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## Review Paper

# Encapsulation Of Itraconazole by Using Various Techniques for The Effective Drug Delivery

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## ABSTRACT

In this review we have made a detailed study regarding the various type of techniques used in the encapsulation for the effective delivery of itraconazole. The parameters regarding the encapsulation have been considered and the detail study has been made. The encapsulation techniques are the advanced type of Novel Drug Delivery System. This system of drug delivery has shown the great effect as compared too other drug delivery systems. Itraconazole drug is encapsulated to increase its effect in the treatment. Its antifungal activity has been boosted by using the Encapsulation of itraconazole. Fungal infection is commonly observed in wide number of population so to cure this type of infection itraconazole had shown greater effect. The detail study regarding the fungal infection has been made in this review.

## INTRODUCTION

### Novel Drug Delivery System: -

From few decades conventional dosage form is been used i.e. prolonged release and sustained release but this method of drug delivery is unable to satisfy or to hold a drug and also found less effective for targeted delivery of drug on the particular organ. To overcome this or to avoid such cases novel drug delivery system has been introduced. This system helps to increase the bioavailability as well as pharmacological activity of the drug and also helps to protect the drug

physical and chemical degradation. Novel drug delivery system is been used from few decades for the effective delivery of the drug.

### Types of Novel drug delivery system: -

- Nanoparticles
- Microspheres
- Dentrimer
- Micelles
- Phytosomes
- Implantation
- Microcapsules
- Nanocapsules

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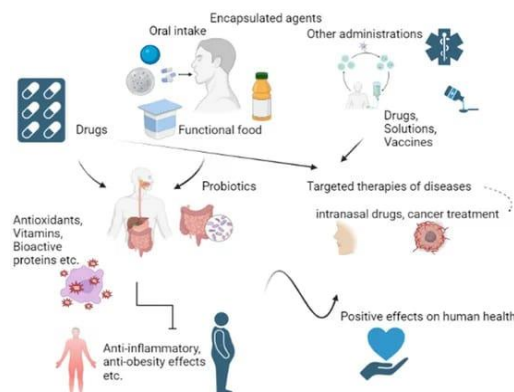


- Encapsules
- Microsponge

**Encapsulation: -**

Encapsulation for delivery therapeutics agents and sensitive compounds effectively in the human body. Encapsulation involves surrounding these agents with protective coatings or shells, which ensures their stability, targeted delivery, and reduces side effects. This approach is crucial, especially for administering poorly soluble, toxic, or sensitive drugs, as well as for enhancing the efficacy of nutrients and functional food components. Encapsulation techniques are beneficial across various administration routes, with oral administration being the most common due to its convenience and patient compliance. However, other routes such as intravenous, subcutaneous, and even implantation into tumors

have also been explored, demonstrating the versatility and applicability of encapsulation in medical treatments and functional foods. The field of encapsulation continues to evolve with new techniques being developed to cater to specific properties of the agents and their intended modes of administration. These advancements are driven by the increasing demand for effective delivery system that can enhance therapeutic outcomes while minimizing adverse effects. Overall, encapsulation plays a pivotal role in modern healthcare and nutrition by ensuring the controlled and effective delivery of therapeutic agents and nutrients, thereby contributing to improved health outcomes and quality of life for individuals. [02,03]



In recent years, the global economy’s growth has driven an increased demand for energy, promoting a search for more energy-efficient technologies to mitigate environmental impacts. Renewable energy sources (RES) like solar radiation, biomass, geothermal heat, and wind are gaining traction as cleaner, sustainable alternatives to conventional fuels such as nuclear and fossil fuels. Solar energy stands out as a particularly promising RES, persistently available day after day, albeit variable and dependent on daylight hours. Despite significant growth in solar energy electricity production worldwide, its output fluctuates widely throughout the day and across seasons. To address this variability, thermal energy storage (TES) has

emerged as a crucial technology. TES system store heat during periods of excess generation and release it when demand peaks. Among TES methods, latent heat storage (LHS) using phase change materials (PCMs) has proven highly effective. PCMs change phase (typically solid to liquid) at a constant temperature, storing and releasing large amount of thermal energy efficiently. Unlike sensible heat storage, which uses materials with lower storage capacities, PCMs offers high storage density with minimal temperature differences between charging and discharging phases. This characteristic makes LHS system compact and suitable for various applications, including construction, refrigeration,

air conditioning, textiles, food, aerospace, and waste heat recovery. The selection of PCMs for specific applications hinges on their phase change temperatures, ensuring optimal performance in diverse environmental and industrial settings.

Encapsulation in food processing involves enclosing active substances within a coating, membrane, shell, or matrix to control their release. This technique is crucial for modifying the release rate or location of substance, as defined by European Directive 3AQ19a. Controlled release systems are used to overcome challenges like stability and taste alteration when incorporating nutrients such as calcium, vitamins, or fatty acids into foods. Two primary modes of controlled release are delayed (eg. Protecting probiotics from gastric acidity) and sustained (eg. Maintaining flavour release in chewing gum). Various encapsulation technologies enable the production of microcapsules and micro particles with specific properties, supporting diverse applications in food products. [01]

#### **Encapsulation Techniques:-**

Encapsulation techniques play a crucial role across various industries including food, pharmaceuticals, agriculture, textiles, and more. These methods range from simple coating processes to complex emulsification and drying procedures:-

##### **1.General Methods :**

**Coating Method:** - This involves coating an active ingredient with a solution of shell material using techniques like pan coating, spray coating, or fluidized bed coating. The coated material is then dried to obtain encapsulated particles suitable for handling and storage.

**Emulsification and Drying:** - Here, a core material (such as oil or enzymes) is emulsified with a solution of a wall material (often polysaccharides or proteins ) to form droplets. These droplets are then dried to produce encapsulated particles in dry powdered form. This

method is effective for protecting sensitive actives and ensuring controlled release. [04,05]

#### **Spray Chilling and Spray Cooling :**

Spray chilling and spray cooling are similar to spray drying. In these methods, a core material is mixed with a liquid coating or wall material and then sprayed. However, unlike spray drying, there is no water to evaporate.

**-Spray Chilling:** The mixture is sprayed into cool or chilled air. The coating solidifies around the core. Typically, the coating is a type of vegetable oil with a melting point between 32°C and 42°C.

**- Spray Cooling:** The mixture is sprayed into cool air as well, but the coating is usually a vegetable oil with a melting point between 45°C and 122°C. Other materials can also be used. Both methods are used to encapsulate solid materials like vitamins, minerals, or acids. By choosing the right melting point for the coating, these methods can control the release of the core material.

#### **4.Extrusion:**

Extrusion encapsulation involves mixing the core material with a molten carbohydrate mass. This mixture is then forced through a die into a dehydrating liquid, which hardens the coating and traps the core material inside.

#### **Steps Involved:**

1. **Mixing:** The core material is combined with a molten carbohydrate.
2. **Extruding:** This mixture is pushed through a die into a liquid like isopropyl alcohol, which hardens the coating.
3. **Cutting and Drying:** The hardened strands are cut into small pieces, separated, and dried.

#### **History:**

- The process was first patented in 1957 and further developed in 1962.

- Schultz and his team at the United States Department of Agriculture were the pioneers. They initially mixed orange oil with a molten carbohydrate and allowed it to cool on a stainless



steel sheet. Once solid, the material was ground into a powder.

- Swisher improved this method by using extrusion to form the material, as described in his patents.

#### **Advantages:**

- The extrusion method ensures that the core material is completely surrounded by the wall material, providing excellent shelf life.

- It removes any residual oil or core material from the surface, ensuring thorough encapsulation.

- This method produces larger particles, which can be useful when visible flavor pieces are desired.

#### **2. Chemical methods :**

##### **1. Interfacial polymerization (IFP) :**

In this technique, a capsule shell is made by creating a reaction at the surface of a droplet or particle. This is done using special chemicals called multifunctional monomers, such as isocyanates and acid chlorides.

**1. Mixing Ingredients:** First, a multifunctional monomer is dissolved in a liquid core material. This mixture is then spread out in a water-based solution that contains a dispersing agent.

**2. Adding a Co-reactant:** A second chemical called a co-reactant, which is a multifunctional amine, is added to this mixture.

**3. Creating the Shell:** The chemicals react quickly at the surface of the droplets or particles, forming a capsule shell.

#### **Depending on the chemicals used:**

- Isocyanate + Amine: Forms a polyurea shell.

- Acid Chloride + Amine: Forms a polynylon or polyamide shell.

- Isocyanate + Hydroxyl Monomer: Forms a polyurethane shell.

#### **2. In situ polymerization :**

When making capsules, small building blocks called monomers are added to a special container. These monomers link together to form a solid shell around a core material, like wrapping a gift. No extra chemicals are added to the core itself; the shell forms only in the surrounding liquid.

At first, a small, simple version of the shell material is created. Over time, this material gets bigger and builds up on the surface of the core, forming a solid capsule shell. For example, capsules can be made by reacting urea with formaldehyde in an acidic solution, creating a shell around liquids that don't mix with water. In another case, researchers made tiny magnetic beads by adding styrene and acrylic acid to a container with nano-sized magnetic particles. They used a chemical to start the reaction at 85°C (185°F) to create the beads. The successful design and operation of encapsulation system depend on understanding the physiochemical mechanisms involved, interactions between the active ingredients, and its release behaviour from the shell material. Additionally, incorporating stabilizing agents can enhance the efficacy of the encapsulation process. Recent advancements in these techniques have significantly impacted food research, allowing for improved delivery of bioactive compounds, controlled release of flavours or nutrients, and enhance stability of sensitive ingredients. These encapsulation methods continue to evolve, driven by ongoing research and application in diverse industrial sectors. [04,05]

#### **Fungal Infection: -**

Usually, people live peacefully with tiny microorganisms around them. Infections only happen when something goes wrong with our body's defenses or when there are too many harmful germs. Most infections don't show obvious signs, but sometimes they do, and that's when we have an infectious disease. Many types of germs can cause infections, including bacteria, viruses, parasites, fungi, prions, worms, and helminthes. Common viral infections are the most frequent, while bacterial infections were once the most feared. As treatments for bacterial infections have improved, fungi have become a bigger threat. Yeasts and molds are now among the top 10 germs



found in patients in Intensive Care Units (ICUs). About 7% of fever cases in patients with low white blood cell counts are due to serious fungal infections. *Candida*, a type of yeast, is now the fourth most common germ found in hospital blood samples in the USA, even more common than many bacteria that used to be feared. Since the 1980s, there has been an increase in serious fungal infections in patients who aren't at the end stage of their illness. Because there aren't many autopsies done, the true number of fungal infections might be higher than we think. This is partly because fungal infections often don't show clear symptoms, making them hard to detect. Fungi have become tough opponents for very sick patients for several reasons. Despite their use in making bread, beer, and cheese, fungi are primarily decomposers. They break down decaying organic matter, including dead bodies. When they sense decay, they grow rapidly and continue to expand, even if medical treatments are trying to keep a patient alive. In fact, modern treatments can sometimes make fungal infections worse. They might weaken the immune system or disrupt the body in ways that help fungi grow. Let's take a closer look at these unique infectious agents known as fungi or mycoses. [01,02] Fungi, as you pointed out, can indeed be formidable adversaries for seriously ill patients due to their unique biological characteristics and their ability to exploit certain conditions within the body. Here's a deeper look into why fungi can be such significant challenges in medical settings:

### **1. Opportunistic Nature**

Fungi are opportunistic pathogens, meaning they generally only cause infections when the body's immune defenses are compromised. This is often the case in patients undergoing aggressive treatments such as chemotherapy, organ transplants, or those with advanced illnesses. These treatments can weaken the immune system,

making the body more susceptible to fungal infections.

### **2. Adaptability and Survival**

Fungi are incredibly adaptable and can thrive in a variety of environments. They can utilize a wide range of nutrients, including those found in decaying organic matter, which allows them to persist in the human body, especially in areas where the immune system is weakened. This adaptability also means they can resist many types of treatments and interventions.

### **3. Diagnostic Challenges**

Fungal infections can be difficult to diagnose because their symptoms often overlap with those of other infections or conditions. Additionally, traditional diagnostic methods may not always detect fungal pathogens quickly or accurately, leading to delays in treatment. Some fungi grow slowly or produce non-specific symptoms, which can make early detection challenging.

### **4. Resistance to Treatments**

Many fungi have developed resistance to common antifungal medications, making infections harder to treat. This resistance can arise due to overuse or misuse of antifungal drugs, or due to the intrinsic resilience of certain fungal species. As a result, infections caused by these resistant strains can become severe and difficult to manage.

### **5. Environmental and Medical Factors**

In medical settings, factors such as the use of broad-spectrum antibiotics can disrupt the normal microbial flora, allowing fungi to proliferate unchecked. Moreover, invasive procedures and devices (like catheters and ventilators) can provide a direct route for fungi to enter the body, leading to serious infections.

### **6. Biofilm Formation**

Many fungi can form biofilms, which are clusters of fungal cells encased in a protective matrix. Biofilms can develop on medical devices and within the body, making the fungi more resistant to both the immune system and antifungal



treatments. This protective layer complicates the eradication of the infection and increases the likelihood of persistent or recurrent infections.

Fungal infections are caused by fungi, which can be either yeasts or molds. These infections can occur through inhalation, skin contact, or entry through cuts, wounds, or injections. They are more common in people with weakened immune systems, such as those with HIV/AIDS, undergoing cancer treatment, or on immunosuppressive medications. [01,02]

### **Types of Fungal Infections :**

**1. Superficial Mycoses:** Affect outer layers of skin, nails, or hair.

**2. Subcutaneous Mycoses:** Involve deeper layers of skin and subcutaneous tissues.

**3. Systemic Mycoses:** Affect internal organs and are often more serious, potentially spreading throughout the body.

### **Common Fungi and Infections:-**

- *Candida albicans* : Causes infections such as oral thrush and vaginal yeast infections. Usually present in the body without causing harm but can overgrow.

- *Aspergillus* : Can cause invasive aspergillosis, especially in immunocompromised individuals.

- *Cryptococcus*: Can lead to *Cryptococcus* meningitis, particularly in those with weakened immunity.

- *Histoplasma*: Causes histoplasmosis, particularly in those exposed to bird or bat droppings.

- *Coccidioides*: Causes coccidioidomycosis, or Valley fever, which is common in certain geographic areas.

- *Blastomyces*: Causes blastomycosis, typically found in North America.

### **Risk Factors :-**

- Weakened immune systems (e.g., HIV/AIDS, cancer treatments, organ transplants)

- Chronic diseases (e.g., diabetes)

- Environmental exposures (e.g., working with soil, bird droppings)

- Certain medications (e.g., immunosuppressant)

### **Prevention and Treatment :-**

- **Prevention:** Maintain good hygiene, keep skin clean and dry, avoid contact with potentially infected animals, and wash hands frequently.

- **Treatment:** Generally involves antifungal medications. The choice of treatment depends on the specific type of infection. In severe cases, surgical intervention may be necessary to remove infected tissue.

### **Global Impact :-**

- Fungal infections affect over 1 billion people globally each year.

- Estimated deaths from fungal diseases were 1.7 million in 2020.

- Significant conditions include:

- Fungal asthma: over 10 million cases annually.

- Long-term aspergillosis: around 3 million cases.

- Fungal keratitis: about 1 million cases leading to blindness.

- *Cryptococcus* meningitis: over 200,000 cases.

- Invasive candidiasis: around 700,000 cases.

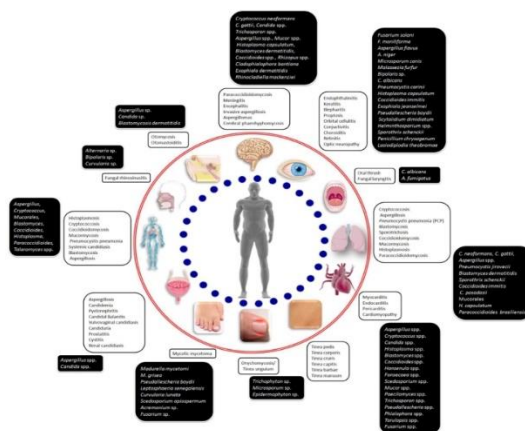
- *Pneumocystis pneumonia*: 500,000 cases.

- Invasive aspergillosis: 250,000 cases.

- Histoplasmosis: 100,000 cases.

Fungal infections can also be transmitted from animals to humans, such as *Microsporum* from cats. This version organizes the information into clear sections, providing an overview of fungal infections, their types, risk factors, prevention, treatment, and global impact. [01,02]

### **Fungal Pathogens and Transmission Routes:-**



Spectrum of fungal infection and their etiological agents in humans [02]

**Sub-Kingdom Dikarya :-**

- Phyla: Ascomycota and Basidiomycota
- Ascomycota: Known for causing a range of infections including:
- Oropharyngeal , Otolaryngeal , Dermatological ,Ophthalmic, Neuronal, Genitourinary, Cardiac, Pulmonary, Systemic infections, Basidiomycota, Cryptococcus: Known for invasive meningitis, Malassezia: Known for superficial skin infections.

Transmission Routes :-

**1. Direct Contact:**

- Dermatophytic fungi infect damaged skin.
- Genera include:
  - Microsporum
  - Epidermophyton
  - Trichophyton
  - -Sporothrix
  - Malassezia

Mechanism: Produce proteolytic enzymes causing superficial mycoses in keratinized tissues.

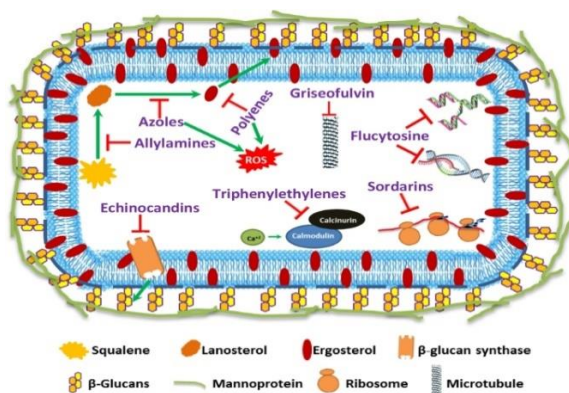
**2. Inhalation:**

- Fungal spores or conidia are inhaled, leading to pulmonary infections.
- Key pathogens include:
  - Blastomyces dermatitidis: Causes Blastomycosis.
  - Paracoccidioides brasiliensis and P. lutzii: Cause Paracoccidioidomycosis.
  - Histoplasma capsulatum: Causes Histoplasmosis.
  - Pneumocystis jirovecii: Causes Pneumocystis pneumonia.
  - Aspergillus fumigatus and A. flavus: Cause Aspergillosis.
  - Coccidioides immitis and C. posadasii: Cause Coccidioidomycosis.
  - Cryptococcus neoformans and C. gattii: Cause Cryptococcosis.

**3. Both Direct Contact and Inhalation:**

- Talaromyces marneffeii: Causes talaromycosis. [02]

**Antifungal agents and their mechanism of actions :-**



Existing and new cellular targets including mode of actions of antifungal drugs. [04]

### 1. Azoles:

- Examples: Imidazoles (miconazole, ketoconazole), Triazoles (fluconazole, voriconazole).

- Mechanism of Action: Azoles inhibit the enzyme sterol 14 $\alpha$ -demethylase, which is crucial for converting lanosterol to ergosterol. Ergosterol is a key component of fungal cell membranes, and its reduction affects membrane stability and fluidity.

### 2. Polyene:

- Examples: Amphotericin B, Nystatin.

- Mechanism of Action: Polyenes interact with fungal cell membranes through hydrophobic interactions, binding to sterols (mainly ergosterol). This interaction creates membrane pores, leading to leakage of cell contents and cell death.

### 3. Echinocandins:

- Examples: Caspofungin, Micafungin, Anidulafungin.

- Mechanism of Action: Echinocandins inhibit the enzyme 1,3- $\beta$ -d-glucan synthase, which is essential for synthesizing 1,3- $\beta$ -d-glucan, a vital component of the fungal cell wall. This results in impaired cell wall integrity and exhibits fungistatic activity.

### 4. Allylamines:

- Examples: Terbinafine, Naftifine.

- Mechanism of Action: Allylamines inhibit squalene epoxidase, an enzyme involved in the conversion of squalene to lanosterol. This

inhibition impairs ergosterol biosynthesis, affecting fungal cell membrane integrity.

### 5. Pyrimidine Analogues:

- Example: 5-Fluorocytosine (5-FC).

- Mechanism of Action: 5-FC is taken up by fungal cells via cytosine permeases and is converted to 5-fluorouracil. This metabolite interferes with nucleic acid synthesis (both DNA and RNA), thereby inhibiting protein synthesis.

- Amphotericin B and miconazole have been reported to induce oxidative stress, which can further enhance their antifungal activity.

- Other agents target additional cellular processes:

- Sordarins: Inhibit protein synthesis.

- Griseofulvin: Inhibits microtubule assembly, disrupting cell division.

- Triphenylethylenes: Inhibit calcineurin signaling, affecting cell signaling pathways crucial for fungal adaptation. [03 , 04]

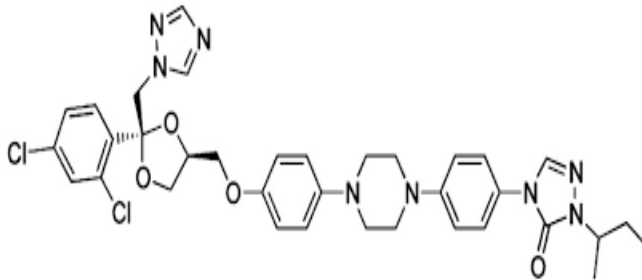
### Itraconazole:

### Pharmacological Evolution And Clinical Impact L:

Itraconazole, a broad-spectrum triazole antifungal agent, was first introduced in 1987. It initially offered a promising alternative to the then-existing antifungal treatments, such as amphotericin B and fluconazole. The initial clinical formulation was a capsule containing sugar-coated pellets, which was notably effective for treating skin and nail fungal infections. However, its use in patients with compromised immune systems, such as those who are neutropenic, was less successful due to issues with bioavailability. In neutropenic patients,

conditions like achlorhydria, mucositis, nausea, and anorexia significantly impacted drug absorption, leading to a bioavailability of approximately 22%. This limited the drug's effectiveness in these critical cases. To address these challenges, a new formulation of itraconazole was developed in the form of an oral solution. This formulation utilized  $\beta$ -hydroxypropyl-cyclodextrin, an oligosaccharide made from seven glucose molecules, to incorporate itraconazole into an aqueous solution. Cyclodextrin, which is hydrophilic on the outside and lipophilic on the inside, facilitates the drug's absorption into the systemic circulation. Once in the bloodstream, itraconazole is released from the cyclodextrin complex. Cyclodextrin itself is inert, undergoing renal elimination without metabolic changes. The advent of this new formulation enabled more effective clinical trials and a better understanding of itraconazole's dose-response relationship. This clarified some of the earlier issues and expanded the drug's applications, including antimycotic prophylaxis, empirical antifungal therapy, and, to a lesser extent,

treatment of proven invasive fungal infections. [84,85] Itraconazole, a triazole antifungal agent introduced in 1984, is used to treat fungal infections either orally or intravenously. It is known for its broader spectrum of activity compared to fluconazole, particularly against *Aspergillus* species (a group of conidial fungi), which fluconazole does not effectively target. Itraconazole's mechanism of action is similar to that of other azole antifungals. These drugs inhibit the enzyme CYP450 14 $\alpha$ -demethylase in fungi, which is crucial for converting lanosterol to ergosterol, a vital component of the fungal cell membrane. By binding tightly to this enzyme, itraconazole disrupts ergosterol biosynthesis, leading to impaired cell membrane function. Triazole antifungals, including fluconazole, itraconazole, and voriconazole, have a lower affinity for mammalian P450 enzymes compared to fungal P450s, which helps minimize toxicity to the host. The action of these drugs is primarily fungistatic, meaning they inhibit fungal growth, but they can be fungicidal, or kill the fungi, at higher concentrations. [08]



Itraconazole (ITZ) chemically, 2-Butan-2-yl-4-[4-[4-[4-[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy] phenyl] piperazin-1-yl] phenyl]-1,2,4-triazole-3-one.

### Clinical pharmacology and pharmacodynamics properties :-

Itraconazole is an antifungal agent with distinct pharmacokinetic and pharmacodynamic properties that influence its use and effectiveness in treating

fungal infections. Here's a summary of its key characteristics:

#### 1. Bioavailability:

Capsules: 22% in neutropenic patients.

Oral Solution: 55% bioavailability.

#### 2. Elimination Half-Life:

After a single dose: 24 hours.

At steady state: 34 hours.

#### 3. Volume of Distribution:

Large, approximately 11 L/kg, due to high lipophilicity.

Achieving steady state can take up to 14 days without a loading dose.

#### **4. Protein Binding:**

Very high (99%).

This high protein binding means itraconazole cannot be removed by haemodialysis.

#### **5. Metabolism:**

Metabolized in the liver via the cytochrome P450 system. It is a substrate and a potent inhibitor of CYP3A4, which affects the metabolism of many other drugs.

#### **6. Renal and Hepatic Consideration:**

**Renal Insufficiency:** Oral itraconazole dose does not need to be adjusted. Intravenous itraconazole is contraindicated if creatinine clearance is below 30 mL/min.

**Hepatic Insufficiency:** No initial dose adjustment is needed in cases of minor to moderate hepatic insufficiency. Dose adjustments can be made based on drug monitoring.

#### **7. Active Metabolite:**

Hydroxy-itraconazole, which has the same antifungal spectrum as itraconazole but at higher concentrations (approximately double that of the parent drug), enhancing overall antifungal activity.

#### **8. Pharmacodynamics:**

**Mechanism :** Inhibits 14-alpha-demethylase, crucial for ergosterol synthesis in fungal cell membranes.

**Activity:** Fungistatic against *Candida* species and fungicidal against *Aspergillus* species at higher doses.

Careful monitoring and consideration of drug interactions are essential for the safe use of itraconazole, particularly due to its strong inhibition of CYP3A4 and its complex pharmacokinetic profile. [85]

#### **Failure Treatment Of Itraconazole**

1. Primary In Vitro Resistance and Bioavailability:

- Some dermatophytes may exhibit primary resistance to azole antifungals in laboratory settings. However, more commonly, treatment

failures are attributed to issues with drug absorption rather than inherent resistance.

- Itraconazole's effectiveness can be compromised by inadequate bioavailability, which is influenced by factors such as the concurrent use of antacids and the patient's immune status.

#### **2. Impact of Generic vs. Innovator Formulations:**

- Reports indicate that substituting innovator itraconazole (Sporanox®) with generic itraconazole capsules has led to treatment failures. This is due to inadequate plasma levels of the generic formulation.

- A specific case study showed no clinical improvement in onychomycosis when treated with generic itraconazole, whereas the same patient responded well to Sporanox® capsules.

#### **3. Bioavailability Studies:**

- A randomized crossover study comparing generic and innovator itraconazole revealed a significant discrepancy in bioavailability. The relative bioavailability of the generic formulation was only 3.5% compared to the innovator product, indicating poor absorption of the generic form.

#### **4. Clinical Implications:**

- These findings highlight the importance of ensuring that generic itraconazole meets stringent quality and bioequivalence standards to achieve comparable therapeutic outcomes.

- Ensuring that generic formulations maintain adequate drug levels is crucial to prevent resistance and treatment failures. This is particularly important in patients who are immunocompromised or are using medications that affect drug absorption.

#### **5. Recommendations:**

- Patients and healthcare providers should be cautious when using generic itraconazole, especially when clinical responses are unsatisfactory with the generic form.

- Regulatory agencies and pharmaceutical companies must ensure that generics are

rigorously tested to match the innovator's bioavailability and efficacy. [6,7].

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