a lot of scientific attention. The significance of nanoparticles' size and charge, as well as the presence of serum, on the interactions between microorganisms and nanomaterials has been the subject of several reports [2].

2. Overview of Antifungal Drug Delivery

Worldwide, fungal infections affect millions of people annually. There are a great many contagious contaminations, from shallow, influencing skin, to fundamental diseases with the intrusion of inward organs [5]. Mycosis is a fungi that affects humans, and which can be categorized into one of four groups based on how deeply it penetrates the body's tissues:

- ➢ Fungi that only grow on the skin or hair's surface are the cause of superficial mycosis.
- ➢ Infections such as athlete's foot and ringworm are examples of dermatomycosis, or cutaneous mycosis, in which growth only occurs in the superficial layers of the skin, nails, or hair.
- ➢ The subcutaneous, connective, and bone tissue are all affected by subcutaneous mycosis, which spreads below the skin.
- ➢ Fundamental or profound mycosis can taint inside organs and turn out to be broadly spread all through the body. This type is frequently deadly.

Novel delivery systems for approved and investigational compounds, as well as the utilization of the cell membrane, cell wall, and virulence factors as potential antifungal targets, are all components of the creation of new treatments for invasive fungal infections [6]. Materials with overall dimensions below 100 nm are known as nanoparticles. With a wide range of uses, these materials have become significant players in modern medicine in recent years [7].

Recent advances in the drug delivery systems are significantly important for improving patient acceptability and therapeutic efficacy, which is achieved by the alleviation of possible side effects and decreases in the dose required [3]. In parallel with the excessive use of immunological disorder therapies, the proportion of weak patients is rising [8]. In terms of medical treatments, quicker diagnosis, cellular regeneration, and drug delivery, nanotechnology has sparked a revolution. The emerging field of science has demonstrated undeniable versatility. There are three main categories of materials used to make nanoparticles, i.e., metals, polymers, or lipids, each of which produces a different kind of nanoparticle [5].

The purpose of this review was to provide a comprehensive explanation of the various types, techniques, advantages, and disadvantages of NPs used for the delivery of antifungal drugs to the skin and the body. In addition, it discusses the obstacles preventing the clinical application of some promising nano-formulations, and highlights the potential of various antifungal NPs against superficial and systemic fungal infections.

3. Nano Techniques for Antifungal Drug Delivery

Drugs can be attached to uniquely designed carriers to achieve cell-specific targeting. The potential of nanoparticle structures, smaller than 100 nm in at least one dimension, as drug carriers has been demonstrated by recent advancements in nanotechnology [9]. Due to their ability to alter and enhance the drugs' pharmacokinetic and pharmacodynamic properties, nanoparticles have been used in pharmaceutical formulations [5]. Firooz et al. describe novel nano-based formulation approaches used to improve Econazole penetration through the skin for the treatment of superficial fungal infections [10]. Some examples of nanoparticle-based antifungal drug delivery are solid-lipid nanoparticles, liposomes, niosomes, microemulsion, nano-emulsion, metal nanoparticles, nanogels, polymeric nanoparticles, quantum dots, colloidal gold, nano diamonds, dendrimers, nanocrystals, carbon nanotubes, etc.

3.1. SLN (Solid-Lipid Nanoparticles)

The active treatment is distributed within a lipid core matrix in these nano-lipid carriers. Lipids and surfactants that have been imprinted by nanoparticles make up these matrices. High homogenization or the creation of a microemulsion can be used to make solid lipid nanoparticles. The oil phase of SLNs does not contain an emulsion of solid lipids [11]. Because the utilized lipids are physiologically identical, the advantages of SLNs include a low risk of toxicity and biocompatibility. Lipid particles of a smaller size are able to come into close contact with the stratum corneum, allowing the drug to be absorbed through the dermis and released in a controlled manner [12,13]. Their formulation leaves a film on the skin and prevents water from evaporating. The skin stays hydrated, and maintains its barrier function as a result. Because of their spherical shape, lipid nanoparticles have excellent lubrication properties, preventing allergy and the irritation of the skin. Their release kinetics are well-modulated, and they have a high capacity to bind drugs. Encapsulation prevents the active ingredients from deteriorating. A wide range of preparations can be sterilized using the commercial method. Bioavailability remains high, and the stability is excellent for the long term. However, there are a few limitations to SLNs, such as the limited availability of drugs soluble in appropriate lipids [14,15].

3.2. Liposomes

Amphiphilic lipids (cholesterol and phospholipids) make up these spherical bilayer phospholipid vesicles. They can handle both hydrophilic and lipophilic drugs, among other substances. They might hold drugs that are lipophilic in their lipid bilayer, and hydrophilic molecules in their aqueous core. The drug is protected from degradation by the amphiphilic phospholipid and the ultra-flexible liposomes, which also increase skin permeability. These are thought to be suitable for topical drug delivery, due to their capacity to alter the bio distribution profile of the drug that has been entrapped. They can be absorbed on the skin's outermost surface, or penetrate deeper into the skin's layers. The liposomal formulation's therapeutic performance is heavily influenced by the drug release profile, the morphology of the liposome, and skin retention. Amphotericin-B has broad antifungal activity, but its ability to bind cholesterol in mammalian cells causes unwanted toxicity. Due to its capacity to form a complex with Amphotericin, liposomal Amphotericin B can reduce toxicity. For topical antifungal drug delivery, a variety of liposomes, including conventional, deformable, and mucoadhesive liposomes, have been investigated. When compared to the gel and cream formulations, the drug retention in the skin of the liposomal gel of ketoconazole is higher. A variety of phospholipids can be used to make liposomes in a variety of ways. A new class of phospholipid vesicles known as deformable or elastic liposomes are intended to enhance the delivery of antifungal drugs to the skin and dermis. Cationic liposomes have been found to be useful in ongoing efforts to boost antifungal activity. The antifungal activity of the Amphotericin B (AmB)-loaded cationic liposome, which had a zeta potential between 40 and 60 mV and a size range of 400 to 500 nm, was higher than that of the plain drug [16,17]. Due to the toxicity of its cationic components, however, the clinical application of cationic liposomes is limited. Despite their benefits, the drug–drug-carrier compatibility complex, drug expulsion, scale-up procedures, and stability are the main issues with liposomal formulations [18].

3.3. Niosomes

These are a kind of round lipid vesical organized by non-ionic surfactants. Their interaction with the stratum corneum reduces transepidermal water loss. Skin penetration is influenced by the types of surfactants, drug properties, and morphological characteristics of niosomal preparations [19]. It was discovered that ketoconazole in niosomal forms had a greater therapeutic effect [20]. Gupta et al. found that itraconazole and miconazole niosomes worked, which shows that they are good for carrying drugs. Different surfactants (range 40, length 60, and Brij 72) were utilized to prepare fluconazole-stacked niosomes [21].

3.4. Microemulsion

For skin and transdermal medication organization, these are straightforward, stable, and isotropic scatterings of oil in water settled by surfactants and co-surfactants with drop sizes of 0.1–1.0 m. Because of their exceptional ability to increment drug dissolvability, these have been reported to be extremely encouraging conveyance frameworks and hostile to parasitic specialists [22]. Due to their low aqueous solubility, many azole drugs' antifungal spectra are compromised. In a recent study, Ashara and colleagues determined the solubility of Voriconazole in a microemulsion system, made with Neem oil Acrysol^{TM} K-150 (Made by Corel Pharma Chem, Ahmedabad, Gujarat India), Polyethylene glycol (PEG) as the oil phase, surfactant, and co-surfactant, respectively [23]. They offer benefits such as expanding drug dissolvability, high warm solidness, high penetrability, simple assembly, optical clearness, and minimal expense. Because micro emulsions are the best delivery system for topical and transdermal systems, they exhibit excellent biocompatibility. The presence of oils and surfactants in microemulsion definitions work with drug porousness across the layer corneum [24].

3.5. Nanoemulsions

In the emulsified oil stage, water, and amphiphilic atoms make up this steady, single stage, isotropic scattering, which has bead sizes ranging from 5 to 200 nm. Both kinetically and thermodynamically, these are stable. Nanoemulsions are thought to be suitable for the skin penetration of both lipophilic and hydrophilic drugs, due to the high concentration of surfactants [25]. In order to lessen the adverse effects of encapsulated drugs' systemic absorption, a nystatin-loaded nanoemulsion was developed by Fernandez et al. Permeability focuses on the discovery that the prescribed dose was sufficient to protect the desired enemy from contagion without requiring any prior ingestion. Additionally, because they are less irritating to the skin and typically require significantly less surfactant to prepare than microemulsions, nanoemulsions have significant commercial potential [26].

3.6. Metal Nanoparticles

Metal nanoparticles are becoming increasingly popular due to their distinctive structural and functional properties. They are a distinct collection of metal atoms with distinctive optical properties and a size of 10 to 100 nm [27]. In the case of gold nanoparticles, the optical properties of metal nanoparticles have been clearly demonstrated. Gold nanoparticles with sizes between 5 and 200 nm have a color that is reddish-ruby, whereas those with sizes between 100 and 200 nm have a color that is bluish. Because of their high aspect ratio, the nanoparticles accelerate diffusion even below the critical temperature. The resonant oscillation of their free electrons in the presence of light, also known as localized surface plasmon resonance (LSPR), is what gives gold, silver, lead, and platinum nanoparticles their optical properties. Strong plasma absorption, the imaging of biological systems, the ability to find chemical information on a metallic nanoscale substrate, and surface-enhanced Raman scattering are all advantages of metallic nanoparticles [15,28]. Patil et al. said that the advantages of a tablet made from silver nanoparticles and fenugreek seed extract include the nanoparticles' high surface area to volume ratio, which results in both chemical and physical differences in their properties compared to the bulk [29]. Disservices of metallic nanoparticles incorporate pollution, trouble in union, molecule unsteadiness, and being organically hurtful. Metallic nanoparticles should ideally be prepared using a method that minimizes the use of reagents that can control the size and is easily reproducible, readily available, and cost-effective. Physical, chemical, and biological processes create these. Steric stabilization and electrostatic stabilization are the methods used to stabilize metallic nanoparticles. Between 10 and 100 nm of various shapes and sizes of gold, nickel, silver, iron metallic nanoparticles have been looked at as medication conveyance frameworks. The process by which various topical drug carriers pass through the stratum corneum is discussed in [3,4].

3.7. Nanogels

The term "nanogel" alludes to hydrophilic polymer nanoparticles that range in size from 20 to 200 nm and are cross-connected. They can be taken by mouth, topically, vaginally, orally, through the eyes, or by any other method. Due to their smaller size and soft membranes, they enable the desired drug release behavior and exhibit improved skin permeation and diffusion-based swelling. Overall, they are extremely biocompatible and offer a significant number of hydrophilic medications [30]. The hydrophilic nature of some nanogels limits the good encapsulation property of hydrophobic drugs. The advantages of nanogels include high biocompatibility, high biodegradability, enhanced permeation capability, and the capacity to cross the blood–brain barrier [31]. It was discovered that nanogels can be used to administer a wide range of medications, including hydro- and lipophilic medications. One of the most common disadvantages of nanogel processing is the difficulty in separating the finished product from the surfactant and solvent, despite its low cost [32].

4. Discussion

Drugs with low solvency have biopharmaceutical conveyance issues, including restricted bioavailability after oral admission, lower capacity to spread to the external layer, a prerequisite for a higher amount for intravenous admission, and unfortunate impacts from the immunization cycle. The drug delivery mechanism can be improved by incorporating nanotechnology to overcome all of these limitations. While liposomes and niosomes have demonstrated a number of advantages in the delivery of antifungal agents, they also have a number of disadvantages that limit their application in the medical field and in various formulations. The most common concern about liposome vesicles is that the phospholipid bilayer may be highly susceptible to hydrolysis or oxidative degradation due to external triggers such as temperature or pH, which contribute to both physical and chemical instability and cause drug leakage. In addition, after liposomal vesicles have been administered systemically, they are primarily be absorbed by the liver, which has the greatest capacity among the other reticuloendothelial system (RES) organs for liposomal uptake, followed by the spleen. The macrophages and phagocytic cells clear the vesicles, recognizing them as foreign particles in the body. Last but not least, the large-scale production of liposomes is frequently hindered by the time-consuming steps involved in their preparation, which should be performed in a laboratory.

Then, nanoparticles overcome a range of issues in the conveyance of antifungal medications in conventional techniques, for example by decreasing drug dependability and unfortunate medication pharmacokinetics, and restricting entrance through the tissues, unfortunate aqueous solvency, diminished drug viability, and secondary effects. As previously stated, the first nanoparticle to be developed was the phospholipid-based liposome. However, deformable liposomes are then introduced due to their poor penetration of the stratum corneum. The sustained release property of polymeric nanoparticles improved drug efficacy and decreased drug toxicity. However, macrophages may internalize the polymer and degrade it, resulting in cytotoxic effects. After that, solid lipid nanoparticles have been used in place of polymeric particles. However, their disadvantages include drug expulsion during storage and a low capacity for drug loading. The introduction of a nanostructured lipid carrier (NLCs) followed. This had improved drug loading, drug release, and stability due to its specific lipid and oil proportions.

Micro-particulate-encoded drugs in polymer coverings have shielded drugs from corruption prior to arriving at target tissues, thus expanding the bioavailability of medications. Microemulsions with the watery and oil stages upgraded the medication delivered through skin and transdermal courses. Microemulsions are more stable in extreme temperatures, and perform sustained release and improve skin penetration. The microemulsion begins to work much more slowly than conventional drug delivery methods such as cream. The development of colloidal carriers has made it possible to treat fungal infections more quickly and with fewer side effects.

5. Conclusions

In conclusion, fungal infections are an issue throughout the whole world, and can be a life-threatening disease for the immune-compromised patient. Since our medical system has had an over-reliance on antibiotics to fight fungal infections for a long time, a lot of other drugs have lost their effectiveness in treating fungal infection. Therefore, novel drug delivery systems such as nano-particulate-based drug delivery systems, colloidal carriers, and miscellaneous delivery systems have been introduced. These systems mainly help in reducing the toxicity and increasing the efficacy of antifungal drugs, thus increasing the therapeutic effect of antifungal drug treatment.

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