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Polymeric Nanoparticles of Voriconazole

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Abstract

Voriconazole is a triazole antifungal medication that is commonly used to treat newly identified fungal pathogens as well as invasive fungal diseases such aspergillosis and candidiasis. Due to its poor water solubility, topical use requires effective solubilization. Nanotechnology-based techniques can overcome the challenges given by its low aqueous solubility by lowering the total dosage, preventing systemic absorption, allowing controlled drug release at the target site, and ensuring prolonged retention of the dosage form on the skin. For topical antifungal applications, the drug must penetrate the stratum corneum, the skin's outermost layer, to reach deeper depths, particularly the follicular epithelium. Examples of nano-formulations that hold tremendous potential for improving the skin penetration profile of antifungal drugs include colloidal systems, vesicular carriers, and nanoparticles. This review highlights significant studies on voriconazole nano-based formulations.

Invasive fungal infections increase morbidity and mortality rates worldwide. However, these infections have limited treatment choices due to their low bioavailability and toxicity, which makes therapeutic monitoring necessary, especially in the most severe instances. Voriconazole is a common azole used to treat invasive aspergillosis, many hyaline molds, many dematiaceous molds, Candida species, including fluconazole-resistant species, and infections caused by endemic mycoses, in addition to illnesses affecting the central nervous system. Despite its broad range of effectiveness, voriconazole's use is limited by its non-linear pharmacokinetics, which can lead to supratherapeutic dosages and higher toxicity depending on individual polymorphisms during its metabolism. In this sense, nanotechnology-based drug delivery techniques have successfully improved the physicochemical and biological characteristics of a number of therapeutic classes, including antifungals.

Keywords: Voriconazole, Antifungal, Topical delivery, Polymeric Nanoparticles.

1.0 INTRODUCTION

Voriconazole (VRZ) is a second-generation synthetic triazole derived from fluconazole. Its chemical designation is (2R, 3S)-3-(5-fluoro-4-pyrimidinyl)-2-(2,4-difluorophenyl)-1,2,4-triazol-1-yl-(1H)-2-butanol. Originally developed for patients with weakened immune systems suffering from severe invasive fungal infections, VRZ is now widely used to treat aspergillosis and candidiasis infections affecting the skin, wounds, abdomen, kidneys, and bladder walls. It is particularly effective against Candida species resistant to fluconazole. VRZ functions by inhibiting fungal cytochrome P-450-mediated 14-alpha-lanosterol demethylation, which prevents the conversion of lanosterol to ergosterol, a crucial component of fungal cell membranes.[1]

Voriconazole (VRZ) is available in oral tablet form as well as a lyophilized powder for intravenous injection. While oral and intravenous administration are common, enhancing topical delivery through nanoparticles has been explored as an alternative approach. To improve transdermal drug delivery and achieve therapeutic concentrations in the stratum corneum and deeper skin layers, penetration enhancers—also known as sorption promoters or accelerants—are often used to temporarily reduce the skin's barrier resistance. Recent studies have investigated various substances, including nanoparticles, for their potential to enhance the penetration of antifungal agents.[1][2][3]

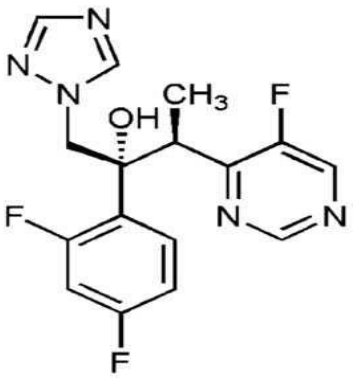

Fig.1

2.0 General Aspects

Voriconazole (VCZ) is an antifungal agent from the azole class, developed through the structural modification of fluconazole. It has low water solubility, with a log P value of 1.82 and pKa values of 2.01 and 12.7. VCZ works by inhibiting cytochrome P450 (CYP450)-mediated 14α-lanosterol demethylation, a crucial process in ergosterol synthesis, which is essential for maintaining fungal cell membrane integrity. It exhibits fungicidal activity against most molds, except those belonging to the Mucorales order. Additionally, VCZ is effective against hyaline fungi, including Fusarium species and the Scedosporium apiospermum complex, except for S. prolificans.[3][4]

Voriconazole (VCZ) is effective against all Aspergillus species, including *A. terreus*, which is naturally resistant to amphotericin B. However, like other azole antifungals, VCZ has a fungistatic effect against *Candida* species. Some fluconazole-resistant strains of *Candida glabrata* remain susceptible to VCZ, while intrinsically fluconazole-resistant species such as *Candida krusei* also respond to VCZ treatment. However, resistance to fluconazole can sometimes lead to cross-resistance with VCZ. While *Candida albicans* was once responsible for the majority of invasive candidiasis cases, there has been a significant increase in infections caused by non-*albicans Candida* species, including *Candida glabrata*.[5][6]

2.1 Pharmacokinetics: Voriconazole (VCZ) is classified as a Class II drug, characterized by low solubility but high permeability. Its poor water solubility poses challenges for administration through multiple routes. VCZ is commercially available in tablet form, oral suspension, and intravenous solution. Due to cytochrome P450 polymorphisms, its pharmacokinetics follow a non-linear pattern and exhibit significant variability among individuals.[2][4][7][9]

2.2 Absorption : Voriconazole (VCZ) is quickly absorbed, with plasma concentrations affected by various factors such as inflammation, body weight, age, administration method, and genetic polymorphisms. Following oral intake, peak plasma levels are typically reached within one to two hours, with an absorption rate of approximately 96%.[2][4][7]

2.3 Distribution: The volume of distribution for voriconazole (VCZ) is estimated to be between 2 and 4.6 L/kg, indicating its distribution in both intravascular and extravascular compartments. Although studies have attempted to assess its plasma protein binding both in vitro and in vivo, it has not been fully characterized. However, glycogen-α-1-acid and albumin have been identified as binding proteins. [2][4][7]

2.4 Metabolism: Voriconazole (VCZ) undergoes extensive metabolism in the liver, primarily through cytochrome P450 (CYP450) enzymes, including CYP2C19, CYP3A, and CYP2C9. Genetic variations in these enzymes can influence metabolism rates, leading to classifications such as poor, intermediate, or rapid metabolizers. CYP2C19 plays a key role in converting VCZ into its inactive form, VCZ-N-oxide.[2][4][7]

2.5 Excretion: With a half-life of approximately six hours, only about 2% of voriconazole (VCZ) is excreted unchanged in the urine. [2][4][7]

3.0 Fungal infection

3.1 Aspergillosis in the Pulmonary System

Pulmonary aspergillosis is an infection caused by the conidial saprophytic fungus *Aspergillus*, which is commonly present in soil, construction dust, and some medical equipment. This condition primarily affects individuals with weakened immune systems or existing lung disorders. The main forms of pulmonary aspergillosis include invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA), and allergic bronchopulmonary aspergillosis (ABPA). The progression of these infections depends on the interaction between the host and the fungus.[8][9]

3.2 Candida Infections

Candida albicans is the leading species causing Candida infections. The primary clinical presentations of these infections include invasive candidiasis, oral candidiasis, denture stomatitis, and neonatal candidemia. Invasive candidiasis, which is one of the most severe

forms of the infection, mainly affects individuals with weakened immune systems, such as organ transplant recipients and chemotherapy patients. Mortality rates in the latter group can be as high as 70%.

Invasive infections are often triggered by damage to the skin and gastrointestinal barriers, such as gastrointestinal perforations. Given that Candida species are common commensals in the skin and gut microbiota, these disruptions can result in systemic infections. Around 15 different Candida species are recognized as causative agents of infections in humans.[3][4][9][10]

4.0 Introduction to Characteristics of Polymeric Nanoparticles

Administering the antifungal drug voriconazole via polymeric nanoparticles is an innovative and efficient strategy for treating fungal infections. Voriconazole, a broad-spectrum triazole antifungal, is widely used to manage invasive aspergillosis and other severe fungal conditions. However, its clinical use is often restricted by issues such as poor solubility, a short half-life, and the risk of systemic toxicity. Polymeric nanoparticles help overcome these challenges by improving the drug's effectiveness and safety profile.[1][2][3][4][5]

Polymeric nanoparticles have gained widespread interest in drug delivery and biomedical research due to their adaptable and customizable properties. These nanoscale systems, typically measuring between 10 and 1000 nm, are developed using either natural or synthetic polymers. Their distinct physicochemical and structural features make them well-suited for controlled and targeted drug delivery applications.[4][5]

The small size of polymeric nanoparticles enhances their ability to cross biological barriers, enabling effective drug delivery to targeted tissues. Their surface characteristics—whether smooth, porous, or rough—significantly influence cellular uptake, circulation duration, and drug release patterns.

These nanoparticles are typically made from biocompatible and biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, or polycaprolactone (PCL). These materials help reduce cytotoxicity and ensure safe breakdown into non-toxic byproducts that can be easily eliminated from the body. [1][2][3]

Polymeric nanoparticles can encapsulate hydrophilic or hydrophobic drugs efficiently, offering protection against degradation and controlled release over extended periods. The release profile can be tailored by modifying the polymer type, molecular weight, and preparation method. [4][5][9][10]

Polymeric nanoparticles can be modified on their surface with ligands, targeting agents, or hydrophilic polymers like polyethylene glycol (PEG). These alterations enhance stability, increase target specificity, and extend their circulation time in the bloodstream. [1][2][3][4][5]

Nanoparticles enhance the solubility and stability of drugs with poor water solubility by encapsulating them within a polymeric matrix. This property improves both bioavailability and therapeutic effectiveness.

Polymeric nanoparticles can be tailored for different administration routes, including oral, topical, intravenous, and pulmonary, expanding their potential in drug delivery systems. Additionally, their capability to carry multiple therapeutic agents simultaneously increases their effectiveness in complex treatments.

These attributes make polymeric nanoparticles a promising approach for optimizing drug delivery, reducing adverse effects, and enhancing patient adherence in the treatment of various diseases.[6][7][8][9]

4.1 Nanostructured Lipid Carriers and Solid Lipid Nanoparticles

Solid lipid nanoparticles and nanostructured lipid carriers have shown great potential as delivery systems for active compounds in skin applications. These carriers are widely used to enhance penetration and facilitate the controlled release of medications and cosmetic ingredients. Composed of physiological and biodegradable lipids, they are generally considered inert and are either classified as GRAS (Generally Recognized As Safe) or have regulatory approval. Additionally, they can be produced on a large scale and pose lower toxicity risks compared to polymer-based systems.[3][4][5]

Nanostructured lipid carriers (NLCs), the advanced version of solid lipid nanoparticles (SLNPs), feature a highly organized solid lipid matrix with significant crystal lattice imperfections, providing ample space for drug loading. They were developed to overcome the limitations of SLNPs, such as low drug-loading capacity, particle size enlargement due to aggregation, and drug leakage during storage.[7][8][9]

4.2 Nanotechnology-Based Voriconazole Delivery Systems

Due to their numerous advantages for scientific and societal advancements, interest in researching nanostructured systems has remained strong over time. The application of nanoparticles in the biomedical and pharmaceutical fields has transformed drug delivery processes. These nanostructures can effectively transport both hydrophilic and hydrophobic molecules, regardless of molecular weight, including labile compounds such as proteins, nucleic acids, and vaccines, to ensure their pharmacological effects. Following nanoencapsulation, several drug properties have been observed to change, including solubility, controlled release, pharmacokinetics, protection against degradation, and targeted tissue delivery. Additionally, these systems serve as valuable tools for both therapeutic and diagnostic purposes. Nanoparticles are primarily classified based on their composition.[2][3] [17][18]

Organic nanoparticles are developed using a variety of materials, including lipids, surfactants, natural or synthetic polymers, and proteins derived from animal or plant sources. These materials must exhibit specific mechanical and thermal properties, along with biocompatibility and biodegradability. Depending on these characteristics, different nanostructures can be formed, such as nanocapsules, nanospheres, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nano and microemulsions, and cyclodextrins. Variations in their supramolecular configurations result in differences in size, shape, drug-loading capacity, drug release profiles, biological half-life, cellular interactions, and biodistribution.[17][18]

The chemical composition of a substance determines the electrical charge characteristics of nanoparticle surfaces, influencing their biological and physical stability, as well as their ability to interact with cells and penetrate tissues. Nanoparticle surfaces can be chemically modified to enhance cellular interactions and targeting. Given the various limitations associated with VCZ usage, nanotechnology-based delivery systems offer an effective approach for its distribution.[19][20][21]

5.0 Polymeric Nanoparticles

Polymeric nanoparticles play a crucial role in systems designed for targeted drug and chemical delivery. Their main advantage lies in the ease with which they can influence pharmacokinetic factors, such as absorption, bioavailability, and excretion, during the delivery process.[2] Biodegradable polymers are classified into two types: natural polymers such as chitosan, zein, casein, alginate, gelatin, and albumin, and synthetic polymers like Poly(lactide) (PLA), Poly(lactide-co-glycolic acid) (PLGA), and Poly(ε-caprolactone) (PCL).

Polymeric nanoparticles are created using two main methods: dispersion and polymerization. Despite their potential, these nanostructured systems still face several challenges as drug delivery vehicles, including issues with non-scalable production methods, high research costs, safety concerns, and limitations in overcoming stability and biological barriers. To address these challenges, various systems have been explored under different pathophysiological conditions.[2] Cancer is one of the main diseases where drug delivery systems, particularly those releasing doxorubicin and paclitaxel, have already been approved and demonstrated positive results. Research is also being conducted on their application for neurodegenerative and cardiovascular diseases.[3]

Despite the challenges, polymeric nanoparticles hold significant potential for further development and use. In some delivery methods, such as oral administration, they protect the encapsulated molecule from degradation. They also enable surface modifications through ligand attachment and allow for the controlled release of the drug, targeting specific areas.[3][4][5]

Polymer nanoparticles (NPs), developed in the 1970s, are more stable than liposomes and can be fabricated using similar methods. Additionally, surface modifications are possible, and the controlled release properties of polymer nanoparticles are easier to manage. The two main types of polymer nanoparticles are nanospheres and nanocapsules. Nanospheres are "matrix-type" structures where drugs are uniformly distributed within the matrix, while nanocapsules are "repository-type," with the drug contained in a core surrounded by a polymeric shell. Recently, biodegradable nanoparticles have shown significant potential as drug delivery systems due to their excellent biocompatibility.[2][4][5]

Although polymer nanoparticles have a relatively low encapsulation efficiency, their large molecular weight enables them to quickly trigger an immune response. To address these limitations, a new carrier system known as lipid-polymer hybrid nanoparticles (LPNs) has been developed. The lipid component improves loading efficiency and penetration, while the polymer regulates drug release. As a result, LPNs offer a promising solution for improving biocompatibility and physical stability.[7][8][9]

Several oral thrombolytic drugs have been investigated using the LPNs method. Previous research has demonstrated that chitosan and lipid nanoparticles can enhance the oral bioavailability of heparin. According to Khan, cisplatin-loaded lipid-polymer hybrid nanoparticles (NPs) offer an effective means of delivering the drug directly to tumor sites,

making them a promising platform for controlled cisplatin delivery in cancer treatment.[3][4][5][7][8][9]

Nanoparticles made from biodegradable and biocompatible polymers like polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), and chitosan offer a promising method for targeted drug delivery to the lungs. In recent decades, PLGA nanoparticles, in particular, have been extensively studied in research.[7][8][9]

Modifying the surface of PLGA nanoparticles with a mucoadhesive polymer like chitosan can enhance cellular adhesion and improve retention of the drug delivery system at the target site. This modification may also alter or even reverse the zeta potential of the particles. Additional advantages include the ability to attach targeting ligands to the free amino groups of chitosan, as well as a reduction in the initial burst release of the encapsulated drug. [20][21]

6.0 Conclusion

Voriconazole is a widely used antifungal agent for treating invasive fungal infections, and polymeric nanoparticles offer a promising strategy to enhance its delivery and therapeutic efficacy. Biodegradable polymers like PLGA are particularly favored due to their biocompatibility, controlled release properties, and ability to improve drug stability and bioavailability. Encapsulating voriconazole in polymeric nanoparticles not only increases its solubility and reduces dosing frequency but also minimizes the systemic side effects associated with conventional formulations.

Additionally, polymeric nanoparticles enable targeted drug delivery, ensuring higher concentrations at infection sites while reducing off-target effects. Advancements in nanotechnology and polymer science are further enhancing the potential of these systems, paving the way for more effective and patient-friendly antifungal treatments.

To fully realize the benefits of voriconazole delivery via polymeric nanoparticles, future research should focus on optimizing formulation strategies, scaling up production processes, and conducting comprehensive clinical trials. With these advancements, polymeric nanoparticles could revolutionize the treatment of fungal infections, overcoming current therapy limitations and improving patient outcomes.

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