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DEVELOPMENT AND EVALUATION OF ITRACONAZOLE-LOADED LIPID-POLYMER HYBRID NANOPARTICLES FOR ENHANCED ORAL BIOAVAILABILITY

Sadhna Shrivastava[1], Dr. Santosh Kumar Mishra*[2], Archana Tomar[3]

[1]M.Pharm Student, Sagar College of Pharmacy, Lucknow.

[2]Director, Sagar College of Pharmacy, Lucknow.

[3]Assistant Professor, Sagar College of Pharmacy, Lucknow.

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***Corresponding Author**

Dr. Santosh Kumar Mishra

Director, Sagar College of Pharmacy, Lucknow.

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ABSTRACT

Itraconazole is a broad-spectrum triazole antifungal agent widely used for the treatment of superficial and systemic fungal infections. However, its clinical effectiveness is significantly limited by poor aqueous solubility, pH-dependent dissolution, extensive first-pass metabolism, and variable gastrointestinal absorption, resulting in low and inconsistent oral bioavailability. Recent advances in nanotechnology have provided innovative approaches to overcome these biopharmaceutical challenges. Among various nanocarrier systems, lipid–polymer hybrid nanoparticles (LPHNs) have emerged as a promising oral drug delivery platform due to their ability to combine the structural advantages of polymeric nanoparticles with the biocompatibility and absorption-enhancing properties of lipid-based systems. This review comprehensively discusses the physicochemical and pharmacokinetic limitations of itraconazole and highlights the potential of LPHNs in improving its oral delivery. The review covers the composition, structure, preparation methods, formulation strategies, characterization techniques, and mechanisms responsible for enhanced bioavailability of itraconazole-loaded LPHNs. Particular emphasis is placed on particle size optimization, drug loading, entrapment efficiency, morphological characterization, thermal analysis, in vitro drug release, stability studies, and pharmacokinetic evaluation. Furthermore, the review

summarizes recent findings on dissolution enhancement, intestinal permeation, antifungal efficacy, and safety assessment of hybrid nanoparticulate systems. Current research trends, scale-up challenges, regulatory considerations, and future opportunities in oral antifungal drug delivery are also discussed. Overall, itraconazole-loaded LPHNs represent a highly promising strategy for improving oral bioavailability, enhancing therapeutic efficacy, reducing dose-related toxicity, and advancing the clinical management of fungal infections.

KEYWORDS: Itraconazole; Lipid–Polymer Hybrid Nanoparticles (LPHNs); Oral Bioavailability; Antifungal Drug Delivery; Nanotechnology; Controlled Release; Lipid-Based Nanocarriers; Polymeric Nanoparticles.

1. INTRODUCTION

Fungal infections have emerged as a major global health concern due to the increasing prevalence of immunocompromised conditions, prolonged hospitalization, excessive use of broad-spectrum antibiotics, and the growing population of patients suffering from chronic diseases such as diabetes, cancer, and HIV/AIDS.[1] Superficial fungal infections affecting the skin, nails, and mucosal tissues are highly common, whereas invasive fungal infections can lead to severe morbidity and mortality, particularly in immunocompromised individuals. The management of fungal diseases remains challenging because of limited antifungal agents, poor drug selectivity, systemic toxicity, and the emergence of antifungal resistance. Consequently, the development of effective and safe antifungal drug delivery systems has become an important area of pharmaceutical research.[2]

1.1 Overview of Fungal Infections and Antifungal Therapy

Fungal infections are generally classified into superficial, subcutaneous, systemic, and opportunistic mycoses depending on the site and severity of infection. Common fungal pathogens include *Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*, and dermatophytes such as *Trichophyton* species. Opportunistic fungal infections are increasingly observed among patients receiving immunosuppressive therapy, organ transplantation, chemotherapy, or long-term corticosteroid treatment.[3] Antifungal therapy mainly includes polyenes, azoles, echinocandins, and allylamines. Among these, azole antifungal agents are extensively used because of their broad-spectrum activity and comparatively lower toxicity.[4] Azoles exert their antifungal effect by inhibiting the cytochrome P450-dependent enzyme lanosterol 14α-demethylase, thereby disrupting ergosterol biosynthesis and compromising fungal cell membrane integrity. However, conventional antifungal therapies are often

associated with poor aqueous solubility, limited oral bioavailability, frequent dosing, drug interactions, and systemic adverse effects, which reduce therapeutic efficacy and patient compliance.[5]

1.2 Itraconazole: Physicochemical and Biopharmaceutical Challenges

Itraconazole is a triazole antifungal drug widely used for the treatment of both superficial and systemic fungal infections. It exhibits potent antifungal activity against a broad range of fungal species, including *Candida*, *Aspergillus*, and dermatophytes. Despite its therapeutic effectiveness, itraconazole faces significant physicochemical and biopharmaceutical limitations that hinder its clinical performance.[6] Itraconazole is classified as a Biopharmaceutical Classification System (BCS) Class II drug, characterized by low aqueous solubility and high permeability. The drug exhibits pH-dependent solubility, with higher solubility in acidic environments and extremely poor dissolution at intestinal pH. This poor solubility results in erratic gastrointestinal absorption and low oral bioavailability. In addition, itraconazole undergoes extensive first-pass metabolism, leading to variable plasma concentrations and inconsistent therapeutic outcomes.[7] Conventional oral formulations of itraconazole often require administration with food or acidic beverages to improve absorption. However, variations in gastric pH, gastrointestinal motility, and patient-specific physiological conditions significantly affect drug absorption.[8] Moreover, prolonged administration may produce hepatotoxicity, gastrointestinal disturbances, and drug-drug interactions due to inhibition of cytochrome P450 enzymes. Therefore, improving the solubility, stability, and bioavailability of itraconazole remains a major pharmaceutical challenge.[9]

1.3 Need for Novel Drug Delivery Systems

The limitations associated with conventional antifungal formulations have encouraged researchers to explore advanced drug delivery approaches for improving therapeutic efficacy. Novel drug delivery systems are designed to enhance drug solubility, protect the drug from degradation, improve absorption, provide controlled release, and minimize systemic toxicity.[10] Nanotechnology-based drug delivery systems have attracted considerable attention because of their ability to modify pharmacokinetic and pharmacodynamic properties of poorly soluble drugs. Various nanosystems such as liposomes, solid lipid nanoparticles, polymeric nanoparticles, nanoemulsions, dendrimers, and nanostructured lipid carriers have been investigated for antifungal drug delivery.[11] These systems can increase surface area,

improve dissolution rate, enhance permeation across biological membranes, and facilitate targeted drug delivery.[11] For itraconazole, nanoparticulate delivery systems offer several advantages including enhanced oral absorption, prolonged circulation time, reduced dose frequency, improved drug stability, and increased therapeutic efficiency. The incorporation of itraconazole into nanosized carriers may also reduce adverse effects and overcome issues related to poor solubility and variable bioavailability.[12]

1.4 Lipid-Polymer Hybrid Nanoparticles (LPHNs): Concept and Advantages

Lipid-polymer hybrid nanoparticles (LPHNs) are an emerging class of nanocarriers that combine the beneficial characteristics of both polymeric nanoparticles and lipid-based delivery systems. Typically, LPHNs consist of a polymeric core surrounded by a lipid shell and stabilized by surfactants.[13] The polymeric core provides structural integrity, controlled drug release, and enhanced drug encapsulation, whereas the lipid layer improves biocompatibility, stability, and interaction with biological membranes.[14] LPHNs have gained considerable interest for oral drug delivery because they can effectively encapsulate hydrophobic drugs such as itraconazole and improve their solubility and absorption. The lipid shell enhances gastrointestinal permeability and protects the encapsulated drug from enzymatic degradation, while the polymeric matrix enables sustained drug release and improved stability.[15] Compared with conventional nanoparticles, LPHNs exhibit several advantages including high drug loading capacity, enhanced physical stability, controlled release behavior, improved bioavailability, reduced toxicity, and scalable manufacturing processes.[16] In addition, these hybrid systems can be engineered with surface modifications for targeted delivery and enhanced therapeutic performance. Due to these unique properties, LPHNs represent a promising strategy for overcoming the biopharmaceutical limitations of itraconazole.[17]

1.5 Aim and Objectives of the Review

The present review aims to provide a comprehensive overview of itraconazole-loaded lipid-polymer hybrid nanoparticles for enhanced oral bioavailability and improved antifungal therapy. The review focuses on the physicochemical and biopharmaceutical challenges associated with itraconazole, the rationale for developing nanotechnology-based delivery systems, and the formulation strategies employed in the preparation of LPHNs. Furthermore, the review discusses various methods of preparation, characterization techniques, drug release mechanisms, stability considerations, and in vitro and in vivo evaluation studies

related to itraconazole-loaded LPHNs. Special emphasis is given to recent advancements, therapeutic applications, challenges, and future perspectives associated with hybrid nanoparticulate systems for oral antifungal drug delivery.[17]

2. Itraconazole and Oral Bioavailability Challenges

Itraconazole is a broad-spectrum triazole antifungal agent extensively used in the treatment of superficial and systemic fungal infections. It possesses potent activity against various pathogenic fungi including Candida, Aspergillus, Histoplasma, Blastomyces, and dermatophyte species. Despite its wide therapeutic utility, the clinical effectiveness of itraconazole is significantly limited by its poor oral bioavailability and variable pharmacokinetic profile.[6] These limitations mainly arise from its unfavorable physicochemical characteristics, pH-dependent solubility, extensive metabolism, and inconsistent gastrointestinal absorption. Therefore, understanding the factors influencing the oral bioavailability of itraconazole is essential for the development of improved drug delivery systems.[7]

2.1 Chemical Structure and Properties of Itraconazole

Itraconazole is a synthetic triazole derivative with the molecular formula $C_{35}H_{38}$ systems.[4 and a molecular weight of approximately 705.6 g/mol. The chemical structure of itraconazole contains multiple aromatic rings, triazole moieties, and lipophilic side chains, which contribute to its highly hydrophobic nature. The presence of chlorine-substituted phenyl groups and dioxolane rings enhances its antifungal activity but simultaneously reduces aqueous solubility.[18]

Itraconazole appears as a weakly basic, crystalline powder that is practically insoluble in water but soluble in acidic media and organic solvents. It exhibits high lipophilicity with a log P value greater than 5, indicating strong membrane permeability but limited dissolution in gastrointestinal fluids. Due to these properties, itraconazole is classified under the Biopharmaceutical Classification System (BCS) as a Class II drug, characterized by low solubility and high permeability.[19]

The drug demonstrates polymorphic behavior and exists in different crystalline forms, which may influence dissolution rate and bioavailability. Additionally, itraconazole exhibits poor wettability and slow dissolution kinetics, further restricting its absorption following oral

administration. These physicochemical limitations necessitate the development of advanced formulation strategies to improve its oral delivery.[20]

2.2 Mechanism of Action

Itraconazole exerts its antifungal activity by selectively inhibiting fungal cytochrome P450-dependent enzyme lanosterol 14α-demethylase, which plays a crucial role in the biosynthesis of ergosterol. Ergosterol is an essential structural component of the fungal cell membrane responsible for maintaining membrane fluidity, integrity, and permeability.[21]

By inhibiting ergosterol synthesis, itraconazole causes depletion of membrane sterols and accumulation of toxic methylated sterol intermediates within fungal cells. This disruption alters membrane structure and function, leading to increased membrane permeability, inhibition of fungal growth, and eventual cell death. The drug exhibits fungistatic or fungicidal activity depending on the fungal species and drug concentration.[22]

Itraconazole demonstrates broad-spectrum antifungal activity against yeasts, molds, and dimorphic fungi. In addition to its antifungal effects, itraconazole has shown antiangiogenic and anticancer potential in recent studies due to its ability to interfere with multiple cellular signaling pathways. However, effective therapeutic action requires adequate systemic drug concentration, which is often compromised because of poor oral absorption.[23]

2.3 Factors Affecting Oral Bioavailability

The oral bioavailability of itraconazole is influenced by several physicochemical and physiological factors that limit its dissolution, absorption, and systemic availability. These factors contribute to high interpatient variability and inconsistent therapeutic response.[7]

Poor Aqueous Solubility

One of the major limitations of itraconazole is its extremely poor aqueous solubility. The hydrophobic nature of the drug results in inadequate dissolution in gastrointestinal fluids, thereby limiting the amount of drug available for absorption. Since dissolution is the rate-limiting step for BCS Class II drugs, poor solubility significantly reduces oral bioavailability.[24]

The low dissolution rate of itraconazole also leads to delayed onset of action and incomplete drug absorption. Conventional formulations often fail to maintain sufficient drug concentration in the gastrointestinal tract, resulting in reduced therapeutic efficacy.

Improving the solubility and dissolution behavior of itraconazole is therefore essential for enhancing its oral absorption.[20]

pH-Dependent Absorption

Itraconazole exhibits pH-dependent solubility, with significantly higher solubility under acidic conditions and markedly reduced solubility at neutral or alkaline pH. In the acidic environment of the stomach, itraconazole dissolves more readily, whereas precipitation may occur upon transition to the intestinal pH.[20]

Factors that increase gastric pH, such as antacids, proton pump inhibitors, H_2 receptor antagonists, or achlorhydria, can substantially decrease drug dissolution and absorption. Consequently, patients receiving acid-suppressive therapy may experience reduced therapeutic efficacy due to decreased bioavailability of itraconazole.[25]

The pH-dependent behavior of itraconazole creates challenges in achieving consistent absorption and necessitates formulation approaches capable of maintaining drug solubility throughout the gastrointestinal tract.[7]

First-Pass Metabolism

After oral administration, itraconazole undergoes extensive hepatic first-pass metabolism primarily by cytochrome P450 enzyme CYP3A4. This metabolic conversion reduces the amount of unchanged drug reaching systemic circulation, thereby decreasing bioavailability.[26]

The major metabolite, hydroxy-itraconazole, also possesses antifungal activity; however, variability in metabolic rate among individuals can lead to unpredictable plasma drug concentrations. Additionally, itraconazole acts as a potent inhibitor of CYP3A4, increasing the risk of drug-drug interactions with several commonly prescribed medications.[27]

Extensive metabolism contributes to interindividual variability, altered pharmacokinetics, and inconsistent therapeutic outcomes. Therefore, formulation strategies that improve absorption and reduce presystolic metabolism are highly desirable.[28]

Variable Gastrointestinal Absorption

Gastrointestinal absorption of itraconazole is highly variable and influenced by multiple physiological conditions including gastric emptying time, food intake, intestinal motility, bile

secretion, and gastrointestinal pH. The capsule formulation of itraconazole generally exhibits improved absorption when administered with food, particularly high-fat meals, which stimulate bile secretion and enhance dissolution of the lipophilic drug.[29]

However, variability in gastrointestinal conditions among patients often results in inconsistent absorption profiles. Patients with gastrointestinal disorders, reduced gastric acidity, or malabsorption syndromes may exhibit significantly lower drug absorption. Furthermore, precipitation of itraconazole in the intestine due to pH changes can further decrease drug availability for absorption.[7]

These factors collectively contribute to unpredictable pharmacokinetics and poor reproducibility of therapeutic response following oral administration of conventional itraconazole formulations.[7]

2.4 Limitations of Conventional Dosage Forms

Conventional dosage forms of itraconazole, including capsules and oral solutions, exhibit several limitations that compromise therapeutic effectiveness.[7] The capsule formulation depends heavily on gastric acidity and food intake for optimal absorption, leading to considerable variability in bioavailability among patients. Reduced absorption is commonly observed in individuals receiving acid-suppressive therapy or suffering from gastrointestinal disorders.[30]

Although oral solutions demonstrate relatively improved bioavailability compared with capsules, they are often associated with poor patient acceptability due to unpleasant taste, gastrointestinal irritation, and stability-related issues. In addition, conventional formulations may require frequent dosing because of inconsistent plasma drug concentrations.[31]

Poor aqueous solubility and incomplete dissolution of itraconazole in conventional formulations frequently result in subtherapeutic drug levels, treatment failure, and the potential development of antifungal resistance.[7] Furthermore, high doses may be required to achieve effective therapeutic concentrations, increasing the risk of hepatotoxicity and systemic adverse effects.[32]

These limitations highlight the urgent need for advanced drug delivery systems capable of improving the solubility, stability, absorption, and overall oral bioavailability of

itraconazole.[33] Lipid-polymer hybrid nanoparticles have emerged as a promising approach to overcome these challenges and enhance antifungal therapy.[17]

3. Lipid–Polymer Hybrid Nanoparticles (LPHNs)

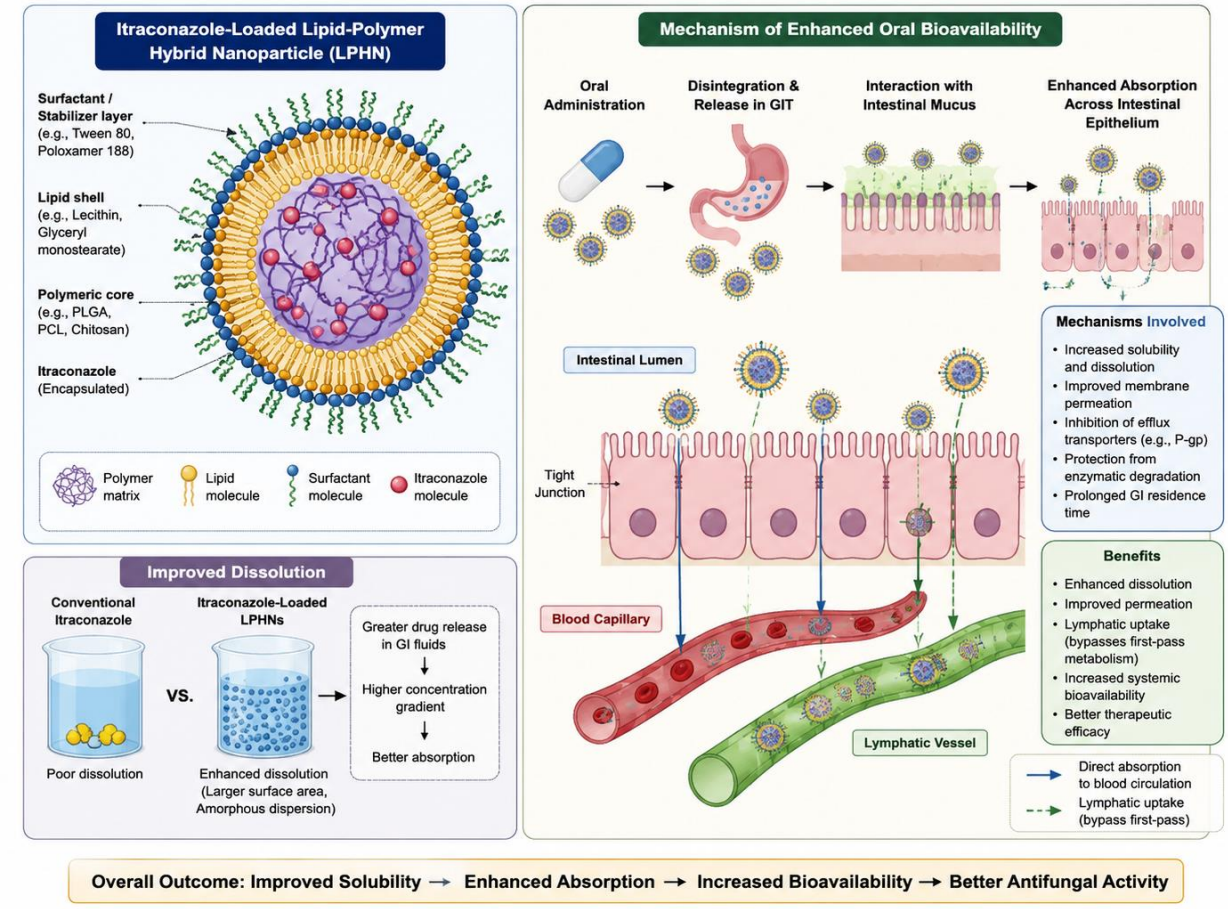
Lipid–polymer hybrid nanoparticles (LPHNs) are an advanced nanocarrier system developed to combine the structural advantages of polymeric nanoparticles with the biocompatibility and drug solubilization capacity of lipid-based systems.[34] These hybrid nanosystems have emerged as promising carriers for oral delivery of poorly water-soluble drugs such as itraconazole. The unique architecture of LPHNs enables improved drug encapsulation, controlled release, enhanced gastrointestinal absorption, and increased oral bioavailability.[17]

In recent years, LPHNs have attracted significant attention in pharmaceutical research because they overcome the limitations associated with conventional nanoparticles, including poor physical stability, burst drug release, low drug loading, and limited scalability. Their multifunctional characteristics make them suitable for delivering hydrophobic antifungal agents with improved therapeutic efficiency.[35]

3.1 Definition and Structure of LPHNs

Lipid–polymer hybrid nanoparticles are colloidal nanosystems composed of a polymeric core surrounded by one or more lipid layers, stabilized by surfactants or emulsifying agents. These nanoparticles integrate the beneficial properties of both polymeric nanoparticles and lipid-based carriers into a single delivery platform.[36] Typically, the structure of LPHNs consists of three major components Polymeric core – responsible for structural rigidity, sustained drug release, and drug encapsulation.[13] Lipid shell or coating – enhances biocompatibility, membrane interaction, and protection of the encapsulated drug.[13] Outer surfactant layer – stabilizes the nanoparticle dispersion and prevents aggregation.[37,38] The polymeric core acts as a reservoir for hydrophobic drugs, whereas the lipid layer improves drug solubilization and facilitates absorption across biological membranes. The nanoscale size of LPHNs provides a large surface area, which enhances dissolution and absorption of poorly soluble drugs following oral administration.[39] The hybrid structure also minimizes the drawbacks associated with individual lipid or polymeric systems. Polymeric nanoparticles alone may exhibit limited biocompatibility and burst release, while lipid-based carriers may suffer from poor stability and rapid drug leakage. LPHNs effectively overcome these limitations by providing enhanced stability, controlled release, and improved therapeutic performance.[13]

Figure 1. Schematic Representation of Itraconazole-Loaded Lipid-Polymer Hybrid Nanoparticles and Mechanism of Enhanced Oral Bioavailabiliity



3.2 Components of LPHNs

The performance and characteristics of LPHNs depend largely on the selection of formulation components, including lipids, polymers, and surfactants. Each component plays a specific role in determining particle size, drug loading, release profile, stability, and bioavailability.[40]

Lipids

Lipids form the outer shell or matrix of LPHNs and contribute significantly to drug solubilization, membrane permeability, and biocompatibility. Both solid and liquid lipids may be used depending on the desired formulation characteristics.[13] Commonly used lipids include, Phospholipids, Stearic acid, Glyceryl monostearate, Compritol®, Lecithin, Cholesterol, Medium-chain triglycerides, Lipids improve the oral absorption of hydrophobic drugs by promoting lymphatic transport and reducing first-pass metabolism. In addition, lipid components protect the encapsulated drug from chemical and enzymatic degradation within the gastrointestinal tract.[41] The lipid shell also enhances interaction with intestinal epithelial membranes, facilitating drug permeation and improving oral bioavailability.[42]

Polymers

Polymers constitute the inner core of LPHNs and provide structural support, controlled release behavior, and improved encapsulation efficiency. Both biodegradable and biocompatible polymers are preferred for pharmaceutical applications.[43] Commonly used polymers include, Poly (lactic-co-glycolic acid) (PLGA), Polycaprolactone (PCL), Chitosan, Eudragit®, Poly (lactic acid) (PLA), Sodium alginate, The polymeric core controls the diffusion and release of the encapsulated drug, thereby maintaining prolonged therapeutic concentrations. Certain polymers such as chitosan also exhibit mucoadhesive properties, which increase gastrointestinal residence time and enhance drug absorption.[44] Biodegradable polymers improve the safety profile of the formulation by degrading into non-toxic metabolites within the body.[45]

Surfactants/Stabilizers

Surfactants and stabilizers are essential for maintaining nanoparticle stability and preventing aggregation during preparation and storage. These agents reduce interfacial tension between lipid and aqueous phases and contribute to uniform particle size distribution.[46] Commonly used surfactants include, Poloxamer 188, Tween 80, Polyvinyl alcohol (PVA), Sodium cholate, span 80, TPGS (D-α-tocopheryl polyethylene glycol succinate), Surfactants improve wettability, stabilize nanosuspensions, and may enhance intestinal permeability by modulating membrane fluidity or inhibiting efflux transporters such as P-glycoprotein. Certain stabilizers also improve the physical stability and shelf-life of LPHN formulations.[47]

3.3 Methods of Preparation

Several techniques have been developed for the preparation of LPHNs depending on the physicochemical properties of the drug and formulation requirements. The selected method influences particle size, encapsulation efficiency, drug release behavior, and stability.[48]

Solvent Emulsification Evaporation Method

The solvent emulsification evaporation method is one of the most widely used techniques for preparing LPHNs. In this method, the drug and polymer are dissolved in an organic solvent to form the organic phase, while lipids and surfactants are dissolved in the aqueous phase.[14]

The organic phase is then emulsified into the aqueous phase using high-speed stirring or sonication to form an oil-in-water emulsion. Subsequent evaporation of the organic solvent leads to precipitation of the polymer and formation of hybrid nanoparticles.[49] This method

offers several advantages including, High drug encapsulation efficiency, Uniform particle size, Controlled drug release, Suitable for hydrophobic drugs, However, the use of organic solvents and multiple processing steps may limit large-scale production.[50]

Nanoprecipitation Method

Nanoprecipitation is a simple and rapid technique commonly used for preparing polymeric and hybrid nanoparticles. In this method, the drug and polymer are dissolved in a water-miscible organic solvent, which is then added dropwise into an aqueous lipid-surfactant solution under continuous stirring.[51]

Rapid diffusion of the solvent into the aqueous phase causes precipitation of the polymer and spontaneous formation of nanoparticles. The solvent is subsequently removed by evaporation.[52] Advantages of nanoprecipitation include, Simplicity and reproducibility, Low energy requirement, small particle size, Mild preparation conditions, this method is particularly suitable for heat-sensitive compounds and hydrophobic drugs such as itraconazole.[53]

High-Pressure Homogenization

High-pressure homogenization is a scalable and industrially applicable technique for the preparation of LPHNs. In this method, the drug-containing lipid and polymer dispersion is passed through a narrow homogenization gap under extremely high pressure.[54]

The intense shear forces and cavitation reduce particle size to the nanometer range and produce a stable nanosuspension. High-pressure homogenization may be performed under hot or cold conditions depending on the thermal stability of the drug.[55] Advantages of this method include, Large-scale production capability, Narrow particle size distribution, improved physical stability, reduced solvent requirement, The technique is highly suitable for commercial pharmaceutical manufacturing due to its reproducibility and scalability.[56]

3.4 Advantages of LPHNs for Oral Delivery

LPHNs offer numerous advantages for oral delivery of poorly soluble antifungal drugs such as itraconazole. The hybrid architecture combines the controlled release properties of polymers with the absorption-enhancing effects of lipids, resulting in improved therapeutic outcomes.[17] Major advantages include, Enhanced aqueous solubility of hydrophobic drugs, Improved oral bioavailability, Increased drug encapsulation efficiency, Controlled and

sustained drug release, Protection of drug from gastrointestinal degradation, Enhanced intestinal permeability, Reduced dosing frequency, Improved patient compliance, Reduced systemic toxicity, Better physical and chemical stability, The nanosized particles provide a larger surface area for dissolution and absorption, while the lipid components facilitate lymphatic uptake and reduce hepatic first-pass metabolism. Additionally, LPHNs can be surface-modified for targeted delivery and site-specific drug release.[14]

3.5 Mechanism of Enhanced Bioavailability

LPHNs improve the oral bioavailability of itraconazole through multiple mechanisms that collectively enhance drug dissolution, absorption, and systemic availability.[14]

Enhanced Solubilization and Dissolution

The lipid matrix and nanoscale particle size significantly increase the surface area available for dissolution. Encapsulation of itraconazole in an amorphous or molecularly dispersed state further improves drug solubility and dissolution rate within gastrointestinal fluids.[57]

Improved Gastrointestinal Permeation

Lipids and surfactants present in LPHNs interact with intestinal epithelial membranes and increase membrane fluidity, thereby enhancing drug permeation across the gastrointestinal barrier. Certain surfactants may also inhibit efflux transporters such as P-glycoprotein, improving intracellular drug accumulation.[58]

Lymphatic Uptake

Lipid-based components stimulate lymphatic transport of lipophilic drugs, allowing a portion of the absorbed drug to bypass hepatic first-pass metabolism. This mechanism increases systemic drug availability and reduces metabolic degradation.[59]

Protection from Degradation

The polymeric and lipid layers protect itraconazole from chemical degradation, enzymatic hydrolysis, and precipitation within the gastrointestinal tract. This protection improves drug stability during transit through the digestive system.[60]

Prolonged Gastrointestinal Residence Time

Mucoadhesive polymers used in LPHNs may prolong retention of nanoparticles within the gastrointestinal tract, increasing the contact time available for drug absorption. Sustained release behavior also helps maintain therapeutic plasma concentrations for extended

periods.[61] Through these combined mechanisms, LPHNs effectively overcome the major biopharmaceutical limitations of itraconazole and represent a promising strategy for enhancing oral antifungal therapy.[62]

Table 1: Summary of Reported Itraconazole-Loaded Lipid/Polymer Nanoparticle Formulations and Their Bioavailability Outcomes.

Formulation Type	Major Components	Preparation Method	Particle Size (nm)	Entrapment Efficiency (%)	Key Bioavailability Findings	Reported Advantages
Polymeric Nanoparticles	PLGA, PVA	Nanoprecipitation	150–250	70–90	Enhanced oral absorption and prolonged plasma concentration	Controlled release and improved stability
Solid Lipid Nanoparticles (SLNs)	Glyceryl monostearate, Tween 80	High-pressure homogenization	100–300	75–95	Increased dissolution rate and higher systemic exposure	Improved solubility and reduced toxicity
Nanostructured Lipid Carriers (NLCs)	Compritol®, oleic acid, surfactants	Melt emulsification	120–280	80–96	Significant improvement in oral bioavailability compared with pure drug	High drug loading and sustained release
Liposomes	Phospholipids, cholesterol	Thin-film hydration	90–200	65–85	Improved drug permeation and antifungal efficacy	Biocompatibility and reduced irritation
Chitosan-Coated Nanoparticles	Chitosan, PLGA, lecithin	Solvent evaporation	180–320	78–92	Enhanced mucoadhesion and intestinal absorption	Increased gastrointestinal residence time
Lipid–Polymer Hybrid Nanoparticles (LPHNs)	PLGA, lecithin, Tween 80	Solvent emulsification evaporation	120–220	85–98	Markedly enhanced oral bioavailability and lymphatic uptake	Combined benefits of lipid and polymer systems
Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)	Oils, surfactants, cosurfactants	Spontaneous emulsification	<100	High drug solubilization	Rapid drug dissolution and improved absorption	Ease of formulation and fast onset
Polycaprolactone-Based Nanoparticles	PCL, phospholipids	Nanoprecipitation	140–260	75–90	Sustained plasma drug levels and enhanced permeability	Prolonged drug release
Hybrid Mucoadhesive Nanoparticles	Chitosan, lipid matrix, surfactants	Ionic gelation/emulsification	150–300	80–95	Improved intestinal retention and	Enhanced mucosal interaction

					bioavailability	
Nanoemulsion-Based Hybrid Systems	Medium-chain triglycerides, polymers	Ultrasonication	80–180	70–88	Improved dissolution and antifungal activity	Better drug dispersion and absorption

Abbreviations

PLGA = Poly (lactic-co-glycolic acid); PCL = Polycaprolactone; PVA = Polyvinyl alcohol; SLNs = Solid lipid nanoparticles; NLCs = Nanostructured lipid carriers; SNEDDS = Self-nanoemulsifying drug delivery systems; LPHNs = Lipid–polymer hybrid nanoparticles.

4. Development and Characterization of Itraconazole-Loaded LPHNs

The successful development of itraconazole-loaded lipid–polymer hybrid nanoparticles (LPHNs) require careful selection of formulation components and optimization of preparation parameters to achieve desirable physicochemical and biopharmaceutical properties. Since itraconazole is a poorly water-soluble drug with limited oral bioavailability, the formulation of stable and efficient nanosystems is essential for improving dissolution, absorption, and therapeutic efficacy.[57]

Characterization of LPHNs plays a crucial role in evaluating nanoparticle quality, stability, drug encapsulation behavior, release profile, and overall performance. Various analytical techniques are employed to investigate particle characteristics, morphology, thermal behavior, crystallinity, and in-vitro drug release properties of the developed nanosystems.[63]

4.1 Formulation Strategies and Optimization

Formulation strategies for itraconazole-loaded LPHNs focus primarily on improving drug solubility, enhancing encapsulation efficiency, controlling drug release, and increasing oral bioavailability. The selection of suitable lipids, polymers, surfactants, and preparation methods significantly influences the final characteristics of the nanoparticles.[64]

Hydrophobic drugs such as itraconazole are generally incorporated into the polymeric core or lipid matrix to improve solubilization and prevent drug crystallization. Biodegradable polymers such as PLGA, PCL, and chitosan are commonly combined with lipids like lecithin, glyceryl monostearate, or stearic acid to produce stable hybrid nanoparticles.[65]

Several formulation variables require optimization, including, Lipid-to-polymer ratio, Drug concentration, Surfactant concentration, Organic solvent type, Homogenization speed,

Sonication time, Stirring conditions, Optimization is often performed using statistical design approaches such as, Factorial design, Box–Behnken design, Central composite design, Response surface methodology, These optimization techniques help identify the ideal formulation conditions for obtaining minimal particle size, high drug entrapment, controlled release behavior, and maximum stability. Proper optimization also improves reproducibility and scalability of the formulation process.[66]

4.2 Particle Size, PDI, and Zeta Potential

Particle size is one of the most important parameters influencing the oral absorption, dissolution rate, cellular uptake, and stability of LPHNs. Generally, nanoparticles within the size range of 50–300 nm are considered suitable for oral drug delivery because they exhibit improved gastrointestinal absorption and enhanced permeation.[39]

Particle size analysis is commonly performed using dynamic light scattering (DLS). Smaller particle size increases the surface area available for dissolution, thereby improving the solubility and bioavailability of itraconazole.[57]

Polydispersity index (PDI) indicates the uniformity of particle size distribution within the formulation. A lower PDI value suggests a homogeneous nanoparticle population and better formulation stability. Typically.[67] PDI < 0.3 indicates narrow size distribution, PDI > 0.5 indicates broad and heterogeneous distribution, Zeta potential represents the surface charge of nanoparticles and is an important indicator of colloidal stability. High positive or negative zeta potential values prevent nanoparticle aggregation through electrostatic repulsion. Generally.[68], Values above +30 mV or below –30 mV indicate good physical stability, Surface charge also affects interaction with biological membranes and mucosal surfaces. Positively charged nanoparticles may exhibit enhanced mucoadhesion and cellular uptake, thereby improving oral absorption.[69]

4.3 Drug Loading and Entrapment Efficiency

Drug loading and entrapment efficiency are critical parameters that determine the therapeutic potential and formulation efficiency of LPHNs.[70]

Drug Loading Capacity

Drug loading refers to the amount of itraconazole incorporated into the nanoparticles relative to the total weight of the formulation. High drug loading is desirable because it minimizes the

amount of carrier material required and improves dosage efficiency.[71] Factors affecting drug loading include Drug solubility in lipid/polymer matrix, Lipid-to-polymer ratio, Preparation method, Surfactant concentration, Drug-polymer interaction,

Entrapment Efficiency

Entrapment efficiency represents the percentage of drug successfully encapsulated within the nanoparticles relative to the total drug used during formulation.[72] High entrapment efficiency is particularly important for hydrophobic drugs such as itraconazole because it, prevents drug leakage, improves formulation stability, Enhances sustained release behavior, increases bioavailability, Entrapment efficiency is commonly determined using ultracentrifugation, dialysis, or filtration methods followed by spectrophotometric or chromatographic drug analysis.[14] The lipophilic nature of itraconazole generally favors high encapsulation within lipid-polymer matrices, making LPHNs suitable carriers for oral antifungal delivery.[73]

4.4 Morphological Characterization (SEM/TEM)

Morphological characterization provides important information regarding nanoparticle shape, surface texture, structural integrity, and aggregation behavior.[73]

Scanning Electron Microscopy (SEM)

SEM is widely used to examine the surface morphology and particle shape of LPHNs. SEM images generally reveal, Spherical or nearly spherical particle shape, Smooth or slightly rough surface morphology, Degree of aggregation, Uniform and non-aggregated nanoparticles indicate successful formulation and improved physical stability.[70]

Transmission Electron Microscopy (TEM)

TEM provides detailed internal structural information and allows visualization of the lipid shell and polymeric core arrangement within hybrid nanoparticles' analysis helps confirm: Core-shell hybrid structure, Particle size consistency, Nanoparticle dispersion, Structural uniformity, Morphological studies are essential for validating successful nanoparticle formation and correlating structural properties with drug release and stability behavior.[74]

4.5 Thermal and Crystallinity Studies (DSC/XRD/FTIR)

Thermal and crystallinity studies are performed to evaluate drug-excipient compatibility, physical state of the drug, molecular interactions, and structural changes occurring during nanoparticle formation.[14]

Differential Scanning Calorimetry (DSC)

DSC is used to analyze thermal transitions such as melting point, crystallization behavior, and phase transitions. Pure itraconazole typically exhibits a sharp endothermic peak corresponding to its crystalline melting point.[75] In LPHN formulations, Reduction or disappearance of the drug melting peak may indicate amorphization or molecular dispersion of the drug within the carrier matrix. Shifts in thermal peaks may suggest interactions between drug and excipients. Conversion of crystalline itraconazole into an amorphous form generally improves dissolution and bioavailability.[76]

X-Ray Diffraction (XRD)

XRD analysis is employed to determine the crystalline or amorphous nature of the drug and formulation. Pure crystalline itraconazole produces characteristic sharp diffraction peaks.[77] In optimized LPHNs, Reduction in peak intensity, broadening of peaks, Disappearance of crystalline peaks, these observations indicate reduced crystallinity or amorphous dispersion of itraconazole within the nanoparticles, which contributes to improved dissolution properties.[76]

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy is used to identify functional groups and evaluate potential chemical interactions between itraconazole and formulation excipients.[78] FTIR analysis helps determine, Drug compatibility with polymers and lipids, Stability of chemical structure, Presence of hydrogen bonding or molecular interactions, Absence of significant changes in characteristic drug peaks generally indicates compatibility and stability of the encapsulated drug within the formulation.[79]

4.6 In-vitro Drug Release Studies

In-vitro drug release studies are performed to evaluate the release behavior of itraconazole from LPHNs under simulated physiological conditions. These studies help predict in-vivo performance and therapeutic efficiency.[73] Drug release studies are commonly conducted using, dialysis bag diffusion method, USP dissolution apparatus, Franz diffusion cells,

Release studies are typically carried out in, Simulated gastric fluid (pH 1.2), Simulated intestinal fluid (pH 6.8), Itraconazole-loaded LPHNs generally exhibit biphasic release behavior characterized by, Initial burst release due to surface-associated drug, Sustained release from the polymeric core, Controlled release behavior helps maintain prolonged therapeutic drug levels, reduce dosing frequency, and improve patient compliance.[80] Drug release kinetics are often analyzed using mathematical models such as, Zero-order kinetics, First-order kinetics, Higuchi model, Korsmeyer–Peppas model, these models help explain the mechanism of drug release, including diffusion-controlled or erosion-controlled release patterns.[81]

4.7 Stability Studies

Stability studies are essential for evaluating the physical, chemical, and storage stability of itraconazole-loaded LPHNs. Stable formulations maintain their particle size, drug content, entrapment efficiency, and release behavior over time.[12] Stability studies are generally conducted according to ICH guidelines under different storage conditions such as: Refrigerated conditions (4°C), Room temperature (25°C), Accelerated conditions (40°C/75% RH), Parameters evaluated during stability studies include: Particle size, PDI, Zeta potential, Drug content, Entrapment efficiency, Physical appearance, In-vitro drug release, Instability may result in, Particle aggregation, Drug leakage, Crystal growth, Reduced encapsulation efficiency, Altered release behavior, Incorporation of suitable stabilizers and optimization of formulation variables significantly improve the shelf-life and storage stability of LPHNs. Stable nanoparticle formulations are essential for successful pharmaceutical development and commercial application of itraconazole-loaded oral nanocarriers.[17]

5. Evaluation of Oral Bioavailability and Therapeutic Performance

The primary objective of developing itraconazole-loaded lipid–polymer hybrid nanoparticles (LPHNs) is to enhance oral bioavailability and improve antifungal therapeutic performance. Comprehensive evaluation of these nanosystems involves assessment of dissolution behavior, intestinal permeation, pharmacokinetic characteristics, in-vivo bioavailability, antifungal efficacy, and safety profile.[82] These studies provide critical information regarding the effectiveness of LPHNs in overcoming the limitations associated with conventional itraconazole formulations.[17]

Improved oral delivery of itraconazole through LPHNs is generally attributed to enhanced solubility, increased gastrointestinal absorption, sustained drug release, and reduced first-pass

metabolism. Evaluation studies help establish the superiority of hybrid nanosystems over conventional dosage forms.[83]

5.1 In-vitro Dissolution and Permeation Studies

In-vitro dissolution studies are essential for evaluating the ability of LPHNs to improve the dissolution profile of itraconazole. Since itraconazole is a poorly water-soluble drug, enhancement of dissolution rate is a key factor for improving oral absorption and therapeutic effectiveness.[84] Dissolution studies are typically performed using USP dissolution apparatus in simulated gastrointestinal media such as, simulated gastric fluid (pH 1.2), Simulated intestinal fluid (pH 6.8) Itraconazole-loaded LPHNs generally exhibit significantly enhanced dissolution compared with conventional capsules or pure drug suspension. The nanosized particles provide a larger surface area for dissolution, while the lipid components improve wettability and drug solubilization. In many cases, the drug exists in an amorphous or molecularly dispersed state within the nanoparticles, further enhancing dissolution behavior.[85] Permeation studies are performed to investigate the ability of nanoparticles to improve intestinal transport of itraconazole. Commonly used models include, Caco-2 cell monolayers, excised intestinal tissue, Franz diffusion cells, LPHNs enhance permeation through several mechanisms such as, Increased membrane fluidity, Improved mucoadhesion, opening of tight junctions, Inhibition of efflux transporters like P-glycoprotein, Enhanced permeation results in increased drug absorption across the gastrointestinal epithelium and contributes to improved systemic bioavailability.[86]

5.2 Pharmacokinetic Evaluation

Pharmacokinetic studies are conducted to assess the absorption, distribution, metabolism, and elimination behavior of itraconazole following oral administration of LPHNs. These studies are generally performed in suitable animal models such as rats, rabbits, or dogs.[87] Important pharmacokinetic parameters evaluated include: Maximum plasma concentration (Cmax), Time to reach maximum concentration (Tax), Area under the plasma concentration–time curve (AUC), Half-life (t½), Mean residence time (MRT), Clearance, Itraconazole-loaded LPHNs often demonstrate. Increased Cmax, Higher AUC values, Prolonged circulation time, Reduced plasma concentration fluctuations, an increase in AUC indicates improved systemic exposure and enhanced oral bioavailability. Sustained release characteristics of LPHNs may also prolong drug half-life and maintain therapeutic plasma concentrations for extended durations.[88] The lipid components facilitate lymphatic transport, thereby reducing hepatic

first-pass metabolism and increasing systemic availability of itraconazole. Improved pharmacokinetic behavior ultimately contributes to enhanced therapeutic efficacy and reduced dosing frequency.[89]

5.3 In-vivo Bioavailability Studies

In-vivo bioavailability studies are crucial for confirming the oral absorption enhancement achieved by LPHNs. These studies compare the bioavailability of itraconazole-loaded nanoparticles with conventional formulations such as capsules, suspensions, or pure drug dispersions.[90] Following oral administration, blood samples are collected at predetermined time intervals and analyzed using analytical techniques such as: High-performance liquid chromatography (HPLC), LC-MS/MS, UV spectrophotometry, The enhanced bioavailability of LPHNs is mainly attributed to, Improved drug dissolution, Enhanced intestinal absorption, Reduced drug precipitation, Increased lymphatic uptake, Protection from degradation, Several studies have reported multiple-fold increases in oral bioavailability of itraconazole following encapsulation into hybrid nanoparticles. Improved bioavailability leads to better therapeutic outcomes and may reduce the required dose and associated adverse effects.[91] Additionally, prolonged systemic circulation achieved through controlled drug release contributes to sustained antifungal activity and improved patient compliance.[92]

5.4 Antifungal Activity Assessment

Evaluation of antifungal activity is essential to determine whether encapsulation of itraconazole into LPHNs maintains or enhances its therapeutic effectiveness against fungal pathogens.[93] Antifungal activity is commonly assessed using, Agar diffusion method, Broth microdilution assay, Minimum inhibitory concentration (MIC) determination, Time-kill studies, Itraconazole-loaded LPHNs are generally tested against fungal strains such as, Candida albicans, Aspergillus fumigatus, Cryptococcus neoformans, Dermatophyte species, Hybrid nanoparticles often exhibit superior antifungal activity compared with conventional formulations due to, Improved drug solubility, Enhanced cellular uptake, Sustained drug release, Increased penetration into fungal cells. Nanoparticles may also improve interaction between the drug and fungal cell membrane, thereby increasing antifungal efficiency. Sustained release behavior helps maintain effective drug concentrations for prolonged periods, resulting in better fungal growth inhibition.[94] In some studies, LPHNs have demonstrated reduced MIC values and enhanced fungicidal activity compared with free itraconazole formulations.[73]

5.5 Toxicity and Safety Evaluation

Safety evaluation is an important aspect in the development of oral nanoparticulate systems. Toxicity studies help determine the biocompatibility and potential adverse effects associated with LPHNs.[14] Toxicity assessment generally includes, Cytotoxicity studies, Hemolysis studies, Histopathological examination, Acute and subacute toxicity studies.

Cytotoxicity Studies, Cytotoxicity is commonly evaluated using cell viability assays such as, MTT assay, Trypan blue exclusion test, LDH release assay, Biocompatible lipids and biodegradable polymers used in LPHNs generally exhibit low cytotoxicity and good cellular compatibility.[95]

Histopathological Evaluation

Histopathological studies are performed to examine possible tissue damage in major organs such as, Liver, Kidney, Intestine, Spleen, Itraconazole-loaded LPHNs often demonstrate reduced organ toxicity compared with conventional formulations because controlled drug release minimizes sudden exposure to high drug concentrations.[96]

Hemolysis and Gastrointestinal Safety

Hemolysis studies assess compatibility of nanoparticles with blood components, while gastrointestinal safety studies evaluate potential irritation or damage to the intestinal mucosa following oral administration.[97] Overall, appropriately formulated LPHNs are generally considered safe due to the use of biodegradable and pharmaceutically acceptable excipients.[98]

5.6 Comparative Performance with Conventional Formulations

Comparative evaluation between LPHNs and conventional itraconazole formulations clearly demonstrates the advantages of hybrid nanoparticulate systems for oral antifungal therapy.[17] Compared with conventional capsules and suspensions, itraconazole-loaded LPHNs offer, improved aqueous solubility, Faster and enhanced dissolution, increased oral bioavailability, better intestinal permeation, Sustained drug release, Enhanced antifungal activity, Reduced dose variability, Lower toxicity, Improved patient compliance Conventional itraconazole capsules exhibit variable absorption because of pH-dependent solubility and dependence on food intake. In contrast, LPHNs provide more consistent drug absorption and reduced interpatient variability.[99] The hybrid nanosystems also improve pharmacokinetic stability and reduce fluctuations in plasma drug concentration. Furthermore, enhanced lymphatic

uptake and protection against first-pass metabolism contribute significantly to superior therapeutic performance.[100] Overall, itraconazole-loaded LPHNs represent a highly promising strategy for overcoming the limitations of conventional oral formulations and improving the clinical management of fungal infections.[101]

6. Future Perspectives and Conclusion

Lipid–polymer hybrid nanoparticles (LPHNs) have emerged as a promising platform for improving the oral delivery of poorly water-soluble antifungal drugs such as itraconazole. By integrating the advantages of polymeric nanoparticles and lipid-based systems, these hybrid nanocarriers offer enhanced solubility, controlled drug release, improved intestinal absorption, and increased oral bioavailability.[17] Despite substantial progress in formulation development and preclinical evaluation, several scientific, technological, and regulatory challenges remain before widespread clinical translation and commercialization can be achieved.[102]

Recent advances in nanotechnology, material science, and pharmaceutical engineering continue to accelerate the development of more efficient and targeted oral nanocarrier systems. Future research is expected to focus on improving formulation stability, scalability, therapeutic efficacy, patient compliance, and regulatory acceptance of hybrid nanoparticulate drug delivery systems.[103]

6.1 Current Research Trends in Hybrid Nanocarriers

Current research in hybrid nanocarriers is primarily directed toward the development of multifunctional and intelligent nanosystems capable of overcoming complex biopharmaceutical barriers associated with oral drug delivery. Researchers are increasingly exploring advanced lipid–polymer combinations to improve drug loading capacity, stability, and site-specific delivery.[104] Several innovative approaches are currently under investigation, including, Surface-functionalized nanoparticles, Stimuli-responsive nanocarriers, Mucoadhesive hybrid systems, Targeted delivery platforms, Bioinspired and biomimetic nanoparticles Surface modification using ligands, antibodies, peptides, or polysaccharides has shown considerable potential for enhancing intestinal uptake and targeted delivery. Mucoadhesive polymers such as chitosan are also being widely studied to prolong gastrointestinal residence time and improve drug absorption.[61] Another important trend involves the incorporation of multifunctional excipients capable of inhibiting efflux transporters and metabolic enzymes to further enhance oral bioavailability. In addition,

researchers are investigating nanocarriers capable of co-delivering multiple therapeutic agents for synergistic antifungal therapy.[94] Artificial intelligence, quality-by-design (Qbd) approaches, and computational modeling are increasingly being utilized to optimize nanoparticle formulations and predict in-vivo performance. These technologies may significantly accelerate formulation development and improve reproducibility in future pharmaceutical applications.[105]

6.2 Challenges in Scale-Up and Commercialization

Although LPHNs demonstrate excellent laboratory-scale performance, large-scale manufacturing and commercialization remain major challenges. One of the primary concerns is maintaining consistent particle size, encapsulation efficiency, and formulation stability during industrial production.[106] Scale-up difficulties are often associated with, Complex manufacturing processes, High production costs, Use of organic solvents Batch-to-batch variability, Limited long-term stability, Preparation methods optimized at laboratory scale may not always be directly applicable to industrial manufacturing. Techniques such as high-pressure homogenization and microfluidization show promise for large-scale production; however, process optimization and equipment standardization are still required.[107] Another challenge involves maintaining nanoparticle stability during storage and transportation. Aggregation, drug leakage, polymorphic transitions, and lipid oxidation may adversely affect formulation quality and therapeutic performance. Therefore, suitable stabilization strategies, lyophilization techniques, and packaging systems must be developed to improve shelf-life.[108] Commercialization is also limited by insufficient clinical data, high development costs, and limited understanding of long-term safety profiles of nanocarrier systems. Addressing these challenges is essential for successful translation of LPHNs from research laboratories to pharmaceutical markets.[13]

6.3 Regulatory Considerations

Regulatory evaluation of nanotechnology-based drug delivery systems remains a complex and evolving area. Due to the unique physicochemical characteristics of nanoparticles, conventional regulatory frameworks may not fully address issues related to safety, quality, efficacy, and reproducibility of nanomedicines.[109] Regulatory agencies such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) require comprehensive characterization and risk assessment of nanoparticulate formulations. Important regulatory considerations include.[110] Particle size distribution, Surface properties,

Drug release behavior, Stability profile, Toxicological evaluation, Biocompatibility, Pharmacokinetic and biodistribution studies the absence of universally harmonized regulatory guidelines for hybrid nanocarriers creates additional challenges for pharmaceutical manufacturers. Standardized analytical methods and quality control parameters are needed to ensure reproducibility and product consistency.[111] Furthermore, long-term toxicity, immunogenicity, and environmental impact of nanoparticles require extensive investigation before regulatory approval can be achieved. Continuous collaboration among researchers, pharmaceutical industries, and regulatory authorities will be essential for establishing clear guidelines for nanomedicine development.[112]

6.4 Future Opportunities in Oral Antifungal Delivery

Future opportunities in oral antifungal delivery are highly promising due to the increasing demand for effective and patient-friendly therapies for fungal infections. LPHNs provide a versatile platform for improving therapeutic performance of poorly soluble antifungal agents and may significantly transform antifungal treatment strategies.[2] Potential future applications include, targeted oral antifungal therapy, Personalized nanomedicine, Combination antifungal delivery, Long-acting oral formulations, Theranostic nanocarriers, Hybrid nanoparticles may also be explored for delivering newer antifungal agents with poor aqueous solubility and limited bioavailability. Advances in nanotechnology could enable the development of smart delivery systems capable of responding to physiological stimuli such as pH, enzymes, or temperature to achieve site-specific drug release.[113]

The integration of nanotechnology with biotechnology and precision medicine may further improve treatment outcomes for invasive fungal infections. Additionally, hybrid nanocarriers may help reduce antifungal resistance by maintaining sustained therapeutic drug concentrations and improving intracellular drug delivery.[2]

Oral nanocarrier systems also offer opportunities for improving patient compliance through reduced dosing frequency and minimized adverse effects. With continued advancements in pharmaceutical sciences, LPHNs are expected to play a significant role in the next generation of oral antifungal therapies.[2]

6.5 CONCLUSION

Itraconazole is an effective broad-spectrum antifungal drug; however, its poor aqueous solubility, pH-dependent absorption, extensive first-pass metabolism, and variable

gastrointestinal absorption significantly limit its oral bioavailability and therapeutic efficacy. Conventional dosage forms often fail to provide consistent plasma drug concentrations, leading to suboptimal therapeutic outcomes and increased risk of adverse effects. Lipid–polymer hybrid nanoparticles have emerged as a highly promising strategy for overcoming these biopharmaceutical limitations. By combining the advantages of lipid-based and polymeric delivery systems, LPHNs improve drug solubilization, enhance intestinal permeability, protect the drug from degradation, and provide controlled drug release. These nanosystems have demonstrated superior dissolution behavior, enhanced oral bioavailability, improved pharmacokinetic performance, and increased antifungal activity compared with conventional formulations. Various formulation strategies and characterization techniques have been successfully employed for the development of stable itraconazole-loaded LPHNs with desirable physicochemical properties. In-vitro and in-vivo studies have consistently shown the ability of hybrid nanoparticles to improve therapeutic performance while minimizing toxicity and dose-related side effects. Despite promising research outcomes, challenges related to large-scale production, long-term stability, regulatory approval, and commercialization still need to be addressed. Continued research and technological advancements are expected to further optimize hybrid nanocarrier systems and facilitate their clinical translation. Overall, itraconazole-loaded lipid–polymer hybrid nanoparticles represent a novel and effective oral drug delivery approach with significant potential to enhance antifungal therapy and improve patient outcomes in the management of fungal infections.

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