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Review Paper

An Overview of Nanofibers for Enhanced Antifungal Therapy

**Manmath Palaskar, Dr. Vijayendra Swamy S. M.*, Wasim Kazi, Vaishnavi
Dopalwar, Sanika Sonwane, Akash Kawale, Vaishnavi Mangnale**

Department of Pharmaceutics, Channabasweshwar Pharmacy College (Degree), Latur, Maharashtra, India

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ABSTRACT

Millions of individuals worldwide suffer from fungal infections, a common but frequently overlooked health issue. Oral thrush, vaginal candidiasis, and skin infections are examples of mild fungal diseases, but in immunocompromised people, they can worsen and potentially become fatal. Aspergillus, Candida, and Cryptococcus are examples of invasive infections that greatly increase morbidity and mortality globally. Despite the widespread use of oral, topical, and parenteral antifungal treatments in clinical practice, their effectiveness is often restricted. Treatment outcomes are still compromised by poor drug penetration, brief retention at the site of infection, systemic adverse effects, repetitive dosing, and the developing issue of antifungal resistance. Nanotechnology has emerged in recent years as a promising solution to tackle these limitations, with particular attention given to nanofibers as advanced systems for drug delivery. Nanofibers, typically generated through electrospinning, provide a large surface area, a porous framework, and a close similarity to the extracellular matrix. These characteristics enable them to be created as thin, flexible and adaptable mats that bond effectively to skin and mucosal areas, guaranteeing extended residence duration and regulated drug release while minimizing systemic exposure. This review emphasizes the drawbacks of traditional antifungal treatments and explores the increasing significance of nanofiber-based systems, concentrating on their fabrication, assessment, recent advancements, and uses in targeted antifungal therapy.

INTRODUCTION

Fungal infections silently impact millions across the globe, yet they are often disregarded until they escalate into more serious conditions. For numerous people, fungal illnesses start as typical

issues like oral thrush, vaginal yeast infections, or superficial skin ailments. In at-risk groups, particularly those who are immunocompromised, transplant recipients, cancer sufferers, and individuals with chronic health conditions, fungi can penetrate deeper tissues and enter the

***Corresponding Author:** Dr. Vijayendra Swamy S.M.

Address: Principal, Channabasweshwar Pharmacy College (Degree), Latur-413512, Maharashtra, India.

Email ✉: palaskar.m001@gmail.com

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bloodstream, resulting in potentially fatal systemic mycoses. The worldwide impact of fungal diseases is significant, with *Candida*, *Aspergillus*, and *Cryptococcus* species being key players in causing illness and death.^[1,32,33] Despite progress in healthcare, the advancement of antifungal therapies has not kept up with that of antibacterial treatments. The challenges posed by a small number of drug classes, concerns over toxicity, inadequate drug penetration at sites of infection, and the rise of resistance make managing fungal

infections quite challenging. These obstacles have prompted researchers to investigate innovative drug delivery methods, such as nanotechnology-based systems like nanofibers, to enhance therapeutic effectiveness.^[22,26]

1.1 Classification of Antifungal Drugs

Antifungal agents are commonly classified based on their mechanism of action:

Polyenes	• (e.g., nystatin, amphotericin B) bind to ergosterol and disrupt fungal cell membranes.
Azoles	• (e.g., fluconazole, clotrimazole, ketoconazole, itraconazole) inhibit ergosterol synthesis.
Echinocandins	• (e.g., caspofungin, micafungin) block β -glucan synthesis in the fungal cell wall.
Allylamines	• (e.g., terbinafine, naftifine) interfere with squalene epoxidase.
Others	• include antimetabolites such as flucytosine.

Fig No. 1. Classification of Antifungal drugs

Although effective, many of these agents face formulation and delivery limitations, particularly for localized and mucosal infections.

1.2 Available Conventional Treatments for fungal-infection

Traditional antifungal therapy mainly depends on well-known dosage forms such as oral tablets and capsules, topical creams, ointments, gels, lotions, suspensions, and parenteral injections. These formulations are the primary choice in standard clinical practice due to their ease of use, widespread availability, and proven clinical effectiveness. Topical antifungal products are frequently recommended for superficial fungal infections affecting the skin, nails, and mucosal

areas, as they permit direct drug application to the infected site while minimizing systemic exposure. Conversely, systemic fungal infections, which can be life-threatening and primarily affect immunocompromised individuals, necessitate oral or intravenous antifungal treatment to achieve sufficient drug levels in deeper tissues and the bloodstream. Medications given through these routes are critical for treating invasive mycoses but are typically reserved for severe or widespread infections because of their potential toxicity and the requirement for careful clinical supervision.^[22] While these traditional dosage forms are clinically effective, they have specific practical constraints. Topical preparations frequently stay at the application site for a limited time because of

influences like washing, perspiration, saliva production, or vaginal fluids, requiring multiple doses to sustain therapeutic drug concentrations. Oral antifungal medications can exhibit inconsistent bioavailability and are often linked to systemic side effects and interactions with other drugs. Parenteral antifungal treatment, although effective, is intrusive and not ideal for prolonged use. ^[25]In general, although traditional antifungal

therapies remain essential for addressing fungal infections, their constraints related to residence time, dosing frequency, and patient adherence emphasize the necessity for innovative and sophisticated drug delivery methods.

1.3 Limitations of Conventional Antifungal Therapy ^[23,27]

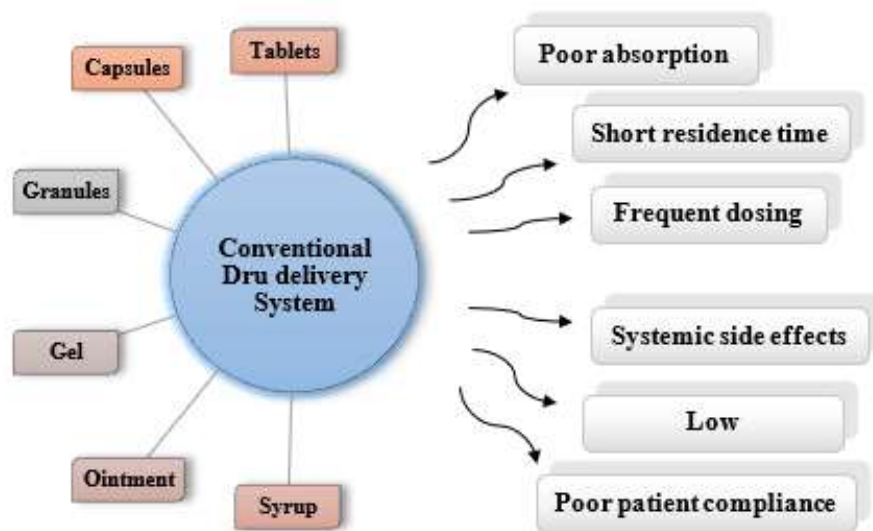


Fig No. 2. Limitations of conventional antifungal therapy

2. Introduction to Nanotechnology

Nanotechnology pertains to the science and engineering of materials at the nanoscale (1–100 nm), where materials display distinctive physical, chemical, and biological characteristics that significantly differ from those of their larger-scale forms. In pharmaceutical sciences, nanotechnology has become a revolutionary method to enhance drug solubility, stability, targeting, and therapeutic effectiveness. By altering materials on a nanoscale, it is now feasible to create sophisticated drug delivery systems that can address numerous challenges linked to

traditional dosage forms. ^[28,29]Nanotechnology's implementation in medicine, commonly known as nanomedicine, emphasizes the targeted delivery of drugs to the specific site of action, minimizing systemic toxicity, and enhancing patient adherence. These benefits are especially significant in managing fungal infections, where extended treatment, drug resistance, and dose-related toxicity are frequent clinical issues. ^[24]Multiple nanotechnology platforms have been investigated for drug delivery, incorporating antifungal treatment. Every system provides unique benefits based on the type of medication and the method of delivery. ^[26]

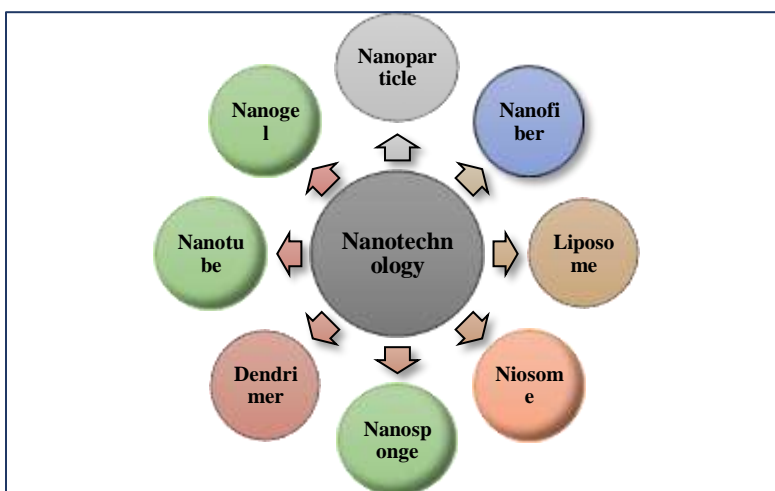


Fig. No. 3 Nanoscale carriers used in drug delivery

Nanofibers redefine nanoscale drug delivery by converting passive carriers into active therapeutic matrices.

3. Nanofibers in Antifungal Therapy:

The constraints identified with traditional formulations and certain nanoscale carriers prompted the investigation of nanofibers as sophisticated drug delivery systems. Nanofibers are usually created through electrospinning methods and have a large surface area-to-volume ratio, interlinked porosity, and structural resemblance to the extracellular matrix.¹⁵⁻¹⁸ In antifungal treatment, nanofibers provide various unique benefits. In contrast to nanoparticles or vesicular systems, nanofibers can be produced as thin, flexible mats or patches that maintain close proximity to the infected area. This attribute is especially beneficial for topical, transdermal, oral, vaginal, and wound-related fungal infections, where extended retention time is essential for successful treatment.^[40] Nanofibers facilitate

prolonged and regulated drug delivery, decrease dosing intervals, and improve localized drug levels while lowering systemic exposure. Furthermore, they can integrate various antifungal agents, such as synthetic medications and natural substances, and can be designed with biodegradable polymers for safe and patient-friendly uses.^[20] With antifungal resistance, toxicity, and treatment failures remaining significant global issues, nanofiber-based systems offer a rational and hopeful advancement in antifungal drug administration. Nanofibers unite the advantages of nanotechnology with site-specific, prolonged delivery, connecting traditional dosage forms and advanced antifungal treatments. The versatility, efficiency, and adaptability of nanofibers make them one of the most sophisticated and clinically significant nanotechnology platforms for future antifungal treatment approaches.^[37,46]

3.1. Advantages of Nanofibers over Conventional Dosage Forms^[1-6]

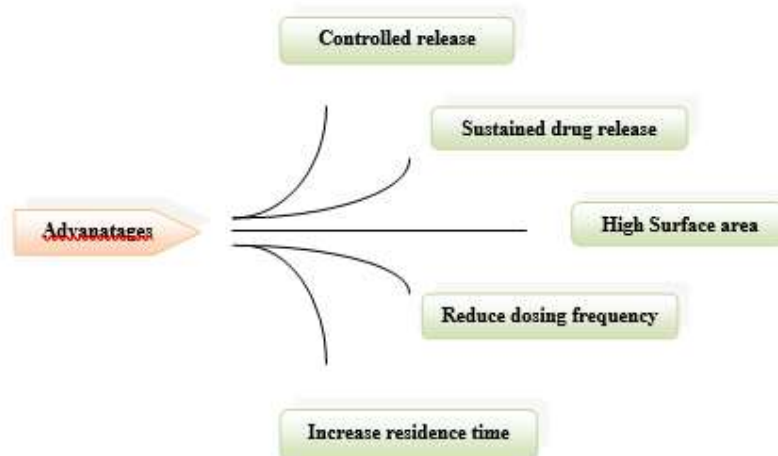


Fig No. 4. Advantages of nanofiber

Studies have shown superior antifungal efficacy using nanofiber formulations loaded with drugs such as amphotericin B, luliconazole, clotrimazole, and terbinafine compared with conventional formulations.

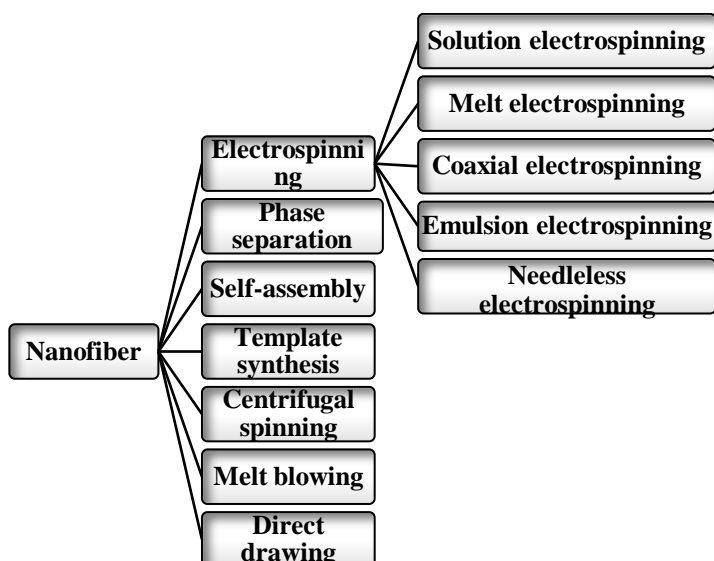
3.2. Polymers Used for the Formulation of Nanofibers ^[2_10]

Choosing the right polymers is a crucial phase in the formulation of nanofibers, as the characteristics of the polymers have a direct impact on electrospinnability, fiber structure, mechanical properties, drug loading capacity, release dynamics, biocompatibility, and biodegradability. The polymers employed in the fabrication of nanofibers can generally be divided into synthetic polymers, natural polymers, and blends or composites of polymers.

Table No. 1. Different polymers used for fabrication of nanofiber

Polymers		
Natural	Synthetic	Blend/ Mixed
Chitosan	Polycaprolactone (PCL)	Chitosan + PVA
Alginate	Polyvinyl alcohol (PVA)	Gellan gum + PVA
Gellan Gum	Polyvinyl pyrrolidone (PVP)	PCL + Gelatin
Gelatin	Polylactic acid (PLA)	PVA + Natural polymer
Collagen	Polylactic co-glycolic acid (PLGA)	PVP + Biopolymer
Cellulose & derivative	Polyethylene oxide (PEO)	-
Silk fibroin	Polyacrylonitrile (PAN)	-
-	Polyurathane (PU)	-

3.3. Fabrication techniques of Nanofibers



The fabrication methods that are commonly used to create nanofibers are listed below.

Fig No. 5. Nanofiber fabrication techniques

Electrospinning Technique ^[18,37-41]

Electrospinning is a recognized technique in nanofabrication that enables the creation of continuous fibers with diameters that can range from micrometers to just a few nanometers. Its simplicity, adaptability, and capacity to produce

nanofibrous structures with higher surface area, interlinked porosity, and adjustable shape have garnered significant attention in materials science, pharmaceutical sciences, and biomedical engineering. Electrospinning is esteemed for its compatibility with many polymers, including synthetic, natural, and composite systems.

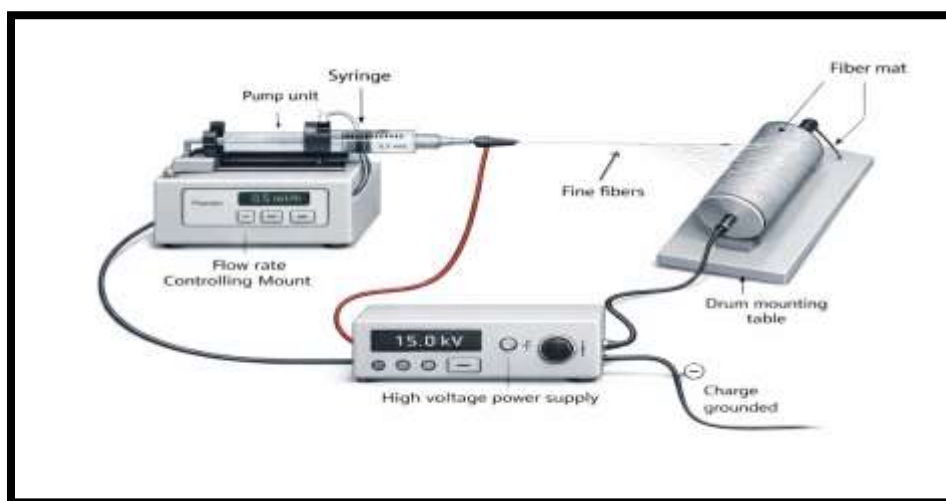


Fig No. 6. Preparation of nanofiber by electrospinning

a. Principle of Electrospinning

Electrostatic forces produced when a high voltage is supplied to a polymer solution or polymer melt

control the electrospinning process. Charges build up on the polymer fluid's surface near the spinneret tip as a result of the electric field. The droplet's surface tension is decreased by electrostatic repulsion as the applied voltage rises. The droplet elongates to form a Taylor cone when a critical voltage is attained, and then a fine charged jet is ejected toward a grounded collector. The polymer jet experiences fast stretching and bending instabilities during flight, which drastically decrease the jet diameter. Solvent evaporation happens concurrently in solution electrospinning, whereas the jet hardens during cooling in melt electrospinning. These processes result in the

production of solid nanofibers that deposit as aligned or nonwoven fibrous mats on the collector.

b. Electrospinning Setup

A syringe pump with a metallic needle, a polymer solution or melt, a collector, and a high-voltage power source are the four primary parts of a standard electrospinning machine. Stable jet formation is ensured by the syringe pump, which regulates the polymer fluid flow rate. Fiber direction and packing density are mostly determined by the collector, which can be either stationary or revolving.

c. Electrospinning Process ^[39,49]

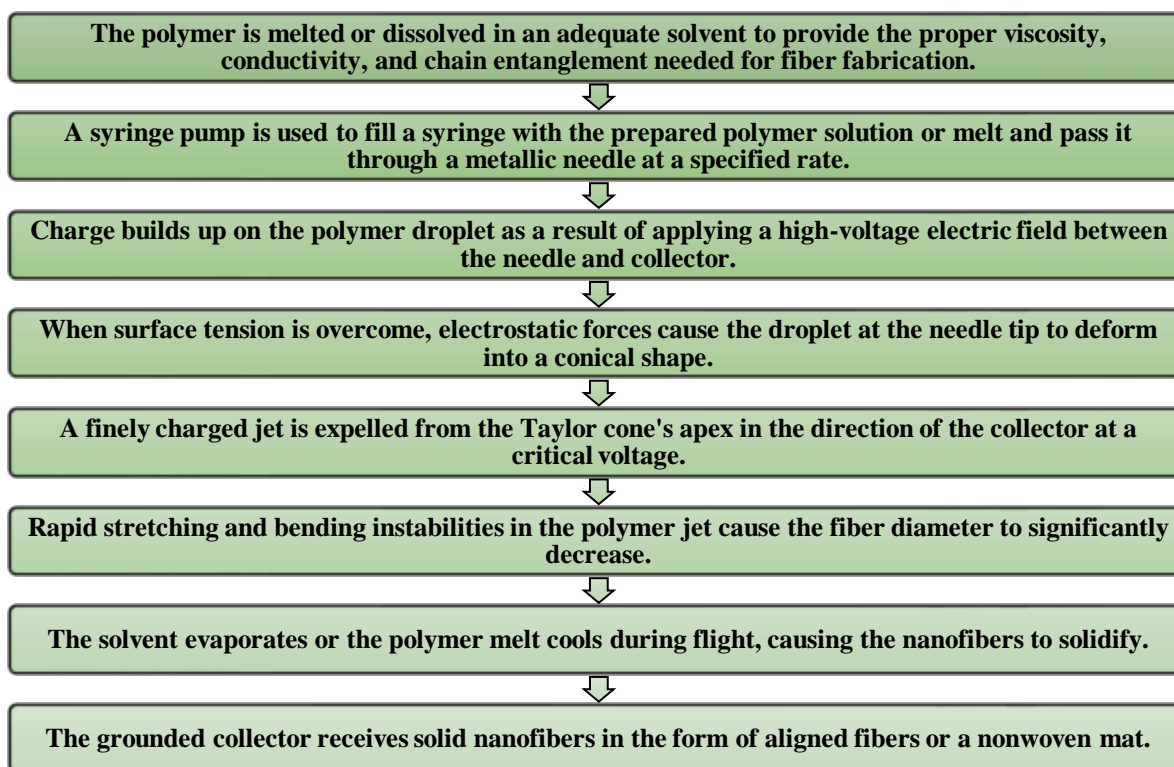


Fig. No. 7. Steps of electrospinning process

Types of electrospinning: ^[40-50]

i. Solution electrospinning:

Uses polymer solutions dissolved in volatile organic or aqueous solvents. It is particularly

suitable for antifungal drugs that are heat-sensitive and allows uniform drug distribution within the nanofibers.

ii. Melt electrospinning:



Involves electrospinning of polymer melts instead of solutions. This approach eliminates the use of toxic solvents but requires elevated temperatures, which may limit its application for thermolabile drugs.

iii. Coaxial electrospinning:

Employs two concentric needles to fabricate core-shell nanofibers. This method is useful for sustained and controlled drug release as well as combination antifungal therapy.

iv. Emulsion electrospinning:

Uses emulsified systems to encapsulate hydrophilic drugs within hydrophobic polymer matrices, providing enhanced drug protection and prolonged release.

v. Needleless electrospinning:

Generates multiple polymer jets simultaneously, improving productivity and scalability compared to conventional single-needle systems. Electrospinning remains the preferred fabrication method due to its simplicity, versatility, and ability to tailor fiber morphology and drug release profiles.

3.4. Evaluation Parameters of Nanofiber [15_18,34,35]

Nanofibers are evaluated using a combination of physicochemical, mechanical, and biological tests.

1. Fiber Diameter and Surface Morphology (SEM)

Scanning electron microscopy (SEM) is utilized to assess fiber thickness, surface texture, consistency, and defects like beads or fiber fusion. Fibers that are uniform and free of beads suggest well-optimized fabrication conditions, which guarantee consistent drug loading and reliable drug release characteristics. Additionally, fiber diameter affects

surface area, adhesion, and dissolution rates, making SEM analysis crucial for the quality control of nanofiber formulations.

Evaluation Process: Dried nanofiber samples are placed on metal stubs and coated with a conductive substance like gold through sputter coating. SEM imaging is conducted at various magnifications, and fiber diameters are analyzed using image processing software to evaluate consistency and quality of fabrication.

2. Internal Structure and Core-Shell Architecture (TEM)

Transmission electron microscopy (TEM) offers insights into the internal architecture of nanofibers, particularly in coaxial or multilayer configurations. It verifies the existence of core-shell structures and the localization of drugs in designated areas within the fiber. This analysis is essential for the development of controlled and sustained drug delivery systems.

Evaluation Process: Ultrathin slices of nanofibers are either prepared or fibers are directly placed onto TEM grids. TEM imaging illustrates the localization of the drug and confirms the structural integrity of multilayer systems.

3. Surface Roughness (AFM)

Atomic force microscopy (AFM) is utilized to evaluate surface roughness and topography at the nanoscale. Surface roughness has a direct impact on mucoadhesion, cellular interaction, and the behavior of drug release. Surfaces with greater roughness typically improve adhesion to skin or mucosal tissues.

Evaluation Process: Nanofiber mats are examined with an AFM probe in either contact or tapping mode to produce three-dimensional surface profiles and roughness measurements.



4. Thickness

Thickness of nanofiber mats is measured using a micrometer. Uniform thickness ensures dose accuracy, reproducibility, and consistent therapeutic performance, particularly for topical and transdermal applications.

Evaluation Process: Thickness is assessed at several locations with a digital micrometer, and the average values alongside the standard deviation are computed.

5. Weight Uniformity

The consistency of weight is assessed through gravimetric analysis, indicating how evenly the drug is distributed among various samples. This is crucial for maintaining consistent dosing and ensuring that each batch is reproducible.

Evaluation Process: Samples of individual nanofibers of the same size are measured using an analytical scale, and the variation is examined through statistical analysis.

6. Drug Loading

The quantity of drug contained in each unit mass of nanofiber is referred to as drug loading and is usually assessed using UV-visible spectroscopy or HPLC. Increased drug loading enhances therapeutic effectiveness and minimizes the frequency of dosage.

Evaluation Process: Nanofibers are solubilized in an appropriate solvent, and the concentration of the drug is assessed through UV-Vis spectroscopy or HPLC.

7. Entrapment Efficiency

Entrapment efficiency measures how effectively a drug is integrated into nanofibers. It is determined by extracting the drug from the fibers and performing quantitative analysis. A high

entrapment efficiency signifies that there is minimal drug loss throughout the fabrication process.

Evaluation Process: A percentage is calculated by comparing the extracted drug quantity to the theoretical drug content.

8. Drug-Polymer Compatibility (FTIR)

Fourier transform infrared spectroscopy (FTIR) is employed to detect possible chemical interactions between the drug and the polymer. Ensuring compatibility is essential for maintaining drug stability and preventing degradation or loss of efficacy.

Evaluation Process: Peak shifts or disappearances in the FTIR spectra of drug-loaded nanofibers, polymers, and pure drugs are noted and compared.

9. Thermal Behavior (DSC)

Differential scanning calorimetry (DSC) assesses thermal characteristics like melting point and glass transition temperature. It aids in identifying drug crystallinity, physical stability, and interactions between polymers and drugs.

Evaluation Process: Thermal transitions, including melting points, are noted as samples are heated at a regulated rate.

10. Crystallinity (XRD)

X-ray diffraction (XRD) analysis is utilized to determine whether the drug in the nanofibers is crystalline or amorphous. Typically, amorphous drug dispersion improves solubility and the rate of dissolution.

Evaluation Process: XRD signals are captured and examined for distinctive crystallographic peaks.



11. Tensile Strength

Tensile strength is assessed with a universal testing machine and reflects the mechanical strength of nanofiber mats. Sufficient strength is necessary for proper handling, application, and longevity.

Evaluation Process: A universal testing equipment is used to stretch nanofiber strips until they break.

12. In-Vitro Drug Release

Drug release investigations, typically conducted using Franz diffusion cells, assess the kinetics and mechanisms of release. Such investigations aid in forecasting in vivo behavior and refining formulation design.

Evaluation Process: Franz diffusion cells with appropriate receptor media are used to assess drug release, and the results are assessed at predefined intervals.

13. Stability Studies

Stability testing conducted under ICH guidelines evaluates shelf life, physical integrity, and the stability of the drug over time, guaranteeing the product's reliability in the long run.

Evaluation Process: ICH-specified storage conditions are used for nanofibers, and their physical characteristics, drug content, and release behavior are routinely assessed.

3.5. Recent Developments in Nanofibers ^[1-14]

In recent years, research on nanofibers has progressed significantly beyond just basic production, largely thanks to enhancements in electrospinning methods and a deeper comprehension of how polymers behave at the nanoscale. Contemporary electrospinning techniques provide precise regulation of fiber

diameter, alignment, porosity, and internal structure, enabling the creation of nanofibers with characteristics customized for particular uses. By producing core-shell fibers, multilayer systems, and high-throughput nanofiber mats with better uniformity, methods including coaxial, emulsion, and needleless electrospinning have increased manufacturing capabilities.. Hybrid and composite nanofibers, which combine the advantages of several polymers, are receiving increasing interest at the material level. Researchers have been able to increase mechanical strength while preserving biocompatibility and controlled degradation by combining synthetic polymers with natural or bioactive elements. Stability, functional performance, and interaction with biological surroundings have all been further improved via surface modification and polymer mixing techniques. Simultaneously, the creation of stimulus-responsive nanofibers, which respond to variations in pH, moisture, or temperature represents a significant advancement toward systems that are more intelligent and flexible.

In order to better mimic natural extracellular matrices, structural design has also changed, with a greater emphasis on aligned fibers, multilayer mats, and patterned structures. The enhancements to the design improve surface interaction, strengthen structural integrity, and boost overall performance. Together, these developments emphasize the evolution of nanofibers from basic fibrous substances to adaptable and multifunctional platforms with significant promise for cutting-edge pharmaceutical and biomedical uses.

3.6. Applications of Nanofibers

Nanofibers have numerous applications in pharmaceuticals, biomedicine, and materials science thanks to their distinctive structural and functional properties. Their extensive surface area,



interlinked porosity, and capacity to be produced as slender, flexible mats render them especially ideal for uses that demand tight surface contact and regulated functionality. In the field of drug delivery, nanofibers are widely investigated as vehicles for localized and regulated release systems. The fibrous structure facilitates an even distribution of drugs throughout polymer matrices, allowing for immediate, sustained, or controlled release profiles based on the design of the formulation. Nanofibers offer significant benefits for topical, transdermal, and mucosal administration, where an extended duration of action and less frequent dosing are preferred.^[34] In the fields of wound healing and tissue engineering, nanofibers are commonly utilized as scaffolds and dressings due to their structural similarity to the natural extracellular matrix. This resemblance encourages cell attachment, growth, and tissue repair, while also offering a defensive barrier. Nanofiber mats can be designed to regulate moisture levels, facilitate gas exchange, and promote healing processes.^[36] Nanofibers are also vital in transdermal and mucosal systems, as their flexibility and surface adhesion enhance their interaction with biological tissues. These characteristics improve treatment effectiveness and patient adherence when compared to traditional dosage forms. In addition to their use in pharmaceuticals, nanofibers are being utilized more and more in biosensors, filtration systems, protective textiles, and biomedical coatings, thanks to their adjustable mechanical properties and extensive functional surface area. Improvements in polymer blending and surface modification have broadened their uses by facilitating multifunctional and responsive nanofiber systems.^[41,43] In general, the adaptability of nanofibers makes them suitable for various applications, establishing them as promising foundations in both existing and developing technologies.

3.7. Future Challenges and Perspectives

In the future, antifungal systems based on nanofibers show significant potential for transforming the management of fungal infections, especially those needing targeted, extended treatment. Although present studies have primarily emphasized proof-of-concept and laboratory-level formulations, upcoming initiatives are anticipated to shift toward scalable manufacturing, clinical verification, and practical implementation. A crucial future focus is the enhancement and standardization of electrospinning methods. Improvements in scalable electrospinning methods, including needleless and multijet technologies, are anticipated to enhance production efficiency and consistency across different batches. Enhanced regulation of processing parameters will facilitate the creation of nanofibers with consistent morphology, drug loading, and release characteristics, crucial for pharmaceutical commercialization. From a formulation viewpoint, advancements in polymer science will be crucial in enhancing the long-term stability and efficacy of antifungal nanofibers. The creation of hybrid and intelligent polymers that can react to environmental factors like pH or humidity may enable more accurate and on-demand drug delivery. These developments may greatly improve results in chronic and recurring fungal infections.^[48] An additional significant future opportunity lies in the clinical application of nanofiber-based systems. As knowledge of nanofiber biocompatibility and degradation characteristics advances, regulatory approval is expected to grow. The development of more defined regulatory frameworks and uniform safety assessment protocols will ease the movement of nanofiber formulations from research studies to authorized antifungal treatments. In this regard, thorough preclinical and clinical investigations will be essential to prove safety, effectiveness, and



patient advantage. In general, ongoing advancements in nanotechnology, materials science, and pharmaceutical engineering indicate that nanofibers are likely to serve as next-generation platforms for delivering antifungal drugs. Their flexibility, capacity to deliver prolonged and targeted treatment, and compatibility with various antifungal medications render them excellent prospects for forthcoming clinical use, especially in situations where traditional dosage forms fall short.^[49]

CONCLUSION

Nanofibers serve as a flexible and efficient medium for the delivery of antifungal medications, overcoming numerous constraints associated with traditional dosage forms. Nanofiber-based systems provide a viable solution for managing fungal infections by increasing local drug availability, lowering toxicity, and enhancing patient compliance. Ongoing interdisciplinary research will be crucial to move these innovations from lab studies to clinical application.

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