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INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)

Vol. 02, Issue 05, May 2022, pp : 359-369

e-ISSN : 2583-1062

Impact Factor : 2.205

NANOFORMULATIONS FOR FUNGAL MUCOSAL DISEASES

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ABSTRACT

Immuno compromised adults and patients Invasive mycoses are especially dangerous in intensive care units. These infections have spread throughout the world. A high morbidity and mortality rate due to late detection and treatment. Furthermore, there are only a few antifungal medications available. Medications on the market, and toxicity and resistance are concerns. Invasive fungal infections necessitate treatment choices. Antifungal drugs could be delivered in nanostructured systems, reducing toxicity and allowing for more precise targeting of their activities. Nanostructured systems When lipid formulations of Amphotericin B were introduced in the 1990s, they were first used for antifungal therapy. Liposomes, solid lipid and nanostructure lipid carriers, and polymeric nanoparticles are all examples of lipid carriers, nanofibers, nanoemulsions, and other antifungal drug delivery systems are discussed in this review. Each of these delivery methods has its own set of benefits and drawbacks. The primary advantages include improved antifungal qualities including bioavailability, toxicity reduction, and target tissue, which enable for more creative therapy alternatives.

Keywords: Fungal, mucosal disease, nanoparticles, nanofibers.

1. INTRODUCTION

Infections of the skin and mucous membranes, as well as invasive and systemic disorders of the internal organs, can all be caused by human fungus [1]. Dermatologists are consulted by patients for a number of causes, including superficial fungal infections [2]. The human population is thought to be affected by superficial mycoses in the 20–25 percent range [3]. Invasive fungal infections are also becoming a major source of morbidity and mortality among AIDS patients, hematologic cancer patients, severe aplastic anemia, myelodysplasia, immune compromised people, organ transplant recipients, preterm neonates, and the elderly [4]. Aspergillus, Cryptococcus, Candida, Coccidioides, Mucor, and Rhizopus are only a handful of the fungal genera that cause deadly infections [5, 6]. In order to increase the therapeutic index, the pharmaceutical industries. The long-term goal is to create therapeutic drugs that can be delivered to specific parts of the body. Drugs that are administered systemically have a significant positive effect, but they can also have harmful repercussions [7]. Many potential new compounds have poor physiochemical properties [8], resulting in Because of its poor solubility and biodistribution, the medication does not reach the site of action. Absorption through the mouth is inadequate. At physiological pH, solubility is poor [9], cellular absorption is insufficient [10]. Fast drug clearance stymies medication research [11, 12]. New medicine candidates must show they arrive at the action site and have an effect [7]. In biomedical research, the use of nanomaterials for biomedical applications is a novel and promising paradigm. Nanomaterials with exceptional physiochemical characteristics, biocompatibility, and low biological toxicity can detect local biological conditions and induce cellular reprogramming for therapeutic efficacy [13-15].

1. Different types of fungal mucosal diseases

- **Paracoccidioidomycosis:**

Paracoccidioidomycosis, a systemic Paracoccidioides brasiliensis causes mycosis. Lutz–Splendore–Almeida disease or Brazilian blastomycosis are other names for it. [16]. Mucous membranes, lymph nodes, bones, and the lungs are all affected by paracoccidioidomycosis. Rural labourers are the most vulnerable since the disease is disseminated by inhaling conidia generated by a saprophytic phase of a fungus present in nature. The infectious particle develops into a yeast pathogenic form after being breathed. [17]. Paracoccidioidomycosis is connected to excessive Consumption of alcoholic beverages, a poor diet, and smoking habits are all risk factors. These circumstances result in a lowered immune response, which promotes fungal proliferation and spread. [18]. In less than 5% of acute–subacute cases, the mucous membranes are damaged. [19].

- **Mucormycosis**

Mucormycosis is a novel life-threatening fungal infection spread by Mucorales species. [20].The most prevalent agents that cause this deadly infection are Rhizopus and Mucor [21]. Rhizopus is a genus and species of the Mucoromycota phylum, Mucoromycetes class, Mucorales order, Rhizopodaceae family, and Rhizopus genus microsporus and delemar in the fungi kingdom. Mucor, on the other hand, is a mould genus. It belongs to the Mucoromycetes class, Mucorales order, and Mucoraceae family of fungi [22]. The basic histological feature of mucormycosis is hyphae vascular invasion; As a result, tissue thrombosis and infarction develop. Large quantities of irregularly branched hyphae can be detected inside the arteries and surrounding tissue. A lack of inflammatory

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response causes edema and necrosis. [23, 24, 25]. Mucormycosis is caused by uncontrolled diabetes, cancer, solid organ or bone marrow transplantation, hematological malignancy, corticosteroid treatment, trauma, and burns. [26]. The introduction of additional risk factors, such as corona virus disease (COVID 19), has resulted in an evolution in mucormycosis epidemiology in recent years [27]. COVID-19 disease patterns can range from mild pneumonia to life-threatening pneumonia with bacterial and fungal co-infections, depending on the severity of the infection. As a result, people with comorbidities or who are immunocompromised are more likely to get serious opportunistic infections. [28]. Mucormycosis is becoming more common in COVID-19 patients around the world, including in India [28-30].

- **Candidiasis**

A diploid fungus i.e. candida sp. that can cause serious infections and harm human health, particularly in those with compromised immune systems [31, 32]. With a death rate of 35 to 100 percent, candidiasis is the fourth nosocomial infection. a source of infection Candida auris (C. auris) is a novel pathogenic species that is found on practically every continent and has gotten a lot of attention because of its pathogenicity, strong resistance to standard antifungals, and rapid spread [33]. C. auris is a member of the Saccharomycetes class and belongs to the phylum Ascomycota. It belongs to the Saccharomycetales order, Metschnikowiaceae family, and Clavispora genus, and is part of the Clavispora/Candida clade [34]. The transition from blastoconidia to filamentous development, hydrolytic enzymes, osmotolerance, biofilm formation, cell adhesion, thermo- tolerance, and the change from white to opaque are only a few of the virulence features that play a role in C. auris pathogenesis [33, 34, 35]. Furthermore, it has been discovered that this new Candida species may live for long periods of time on various surfaces in the environment, as well as disinfectants [31, 34, 36]. C. auris may adapt to and survive various therapies, as well as create an infection in a patient, thanks to all of the aforementioned characteristics [31, 33]. The development of novel antifungals based on nanoparticles could be a potential technique for fighting Candida infections [37].

- **Aspergillosis**

Mycotoxins are toxins produced by mould. Mycotoxins can be found in humans as well as food. Allergies, hepatotoxicity, and cancer are among the acute and chronic consequences of mycotoxins in humans. Niger, fumigatus, flavus, and ochraceus are species of Aspergillus, which belongs to the Ascomycota phylum, Eurotiomycetes class, Eurotiales order, Trichocomaceae family, and Aspergillus genus. [22]. Mycotoxins are produced and released by the moulds Aspergillus flavus (A. flavus) and Aspergillus fumigatus are two species of Aspergillus (A. fumigatus). In hospital settings, mould growth is widespread, resulting in patient discomfort and financial losses [38]. A fumigatus is a saprotrophic fungus that spreads through asexual sporulation and survives in its vegetative mycelia on decaying inorganic material. [39]. Lung infections can be caused by inhaling airborne conidia found both indoors and outdoors. There is a relationship between invasive pulmonary aspergillosis, chronic pulmonary aspergillosis, and severe asthma with fungal sensitivity [40-42]. Aspergillus species is the most common cause of corneal infection. Fungal keratitis, the third clinical manifestation of fungal infections, is associated to saprophyte filamentous fungi such Aspergillus spp. [43]. As a result, Aspergillus species are serious life-threatening pathogens, especially in immunocompromised individuals [44].

Table 1: Causative agents and their infection, pathophysiology and their area of infection [45].

Causative agent	Infection	Pathophysiology	Affected area and symptoms
Cocidioides	Cocidiocomycois	Valley fever is caused by inhaling microspores found in the dust.	The lungs, sinuses, and eyes are all affected.
Candida	Oral candidiasis Invasive candidiasis	The yeast can be found in the colon and on the skin's mucosal layer.	Blood, skin, ear, mouth, and other body organs are affected.
Rhizopus	mucormycosis	A large number of asexual spores are produced. Mucorales spores are commonly inhaled, ingested, or directly inoculated into humans.	Mouth, eyes, ear
Aspergillus	Aspergillosis	Molds in the environment create conidia, which, when inhaled,	Asthma, allergic sinusitis, and allergic bronchopulmonary

		transform into an angiopathic form that infects the lungs and other organs.	Aspergillosis are all examples of allergic bronchopulmonary Aspergillosis.

Table 2: Drugs used in treatment of fungal mucosal diseases: [46]

Chemical class and Antifungal drug	Site of action	Target molecules
Allylamines Terbinafine, Naftifine	Biosynthesis of Ergesterol	Sqalene epoxidase
Azoles **Imidazoles** Miconazole, Econazole, Bifonazole, Clotrimazole, Ketoconazole **Triazoles** Fluconazole, Itraconazole, Terconazole, Posaconazole	Biosynthesis of Ergesterol	Cytochrome P450 14α-Lanosterol demethylase
Morpholines Amorolfine	Biosynthesis of Ergesterol	Sterol reductase and isomerase
Polyenes Amphotericin B, Nystatin	Biosynthesis of Ergesterol	Membrane barrier function
Thiocarbamate Tolnaftate	Biosynthesis of Ergesterol	Sqalene epoxidase
Griseofulvin	Fungal mitotic apparatus	Sliding of microtubules

2. Antifungal drugs need delivery systems?

Because many antifungal drugs are hydrophobic, they require delivery strategies to avoid low water solubility, poor oral bioavailability, and limited formulation possibilities. [47]. For example, clotrimazole, miconazole, econazole, oxiconazole, tioconazole, and sertaconazole are hydrophobic and have a low water solubility. [48, 49]. Systemic antifungal drugs' toxicity and drug-drug interactions are two other key roadblocks that limit their therapeutic utility [50]. Antifungal medicine toxicity is well-known, with dose-limited toxicities such as infusion-related events and nephrotoxicity. Several additional drugs, such as cyclosporine and aminoglycosides, are made more nephrotoxic by AmB. [51]. Despite the availability of typical antifungal drug dose forms such as tablets, creams, and IV infusions, they looked to be ineffective in overcoming these limitations. As a result, it's vital to create new medication delivery technologies to overcome these obstacles. Rationally designed drug delivery systems have the potential to improve drug performance and overcome many of these limitations. Indeed, lipid-based Amphotericin-B (AmB) formulations including AmB lipid complex (ABLC), AmB colloidal dispersion (ABCD), and liposomal AmB (L-AmB) reduced AmB nephrotoxicity while maintaining broad-spectrum antifungal activity. [52]. These promising results sparked the development of a number of novel drug delivery systems aimed at increasing antifungal agent safety while maintaining or boosting efficacy [53, 49].

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Impact Factor : 2.205

Nanoformulation for mucosal fungal diseases:

- **Different types of nanoformulations :**

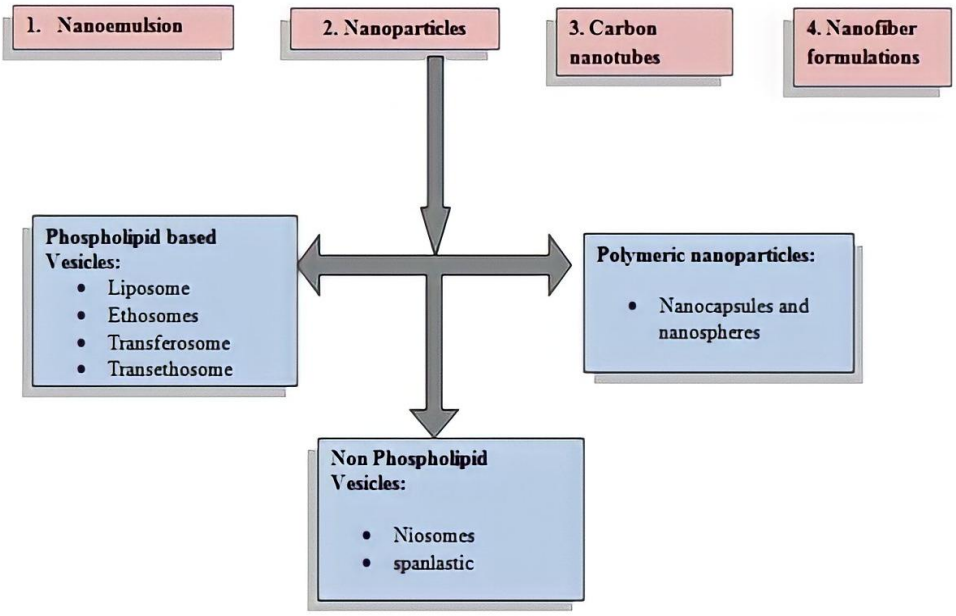

Figure: Types of Nanoformulations

1. Nanoemulsions:

These are emulsified systems that are transparent/ translucent and have droplet sizes of a few nanometers, either a mixture of oil and water, or a mixture of oil and water. Medication penetration is aided by the small droplet size. Nystatin-based nanoemulsions have been shown to reduce nystatin's unfavourable systemic absorption and toxicities. Ex-vivo skin permeation tests on human skin showed that the antifungal effectiveness was acceptable. Furthermore, the nanoemulsion produced showed sustained release when combined with a 2% carbopol gel (80.37 percent release in 8 hours), ketoconazole has improved solubility and permeability, supporting the suggested formulation's potential formulation characteristics [54, 55].

2. Nanoparticles

a) Phospholipid based vesicles:

- **Liposome:**

Liposomes, which date back to the early 1980s, were the first phospholipid-based nanoparticles to be used in drug delivery [56, 57]. Liposomes are bilayered vesicles that have an aqueous core and one or more concentric phospholipid membranes. [58]. Because of their unique structure, liposomes are ideal delivery vehicles for both hydrophilic and hydrophobic medications [59, 60, 61]. Other advantages of liposomes as drug delivery vehicles include biocompatibility, low toxicity, high drug loading capacity, enhanced drug bioavailability and stability, delayed drug release, and minimal pharmacological adverse effects [62]. Cholesterol is commonly integrated into the lipid bilayers of liposomes to increase membrane stiffness, stabilize vesicles, and control drug release rate [63].

- **Transferosome:**

Despite their benefits and accomplishments, liposomes' low penetration through the stratum corneum prompted researchers to alter their bilayer composition in order to overcome this obstacle [64]. Cevc and Blume were the first to integrate edge activators in liposome construction, resulting in deformable liposomes or transfersomes [65]. Edge activators are commonly used surfactants/hydrophilic detergents with high mobility, such as sodium cholate, sodium deoxycholate, Span 60, Span 65, Span 80, Tween 20, Tween 60, Tween 80, and dipotassium glycyrrhizinate [66]. The edge activator is responsible for vesicle lipid bilayers becoming weaker and more deformable [66]. These deformable vesicles outperformed traditional liposomes in terms of medicine penetration and skin contact. [67]. It has been discovered that deformable liposomes can deform and pass through skin pores (5–10 times smaller than their own diameter) without generating considerable drug release prematurely [69]. Ultra deformable liposomes (UDL) containing various edge activators were designed and tested as a topical delivery approach for AmB. [70]. Tween 80 was shown to be the best edge activator in terms of vesicle deformability and greatest AmB liposomal content. In

fungal strains (albicans and non-albicans Candida, as well as clinical isolates of Candida albicans), AmB-UDL sensitivity was higher than in mammalian cells, indicating that UDL can reduce AmB toxicity [68].

- **Ethosomes:**

Ethosomes are soft vesicles that are made up of phospholipids, ethanol, and water [70]. They usually have 2–5% phospholipids, 20–45 percent ethanol, and 100 percent water in them [64]. Touitou et al. first proposed them in 2002 as a way to circumvent the poor epidermal penetration of traditional liposomes [71]. Ethosomes increased penetration more than ethanol alone, hydroalcoholic solution, or ethanolic phospholipid solution, suggesting a synergistic interaction of ethanol, vesicular structure, and skin lipids [72]. Because ethanol has the ability to fluidize ethosomal lipids and stratum corneum intercellular lipids, ethosomes can penetrate the epidermis more efficiently than liposomes. [72, 73]. The capacity to adjust the size of ethosomes is another advantage by regulating their ethanol concentration, which avoids the need for expensive machinery [64]. Ethosome size reduces with increasing ethanol level at constant phospholipid concentrations. Furthermore, because ethosomes include ethanol, which gives them a negative charge, they have superior colloidal stability [74, 64]. The high concentration of ethanol in ethosomes, however, induces "loose" packing of the phospholipid bilayers, resulting in increased leakage of hydrophilic or ionic medications when compared to liposomes. [71]. Ethosomes have shown considerable promise as antifungal drug delivery systems on the skin. For example, in the treatment of Candidiasis patients, Bhalaria et al. developed a fluconazole-loaded ethosomal gel and compared it to liposomal gel, drug hydroalcoholic solution, and fluconazole commercial formulation. [75].

- **Transethosome:**

Transethosome are a new type of vesicular carrier that combines the advantages of ethosomes and deformable liposomes. They include the conventional ethosome formula as well as a permeation enhancer or edge activator **(Table 3)** [76]. Because transethosomes are a relatively novel drug carrier, there are few research on their use for antifungal drug delivery. ethosomes, traditional liposomes, deformable liposomes, and drug polyethylene glycol fluid are all inferior than drug polyethylene glycol solution, voriconazole transethosomes exhibited considerably higher skin penetration (p0.05) [76]. Transethosomes also increased voriconazole skin deposition in the dermis/epidermis layers in vitro and in vivo when compared to other vesicular carriers [77].

b) Non-phospholipid vesicles

- **Niosomes:**

Niosomes are similar to liposomes, but their bilayers are made up of single-alkyl chain non-ionic surfactants instead of phospholipids **(Table 3)** [78, 79]. They were first introduced in 1979 by Handjani-Vila et al. [80]. The hydrophilic head of the surfactant faces both the exterior and inside of the vesicles, while the hydrophobic tail is embedded inside the bilayered structure. [81]. Hydrophilic pharmaceuticals can be incorporated into the aqueous core, but hydrophobic drugs are encased in hydrophobic bilayers [82]. Similar to liposomes, cholesterol is added to increase bilayer stiffness and avoid premature drug release. [83]. Niosomes have a number of advantages over liposomes, including increased chemical stability, a lower cost and the capacity to store them in a controlled environment [84]. Furthermore, Niosomes have a high drug loading capacity, and their attributes can be customized by carefully selecting the composition and production procedure. [85]. Niosomes can also be used to administer medications via a variety of routes, including oral, topical, and parenteral administration. On the other side, particle fusion and aggregation may limit their physical stability. Surfactants used in niosome synthesis include polyglycerol alkyl ethers, crown ethers, ester-linked surfactants, glucosyldialkyl ethers, polyoxyethylene alkyl ethers, Brij, Tweens, and Spans [86].

- **Spanlastic:**

Edge activators were added to the niosome's composition to increase permeability through biological membranes, resulting in a novel class of deformable nanovesicular carriers known as spanlastic [87]. They are primarily made up of Spans, with some edges thrown in for good measure. Tweens, for example, are activators **(Table 3)**. In the same way that transfersomes and transethosomes contain edge activators, they do as well. The first published spanlastic-based delivery method for ketoconazole ocular administration was created using Span 60 and Tween 80 as an edge activator. [87].The spanlastic showed a 2-fold increase in ketoconazole ocular permeability as compared to regular niosomes. They were stable and safe in genotoxicity, cytotoxicity, acute dermal/eye irritation/corrosion, and chronic eye irritation/corrosion tests. Fluconazole-loaded spanlastic were three times smaller than their corresponding niosomes and had three times higher drug permeability through porcine cornea when compared to commercial pharmaceutical eye drops [88].

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Vol. 02, Issue 05, May 2022, pp : 359-369

e-ISSN : 2583-1062

Impact Factor : 2.205

Table 3:- Composition of various vesicular structure [77]

Sr. no	Nanostructure	Composition				
		Phospholipid	Cholesterol	Ethanol	Edge activator	Surfactant
1	Liposome	+	+	-	-	-
2	Transferosome	+	+	-	+	-
3	Ethosomes	+	+	+	-	-
4	Transethosomes	+	+	+	+	-
5	Niosomes	-	+	-	-	+
6	spanlastic	-	-	-	+	+

C. Polymeric nanoparticles:

- **Nanocapsules and nanospheres :**

Nanospheres are colloidal solid nanoparticles in which the drug is dissolved, entrapped, or adsorbed to the surface [89]. At normal temperature, nanocapsules are colloidal particles with a liquid or semisolid centre and a solid polymeric shell. A lipophilic solvent, most often oil, is used as a reservoir for hydrophobic drug encapsulation [90]. Synthetic polymers including poly(lactic acid) (PLA), poly(lactide-co-glycolide) (PLGA), poly(e-caprolactone) (PCL), and poly(alkylcyanoacrylates) (PACA), as well as natural polymers like chitosan, sodium alginate, and collagen, are routinely used to make nanospheres and nanocapsules [91]. A nanocapsule shell can be created through polymerization during nanocapsule production or by precipitation of a prepared polymer on the surface of emulsion droplets. Nanospheres and nanocapsules can be ingested in a variety of ways (parenteral, oral, topical etc). They are more stable, easier to manufacture and store, and less expensive than phospholipid vesicles [92].

- **Polymeric micelles:**

Polymeric micelles are amphiphilic block or graft Co-polymer nanostructures that self-assemble in water above their critical association concentration (CAC) [93]. The hydrophobic segments constitute the core, while the hydrophilic segments create the corona. The hydrophilic corona maintains the micelle's water solubility and colloidal stability, reducing immune system cell uptake and increasing blood circulation time. Poly (ethylene glycol) (PEG) is the most commonly used polymer as a hydrophilic micelle corona because of its hydrophilicity and biocompatibility [94]. PEG also produces a steric barrier, which reduces opsonin protein adsorption on micelle surfaces, resulting in a longer micelle circulation duration in the blood [94]. Polymeric micelles have superior dilution stability than surfactant micelles because to their lower CAC, a feature that is critical due to significant dilution after intravenous injection [95]. The peculiar architecture of polymeric micelles as drug delivery systems, in which hydrophobic medicines are integrated into the hydrophobic core, has sparked curiosity since it leads to a significant increase in their water solubility [96].

3) Carbon nanotubes:

These nanoparticles have the unmistakable ability to permeate living cells without harming or killing them. Drugs can be easily integrated into these structures. When amphotericin B was integrated into carbon nanotubes, it was revealed to be effective against amphotericin B resistant Candida albicans. Topical administration of these particles revealed drug restoration in the skin even after the medicine had been rinsed off the skin [97]. The minimum concentration required to produce fungicidal activity when Nystatin was incorporated into multi-walled carbon nanotubes was found to be 16 g/ml and 14 g/ml for Candida albicans and Candida parapsilosis, respectively, whereas these values were 25 g/ml and 21 g/ml for conventional nystatin formulations [98].

4) Nanofibers:

Nanofibrous structures are prominent in pharmaceutical research due to their several advantages, including high surface area, porosity, and the ability to contain actives in an amorphous state [99, 100]. Electrospinning, in which fibers are generated in an electric field, is the most used method for fiber preparation. Aside from biological applications, such as tissue engineering, optimization of certain physicochemical properties, such as solubility and dissolving properties, has surfaced as a possible research area [101-104]. A large number of pharmaceutically active compounds now have negative physicochemical properties, with low solubility affecting a considerable fraction of them. The latter can make it difficult to administer the medication. Terbinafine, which is used to treat fungal infections, is an example of such a medication. Terbinafine hydrochloride is minimally soluble in aqueous media and

has a hydrophobic character [105, 106]. Oral fungus infections are very common in immunocompromised patients and people with impaired immune systems. Despite the availability of a large spectrum of antifungal medicines, the treatment outcome does not always fulfill expectations. This therapeutic failure can be linked back to the amazing features of the oral cavity, such as the saliva flush effect [107]. These flaws are solved with terbinafine-loaded nanofiber shits. Nanofibers can be found in scaffolds, patches, and films.

3. CONCLUSION

The lack of efficiency of present medicines has been demonstrated by the rise in invasive fungal illnesses as a result of limited antifungal availability and the development of medication resistance. As a result, the need for innovative therapeutic strategies is critical. The advancement of nanotechnology has contributed in the search for new and more effective therapeutic approaches to treat invasive fungal infections. In comparison to standard antifungals, other types of nanoformulations are now being investigated and optimised, with enhanced efficacy and few or no side effects. Nanotechnology has facilitated the creation of nanomaterial- based formulations such as nanoparticles and nanoparticle-based formulations, nanoemulsions, and nanotubes, Nanofibers, for example, can increase not only the treatment's effectiveness but also improves the patient's quality of life by reducing side effects, which is especially important during long-term treatment. Nanoformulations, as detailed in this review article, are more successful in the treatment of mucosal antifungal infections. Coccidioidomycosis and mucormycosis treatment options are limited or in the early stages of development. Several factors have been connected to the present COVID-19 pandemic's increased prevalence of various fungal illnesses. As a result, nanotechnology must continue to improve, and more research is needed to find new therapeutic alternatives that will help the sector progress.

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