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FORMULATION AND EVALUATION OF ITRACONAZOLE AEROSOL FOR ANTIFUNGAL ACTIVITY: A REVIEW

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Abstract - *Itraconazole is an antifungal medication that belongs to the azole class of drugs. While it is primarily available in oral form, there is some research on the use of itraconazole aerosol for antifungal activity.*

One study published in the journal Mycoses in 2016 found that itraconazole aerosol was effective in treating pulmonary aspergillosis in mice. The study found that the aerosol delivery of itraconazole directly to the lungs resulted in higher concentrations of the drug in lung tissue, which improved the drug's effectiveness against the fungal infection.

Another study published in the Journal of Aerosol Medicine and Pulmonary Drug Delivery in 2018 investigated the use of itraconazole dry powder aerosol for the treatment of invasive pulmonary aspergillosis in rats. The study found that the dry powder aerosol formulation of itraconazole was well-tolerated and showed promising antifungal activity.

Overall, these studies suggest that aerosol delivery of itraconazole may have potential for the treatment of fungal infections of the respiratory tract. However, more research is needed to determine the safety and efficacy of this approach in humans. It is important to note that the use of itraconazole aerosol for antifungal activity is not yet approved by regulatory agencies and should only be used under the guidance of a healthcare professional.

Key Words: antifungal medication, itraconazole, azole class, aerosol delivery, pulmonary aspergillosis, antifungal activity, respiratory tract, safety, efficacy, healthcare professional.

1. INTRODUCTION

The history of itraconazole aerosol begins with the recognition of the need for an effective treatment for fungal infections in the lungs, especially in patients with conditions such as cystic fibrosis or compromised immune systems [1]. Systemic antifungal medications, such as oral itraconazole, had limitations in their ability to effectively reach the lungs at therapeutic concentrations [2].

In the early 2000s, researchers began investigating the possibility of delivering itraconazole directly to the lungs using an aerosol formulation [3]. The aim was to achieve higher concentrations of the drug at the site of infection while minimizing systemic side effects. Various studies and clinical trials were conducted to evaluate the safety and efficacy of itraconazole aerosol [4].

One significant milestone in the development of itraconazole aerosol was the initiation of a Phase II clinical trial called the "Study of Itraconazole in Stable Non-Cystic Fibrosis Bronchiectasis" (the ITRA study) in 2013 [4]. This trial evaluated the use of itraconazole inhalation solution in patients with non-cystic fibrosis bronchiectasis, a condition characterized by permanent dilation of the bronchi, often associated with recurrent respiratory infections [5-6].

Based on the positive results from the ITRA study and subsequent studies, in February 2018, the U.S [7]. Food and Drug Administration (FDA) granted Breakthrough Therapy Designation to the itraconazole inhalation solution for the treatment of Aspergillus infections in patients with cystic fibrosis [8-9].

In July 2020, the FDA approved the use of itraconazole inhalation solution under the brand name Tolsura for the treatment of fungal infections caused by Aspergillus in patients with cystic fibrosis [10-11]. It is important to note that the approval specifically relates to patients with cystic fibrosis, and the use of itraconazole aerosol in other populations may vary depending on specific indications and regulatory approvals in different countries [12].

The development of itraconazole aerosol represents a significant advancement in the treatment of fungal lung infections, offering a targeted approach to deliver antifungal medication directly to the site of infection [13]. However, it is always important to consult a healthcare professional for specific information about the availability, indications, and appropriate use of medications [14].

Itraconazole aerosol is a potential method for delivering the antifungal medication itraconazole directly to the respiratory tract for the treatment of fungal infections such as pulmonary aspergillosis [15]. Studies have shown that aerosol delivery of itraconazole can result in higher concentrations of the drug in lung tissue, improving its effectiveness against the fungal infection [16-17]. However,

more research is needed to determine the safety and efficacy of this approach in humans [18-19]. It is important to use itraconazole aerosol only under the guidance of a healthcare professional, as it is not yet approved by regulatory agencies [20].

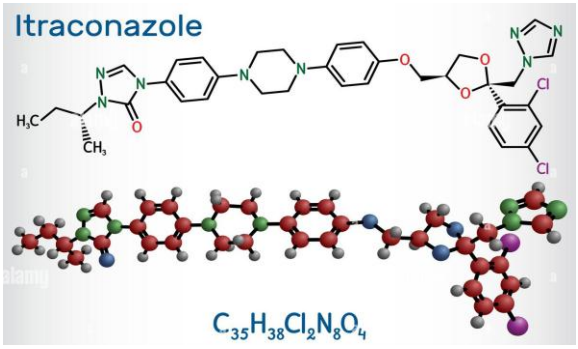

Figure-1: Itraconazole [20]

Itraconazole works by inhibiting the growth and spread of the fungal cells by interfering with their ability to produce a substance called ergosterol, which is essential for their survival. This leads to the weakening of the fungal cell walls and ultimately kills the fungus [21-22].

Itraconazole is available in different formulations, including capsules, oral solution, and injection [23]. Your healthcare provider will determine the most appropriate form and dose of itraconazole for your condition based on the type of infection, the severity of the infection, and other factors. It is important to take itraconazole as prescribed and for the full duration of treatment to ensure the infection is completely eradicated [24].

1.1. AEROSOL

Aerosol refers to a suspension of small solid or liquid particles in a gas, such as air. Aerosols can be created naturally, such as with dust or volcanic ash, or artificially through various industrial and commercial processes, such as spray painting, cooking, or using cleaning products [25-26]. In medicine, aerosols can be used to deliver medication directly to the respiratory system, such as in inhalers or nebulizers [27-28]. However, aerosols can also pose health and environmental risks, such as air pollution or the spread of infectious diseases through respiratory droplets [29].

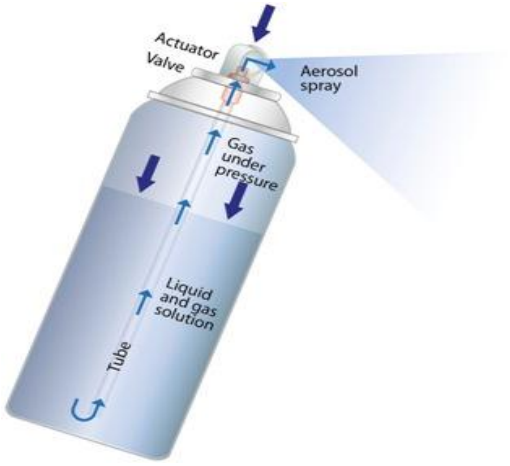

Figure-2: Aerosol [30]

When a liquid is converted into an aerosol, it is typically done through the process of atomization, which breaks up the liquid into tiny droplets or particles. This can be done through mechanical means, such as using a spray nozzle, or through ultrasonic or pneumatic methods [31-32].

Similarly, when a solid is converted into an aerosol, it is typically done through the process of grinding, milling, or crushing the solid material into tiny particles that can be suspended in the gas [32].

Once the particles are suspended in the gas, they can be transported through the air and can be inhaled by people or animals [33-34]. This is the basis for the use of aerosols in a variety of applications, such as medication delivery through inhalers, spraying of pesticides, and the formation of clouds in weather modification [35].

The behavior of aerosols is influenced by a number of factors, including the size and shape of the particles, the density of the particles and the gas, and the concentration of the particles in the gas. These factors can affect how the aerosol behaves in the environment, how long it remains suspended in the air, and how it interacts with surfaces and organisms that it comes into contact with [36].

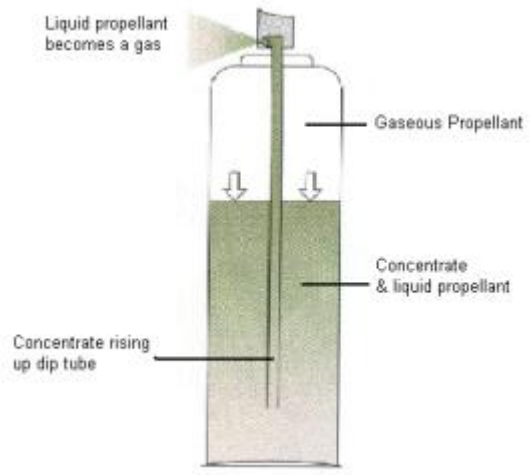

Figure-3: Principle of Aerosol [37]

1.2. PHARMACOLOGICAL APPLICATIONS OF ITRACONAZOLE

Itraconazole is an antifungal medication used to treat various fungal infections. It belongs to the class of drugs known as triazole antifungals and works by inhibiting the synthesis of ergosterol, a component of fungal cell membranes [38]. Some of the pharmacological applications of itraconazole include:

1. Treatment of systemic fungal infections: Itraconazole is effective in treating a wide range of systemic fungal infections, including aspergillosis, blastomycosis, histoplasmosis, and cryptococcosis.

2. Treatment of skin and nail fungal infections: Itraconazole is also used to treat fungal infections of the skin and nails, such as tinea pedis (athlete's foot), tinea corporis (ringworm), and onychomycosis (nail fungus).

3. Prophylaxis in immunocompromised patients: Itraconazole may be used to prevent fungal infections in immunocompromised patients, such as those undergoing chemotherapy or organ transplant.

4. Treatment of fungal sinusitis: Itraconazole may also be used to treat fungal infections of the sinuses, such as allergic fungal sinusitis and fungal ball (aspergilloma).

5. Treatment of systemic candidiasis: Itraconazole may also be used in the treatment of systemic candidiasis, a fungal infection caused by Candida species.

1.3. PHARMACOLOGICAL APPLICATIONS OF AEROSOL

Aerosols have a wide range of pharmacological applications. One of the main advantages of aerosols is that they can deliver drugs directly to the lungs, which can be an effective treatment for respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis [39-40]. Some examples of pharmacological applications of aerosols are:

1. Bronchodilators: Aerosolized bronchodilators such as albuterol and salbutamol are commonly used to treat asthma and other respiratory conditions by relaxing the smooth muscles of the airways, thus increasing airflow to the lungs.

2. Corticosteroids: Inhaled corticosteroids such as fluticasone and budesonide are used to reduce inflammation in the airways and prevent asthma attacks.

3. Antibiotics: Aerosolized antibiotics such as tobramycin are used to treat bacterial infections in the lungs of patients with cystic fibrosis.

4. Antivirals: Aerosolized antiviral drugs such as ribavirin are used to treat respiratory viral infections such as respiratory syncytial virus (RSV) and influenza.

5. Local anesthetics: Aerosolized local anesthetics such as lidocaine are used to numb the airways during medical procedures such as bronchoscopy.

6. Vaccines: Aerosolized vaccines such as influenza vaccines are being developed as an alternative to traditional injection-based vaccines.

2. LITERATURE REVIEW

Several studies have shown that itraconazole aerosols have promising efficacy in the treatment of respiratory fungal infections, particularly in patients with cystic fibrosis (CF) and other lung diseases. In a study published in the Journal of Antimicrobial Chemotherapy, itraconazole aerosols were found to be effective in reducing the growth of Aspergillus fumigatus, a common fungal pathogen in CF patients, in vitro and in vivo.

Another study published in the European Respiratory Journal evaluated the safety and efficacy of itraconazole aerosols in patients with allergic bronchopulmonary aspergillosis (ABPA), a condition characterized by allergic reactions to Aspergillus species. The study found that itraconazole aerosols significantly improved lung function and reduced symptoms in patients with ABPA, without causing significant side effects. Furthermore, a systematic

review and meta-analysis published in PLoS One analyzed the efficacy of itraconazole aerosols in the treatment of fungal infections in CF patients. Despite these promising findings, some studies have reported limitations and challenges in the use of itraconazole aerosols. For example, a study published in the International Journal of Pharmaceutics found that the formulation and stability of itraconazole aerosols can be affected by factors such as temperature and humidity, which may impact their efficacy and safety.

Tejas et.al: Itraconazole microsimulation used the most soluble medicine. Due to medication solubility, microemulsion formulation employed Eucalyptus oil (10.89mg/ml), Tween-20 (0.81mg/ml), and Methanol (0.72mg/ml). Pseudoternary phase diagrams determined the microemulsion surfactant mixture. Co-surfactant (Smix): 1:1, 1:2, 2:1, 3:1. Oil: Smix was 1–9. Phase diagram indicated stable microemulsion zone at 9:1 and 3:1 Smix:Oil ratios. Full-factorial microemulsion optimisation. The optimised ME7 Microemulsion achieved the greatest Transdermal Flux (4.739 mg cm2 h-1) and %Q6 (98.74%) of all 9 batches. ME7 has the greatest desirability, 0.805. Microemulsion permeabilized itraconazole. Optimised itraconazole-loaded microemulsion ME7.

Niyaz et.al: Imidazole derivative fluconazole treats cutaneous and systemic fungal infections. 90% fluconazole bioavailability. In this research, fluconazole gel was formulated for skin delivery. UV spectrophotometry drug analysis. Alcohol absorbed fluconazole best at 260 nm. The concentration-absorbance relationship was linear, with r2 = 0.997. Thus, beer's rule was followed. FT-IR preformulation investigation indicated drug-excipient compatibility.

Esmaeil et.al: Stearic acid grafted upon depolymerized chitosan forms nanoscale micelles. Stearic acid, the micelles' hydrophobic centre, entrapped ITRA and increased its solubility. All formulations had a monomodal 120–200 nm size distribution. In vitro nebulization of ITRA-loaded formulations demonstrated that stearic acid-chitosan polymeric micelles could deliver ITRA and maintain stability.

Jaya et.al: Even while systemic antifungal therapy is clinically beneficial, its effectiveness is reduced by thousand times when it reaches the target site, and high doses and/or extended administration are typically needed to maintain an effective medication concentration. Systemic antifungal medications may cause side effects, patient noncompliance, and reduced drug availability at the infection site, limiting their utility. In such cases, a safe and effective new drug delivery device that reduces dosage and increases drug concentration in the targeted organ with low systemic concentration is needed.

Saudagar et.al: Eudragit RS PO with hydroxypropyl cellulose formed TH film-forming gel. 32 complete factorial design optimised polymer concentrations for drug release and antifungal efficacy. Thus, methodical formulation achieves desired results. The novel film-forming gel reduced fungal load more than market products. This study's film-forming dermal gel meets topical usage requirements. This innovative dosage form improves dosing accuracy and location. The optimised formulation with higher bioadhesive properties may increase terbinafine gel bioavailability and offer an alternative to standard topical preparations.

Chemate et.al: Eudragit RS PO with hydroxyl propyl cellulose formed Terbinafine Hydrochloride film-forming emulgel. Film-forming Emulgel reduces fungal load and is more effective. This study's film-forming cutaneous Emulgel meets topical usage requirements. This innovative dosage form improves dosing accuracy and location. Emulgel's optimised batch (T4) had the best drug release, spreadability, consistency, and % inhibition. Thus, film-forming Emulgel may be a viable alternative to standard dosage forms for treating fungal infections topically.

Poonam et.al: Drug release and gel rheology depend on carbopol-934 and HPMC K4M concentrations. Carbopol-934 gels had a far higher viscosity than HPMC K4M gels, however both gels decreased drug release increasing polymer concentration. Thus, gels for topical application may be made using carbopol-934 and hydroxypropyl methylcellulose in the ratio 1:3. Formulation F3 should be improved for industrial manufacturing.

Adel et.al: TPGS-stabilized and ITZ-encapsulated PLGA-NPs produced stable nano-size drug-loaded particles. However, nanoprecipitation had better shape, particle size, zeta potential, encapsulation efficiency, and drug loading capacity. ITZ nanosuspension released better than lyophilized or spray-dried NPs. ITZ-loaded NPs were somewhat more antifungal than ITZ-aqueous suspension. TPGS stabilised and enhanced permeability, resulting in greater encapsulation and drug loading NPs. Briefly, TPGS-stabilized PLGA-NPs would increase ITZ bioavailability by improving water dispersibility and intestinal permeability, which would boost its antifungal action. Thus, the aforementioned nano-system is an excellent alternative for treating fungal infections due to its effectiveness.

Laxmi et.al: Itraconazole formulations were tested for drug content, pH, viscosity, spreadability, extrudability, and in vitro drug diffusion. Formulation F4 performed best in viscosity tests. F4 had the best drug diffusion and rheology. F4 pH treats skin diseases. Noveon AA1 gels had a higher viscosity than carbopol-971 gels, however both gels decreased drug release increasing polymer concentration. Thus, Carbopol-971p and Noveon AA1 may be used to make topical gels. Formulation F4 should be designed for industrial manufacturing.

Abhinava et.al: Fungal infections remain a health risk. Antifungal chemotherapeutics misused led to multidrug-resistant fungal infections, toxicity, and inadequate

treatment effectiveness. Current literature suggests that other medication delivery mechanisms are being researched. Drug penetration and therapeutic efficacy depend on topical carrier composition. Nanotechnology advances provide a novel therapy for fungal skin infections. Prolonged anti-fungal medication usage may cause adverse effects, patient non-compliance, and reduced target site bioavailability, limiting its therapeutic usefulness. Safe and effective innovative drug delivery technologies that minimise dosage and raise drug concentration in the targeted organ with low systemic concentration are needed to address this challenge.

Narinder et.al: The best strategy to treat fungal infection is to determine the cause and start therapy as soon as feasible (Table 3). Today's superficial fungal infection therapies are innovative. This lowered medication toxicity and increased effectiveness. They may limit medication release and reduce side effects including allergic reactions and irritation. Thus, innovative medication delivery technology is an effective and superior infection treatment.

Manasa et.al: Proniosomes are dry surfactant-coated water-soluble carrier particles. After rehydration in hot aqueous medium, they form niosomal dispersion. Proniosomes store and travel well. Drugs in proniosome vesicles stay in circulation longer, penetrate target tissue better, and lessen toxicity. The formulation contains vesicle-forming non-ionic surfactants. It was chosen for vesicular carriers due to its biocompatibility. Cholesterol and soyalecithin stabilise membranes. Ethanol enhances permeability.

Mrunal et.al: Transdermal film-forming sprays were formulated and characterised in this work. After spraying the solution, polymers at varying concentrations formed a homogenous layer. Evaporation duration, spray angle, spray pattern, volume actuated, drug content, and in-vitro drug release were evaluated. Formulation F1 had excellent physical qualities, drug content, and in-vitro drug transport of 83.075%, hence it was tested for penetration through Ophiophagus Hannah (Cobra) shed snakeskin. Based on all evaluation comments, formulation F1 with 10% Eudragit L-100 and 4% Ethyl cellulose was the best. Thus, evaluation tests suggest that the transdermal filmforming spray formulation may cure superficial fungal infections.

Saba et.al: The nanoemulsion released more medicine than the water solution due to its smaller globules and greater surface-to-volume ratio. F11's prolonged release profile and extended eye surface residence duration may boost intraocular bioavailability in ocular tissues. More antifungal impact was also linked to increased medication release. Based on the findings, nanoemulsions may be suitable for ocular delivery of itraconazole with higher bioavailability, less frequent administration, and better patient compliance. In vivo and ophthalmic toxicity investigations are still needed.

3. CONCLUSION

There are several strategies that can be employed to increase the efficiency of itraconazole aerosols for antifungal activity. Some of these strategies include that the formulation of itraconazole aerosols can be optimized to increase their efficacy and safety. For example, the particle size and distribution of the aerosol can be adjusted to ensure optimal deposition in the lungs, and the use of excipients can improve the stability and solubility of the drug. Combination therapy with itraconazole aerosols and other antifungal drugs can improve the efficacy of treatment and reduce the risk of drug resistance. For example, a study published in the Journal of Antimicrobial Chemotherapy found that combination therapy with itraconazole aerosols and amphotericin B significantly improved the antifungal activity against Aspergillus species. Targeted delivery of itraconazole aerosols to the site of infection can increase their efficacy and reduce systemic side effects. For example, the use of liposomes or nanoparticles can enable targeted delivery of the drug to the lung tissue.

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