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Itraconazole-Loaded Solid Lipid Nanoparticles: An Advanced Approach for Enhanced Treatment of Aspergillosis Caused by Aspergillus fumigatus

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Abstract: Aspergillosis is an opportunistic fungal infection caused mainly by Aspergillus fumigatus, which primarily affects immunocompromised individuals and patients with chronic lung diseases. Itraconazole, a broad-spectrum triazole antifungal agent, is widely used in the treatment of different forms of aspergillosis. However, its clinical effectiveness is limited by poor aqueous solubility, low bioavailability, and variable absorption. Nanotechnology-based drug delivery systems such as Solid Lipid Nanoparticles (SLNs) have emerged as a promising strategy to overcome these limitations. SLNs are submicron colloidal carriers composed of biocompatible and biodegradable lipids that remain solid at both room and body temperatures. Itraconazole-loaded SLNs enhance drug solubility, improve bioavailability, and provide sustained and targeted drug release, thereby increasing therapeutic efficacy while reducing adverse effects. Various preparation methods such as high-pressure homogenization, microemulsion dispersion, melt emulsification with ultrasonication, and high-shear homogenization have been reported for the formulation of itraconazole SLNs. Characterization studies including particle size analysis, zeta potential, entrapment efficiency, and in-vitro drug release demonstrate improved stability and controlled drug delivery. This review highlights the role of itraconazole-loaded solid lipid nanoparticles as an advanced drug delivery system for the effective management of aspergillosis and discusses their advantages, limitations, and potential future applications in antifungal therapy.

Keyword: Aspergillosis, Itraconazole, Solid Lipid Nanoparticles (SLN), Aspergillus fumigatus, CPA (Chronic Pulmonary Aspergillosis), IPA (Invasive Pulmonary Aspergillosis), COPD (Chronic Obstructive Pulmonary Disease), CNS (Central Nervous System), ABPA (Allergic Bronchopulmonary Aspergillosis).

1. INTRODUCTION

Aspergillosis is a fungal infection caused by species of the genus Aspergillus, most commonly Aspergillus fumigatus. These fungi are widely present in the environment, especially in soil, decaying vegetation, and dust. Humans are frequently exposed to Aspergillus spores through inhalation, but infection usually occurs in individuals with weakened immune systems or underlying lung diseases.(1) Aspergillosis primarily affects the respiratory system and can manifest in different forms such as allergic reactions, chronic lung infections, or invasive systemic disease. The severity of the infection depends on the immune status of the host and the extent of fungal growth in the body.

Early diagnosis and appropriate antifungal therapy, including drugs like Itraconazole, are important for effective management and prevention of complications. Aspergillosis has become an important opportunistic infection, particularly in immunocompromised patients and those with chronic pulmonary disorders. (2)

Itraconazole is a broad-spectrum, orally active triazole antifungal agent that has historically served as an important therapeutic option for various forms of aspergillosis, including Allergic Bronchopulmonary Aspergillosis (ABPA), aspergilloma, and Chronic Pulmonary Aspergillosis (CPA), especially in individuals who are intolerant to or resistant to amphotericin B treatment(3).It works by inhibiting the fungal cytochrome P450-dependent enzyme lanosterol 14α-demethylase, which is essential for the conversion of lanosterol to ergosterol, a vital component of the fungal cell membrane; this disruption leads to increased membrane permeability, structural damage, and inhibition of hyphal growth.(4)

While newer triazoles such as voriconazole are now preferred for acute, life-threatening invasive pulmonary aspergillosis (IPA), itraconazole remains a significant option for non-invasive, chronic, or step-down, long-term maintenance therapy. (5)

With many possible uses in drug delivery, clinical medicine, research, and other diverse scientific fields, solid lipid nanoparticles are at the forefront of the quickly evolving nanotechnology sector. Since solid lipid nanoparticles have benefits such as regulated medication release and targeted drug delivery with greater stability, they were created in the early 1990s as a substitute for conventional colloidal carriers such liposomes, polymeric nanoparticles, and emulsions.

They are composed of physiologically biocompatible and biodegradable solid lipids—such as triglycerides, fatty acids, steroids, or waxes—that remain solid at both room and body temperature, dispersed in an aqueous surfactant solution (6). Unlike oil-in-water emulsions, which use liquid lipids, the solid core of SLNs allows for controlled, sustained release of active pharmaceutical ingredients (APIs), improved drug stability, and protection against chemical degradation (7). These carriers offer high drug payloads for lipophilic compounds, and by utilizing Generally Recognized as Safe (GRAS) excipients, they demonstrate low cytotoxicity (8). Their structure, which can be further modified, enables improved bioavailability, increased skin penetration, and, via surface functionalization, targeted delivery to specific tissues(9). Due to their solid matrix, they also provide superior physical stability during processing and storage compared to liquid-based nanoemulsions.

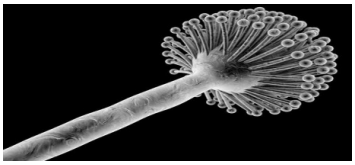
Solid lipid nanoparticles are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine, and research, as well as in other varied sciences.

2. OVERVIEW OF ASPERGILLOSIS

2.1. Definition

Aspergillosis is a spectrum of diseases caused by fungi of the genus Aspergillus, most commonly A. fumigatus, characterized by a wide range of manifestations depending on the host's immune status. While Aspergillus is ubiquitous in the environment and commonly inhaled, it typically causes disease only in immunocompromised hosts, individuals with chronic lung conditions, or those with severe viral infections. (10, 11, 12)

In the environment, Aspergillus species obtain nutrients from dead material and reproduce asexually via conidia. Fewer than 40 species of Aspergillus are capable of causing human disease, with A fumigatus, followed by A flavus, A terreus, and A niger, the most implicated species. (13)



Individuals inhale an estimated few hundred to several thousand Aspergillus conidia daily. Most people do not develop aspergillosis because a robust immune response effectively clears inhaled conidia. Host defences, including physical barriers, innate immunity, and soluble factors, destroy conidia before germination can occur. Neutrophils play a central role in controlling Aspergillus species, which explains the heightened risk in immunocompromised individuals, particularly those with prolonged neutropenia. (13, 14)

When the immune system is compromised (e.g. immunosuppressive therapy prior to organ transplantation) or there is pre-existing pulmonary malfunction (e.g. asthma, cystic fibrosis, TB lesions), A. fumigatus exploits weaknesses in the host defenses which can result in the development of saprophytic, allergic or invasive aspergillosis. If not effectively eliminated by the innate immune response, conidia germinate and form invasive hyphae which can penetrate pulmonary tissues. The innate immune response to A. fumigatus is stage-specific and various components of the host's defences are recruited to challenge the different cellular forms of the pathogen. In immunocompetent hosts, anatomical barriers (e.g. the mucociliary elevator) and professional phagocytes such as alveolar macrophages (AM) and neutrophils prevent the development of aspergillosis by inhibiting the growth of conidia and hyphae. The recognition of inhaled conidia by AM leads to the intracellular degradation of the spores and the secretion of proinflammatory mediators which recruit neutrophils to assist in fungal clearance. During the later stages of infection, dendritic cells activate a protective A. fumigatus-specific adaptive immune response which is driven by Th1 CD4 (+) T cells.(15)

2.2. Types of Aspergillosis

i. Allergic Bronchopulmonary Aspergillosis

The immunological hypersensitivity response to Aspergillus species that colonize the airways is known as allergic bronchopulmonary aspergillosis (ABPA), which primarily affects people with asthma or cystic fibrosis (CF). Despite the fact that asthma and CF are still the main at-risk groups, new evidence suggests that ABPA may also occur in people with COPD, post-tuberculosis lung illness, and non-CF bronchiectasis. The Infectious Diseases Society of America (IDSA) considers ABPA to be an allergic syndrome rather than an invasive fungal infection.(16)

An excessive immune response, marked by increased total IgE, Aspergillus-specific IgE and IgG antibodies, and eosinophilia, is triggered in susceptible people by airway colonization with Aspergillus fumigatus. The clinical symptoms of ABPA are brought on by the inflammatory response that follows .(17)

The immunological evidence of allergy to Aspergillus antigens is frequently accompanied by bronchiectasis, chronic eosinophilia, mucoid impaction (sometimes mistaken for pneumonia), and poorly controlled asthma.(18)

ii. Chronic Pulmonary Aspergillosis

The harmful illness known as chronic pulmonary aspergillosis (CPA) is brought on by a fungal infection of the lung caused by members of the Aspergillus genus, particularly Aspergillus fumigatus. (19)

The distinction between CPA and acute and subacute pulmonary aspergillosis is that the latter has a longer course of illness, lasting over three months. These diseases are commonly found in people who have previously had structural lung conditions such as pulmonary tuberculosis sequelae, allergic bronchopulmonary aspergillosis, sarcoidosis, lung cancer, emphysema, and chronic obstructive pulmonary disease (COPD).(20)

Nevertheless, people with varying degrees of immunosuppression from conditions like diabetes, human immunodeficiency virus (HIV), and alcoholism also exhibit the disease entity of subacute IPA.(21)

iii. Invasive Aspergillosis

Immunocompromised people who undergo steroid therapy, chemotherapy that causes significant neutropenia, hematopoietic stem cell transplantation, and solid organ transplantation are often diagnosed with invasive aspergillosis (IA). (22)

A. fumigatus is the most prevalent cause of invasive aspergillosis globally and has undergone extensive research and analysis. (23, 24)

iv. Aspergilloma

The most prevalent and well-known type of pulmonary infection caused by Aspergillus species is aspergilloma, which typically occurs in a preexisting lung cavity. (25)

Fungal hyphae, inflammatory cells, fibrin, mucus, and tissue debris make up the aspergilloma (fungus ball). Although other fungi, such Fusarium and Zygomycetes, can cause a fungal ball to develop, A. fumigatus is the most often identified species of Aspergillus found in such lesions. (26,27)

Aspergilloma, which can complicate a number of cavitary lung diseases such tuberculosis, sarcoidosis, bronchiectasis, bronchial cysts and bullae, ankylosing spondylitis, neoplasm, and pulmonary infection, is a frequent occurrence. Tuberculosis is the most prevalent of these. (28)

2.3. Epidemiology Pulmonary Aspergillosis

a) Pulmonary

Invasive aspergillosis mostly impacts the immunocompromised population, eg, people living with advanced stages of human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), those with hematologic malignancies, prolonged neutropenia, long-term corticosteroid use, those on immunosuppression, and recipients of hematopoietic or solid organ transplants. (29,30)

Incidence after a hematopoietic stem-cell transplant ranges from 0.5% after an autologous stem-cell transplant to up to 3.9% after a transplant from an unrelated donor. (31)

Invasive aspergillosis can also be seen in critically ill intensive care patients with an underlying pulmonary condition, eg, chronic obstructive pulmonary disease (COPD) or asthma. (32,33)

The incidence of invasive aspergillosis in hospitalized patients rose by 44% between 2004 and 2013, and increased in 2020 and 2021 due to the COVID-19 pandemic. The rise in incidence is, in part, due to improved diagnostics and increased frequency of transplantation procedures. (31)

b) Rhinosinusitis

Other forms of aspergillosis are less common. Approximately 12 million cases of fungal rhinosinusitis are estimated worldwide, with Aspergillus species a common causative pathogen. The most common risk factors are immunosuppression and poorly controlled diabetes mellitus. (29)

c) Cerebral Aspergillosis

Only around 5% of individuals with confirmed invasive aspergillosis have CNS (Central Nervous System) involvement.

In 21% of patients with disseminated aspergillosis, an autopsy investigation revealed CNS (Central Nervous System) involvement. (31)

The main risk factor is immunosuppression, notably prolonged neutropenia brought about by hematologic malignancies and hematopoietic stem cell transplantation. (33)

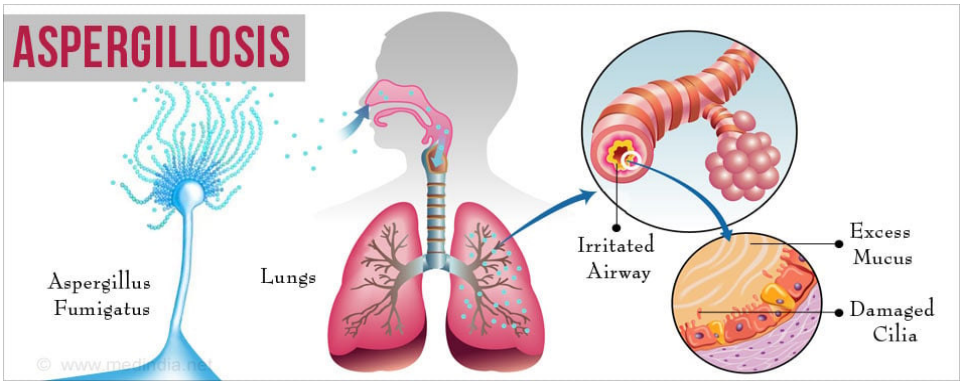
2.4. Pathophysiology of Aspergillosis

Invasive infections are usually acquired by inhalation of spores or, occasionally, by direct invasion through damaged skin.

Aspergillus species tend to infect open spaces, such as pulmonary cavities caused by previous lung disorders (eg, bronchiectasis, tumors, and tuberculosis), the sinuses, or external auditory canals (otomycosis). Such infections tend to be locally invasive and destructive, although systemic spread sometimes occurs, particularly in immunocompromised people with neutropenia, or immunosuppression due to prolonged glucocorticoid use. Aspergillosis can also occur in those with HIV infection, particularly those with advanced HIV disease. Aspergillus Fumigatus is the most common cause of invasive pulmonary disease.Allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to Aspergillus species that results in lung inflammation unrelated to fungal invasion of tissues.Chronic pulmonary aspergillosis most commonly occurs in patients with underlying structural lung disease. An aspergilloma (fungus ball) is a distinctive mass of tangled fungal hyphae, with fibrin exudates and few inflammatory cells, typically encapsulated by fibrous tissue. The fungus usually remains confined within the cavity without significant local invasion. Limited tissue invasion at the periphery of the cavity may occasionally occur.

Aspergillus species can also cause endophthalmitis after trauma or ocular surgery. Intravascular and intracardiac prostheses can become infected by hematogenous seeding.

Primary cutaneous aspergillosis is uncommon but may occur in burns; beneath occlusive dressings; after corneal trauma (keratitis); or in the sinuses, mouth, nose, or ear canal.(34)



3. ITRACONAZOLE

Itraconazole, a triazole antifungal medication, is effective against a wide range of fungi and has a high safety profile. Because it's primary metabolite, hydroxy-itraconazole, possesses significant antifungal activity as well, itraconazole is extremely effective. (35)

It is offered intravenously and orally, and it has a positive pharmacokinetic and pharmacodynamic profile. Formulations. (36)

3.1. Chemical structure

Itraconazole is a triazole antifungal agent with a complex structure characterized by a central five-membered dioxolane ring connected to a triazolone moiety and a phenyl-piperazine-phenyl linker. (37, 38).

3.2. Solid lipid Nanoparticles

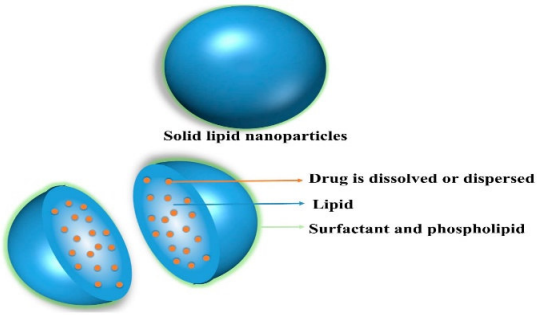
Lipid nanoparticles are strong colloidal carriers composed of lipids that remain solid at room temperature as well as at body temperature. They consist of a solid lipid core in which the medicine is dissolved or dispersed, protected by a surfactant (39). They are colloidal transporters with a size range of 50 nm to 1 m, which is below the micron level. (40)

Triglycerides and phospholipids, which are nanometer in size, make up the very promising medication delivery system known as solid lipid nanoparticles, which have just been researched for regulated release. Solid lipid nanoparticles have several benefits over other nanocarriers, such as biodegradability, biocompatibility, and the capacity to change a drug's physicochemical characteristics. Additional advantages include ease of use, low cost, organic solvent-free processing, good stability, and controlled release features. (41)

Compared to alternative nanocarriers, the composition has greater bioavailability and stability (42).

These carriers are able to load both hydrophilic and lipophilic drugs without affecting their active component.(43)

SLNs are made up of solid lipid, emulsifier and water/solvent (Table 2). The lipids used may be triglycerides (tri-stearin), partial glycerides (Imwitor), fatty acids (stearic acid, palmitic acid), and steroids (cholesterol) and waxes (cetyl palmitate). Various emulsifiers and their combination (Pluronic F 68, F 127) have been used to stabilize the lipid dispersion. The combination of emulsifiers might prevent particle agglomeration more efficiently.



3.3. Itraconazole Loaded Solid Lipid Nanoparticles

Itraconazole-loaded solid lipid nanoparticles (SLNs) are advanced topical carriers designed to enhance the skin penetration, stability, and therapeutic efficacy of this poorly soluble antifungal drug, particularly for treating superficial fungal infections. These nano-carriers provide sustained, targeted release, often improving on traditional, less effective therapies. (44)

3.4. Characterization of Itraconazole SLNs

I. Particle Size and Size Distribution

• Nano-range Size: Optimized formulations typically yield a mean particle size in the range of 100–350 nm.

• Low Polydispersity Index (PDI): The PDI is usually low (e.g., < 0.3), indicating a narrow particle size distribution and high homogeneity.

• Effect of Components: The use of Stearic acid (C18) generally results in slightly larger, yet more stable particles compared to Palmitic acid (C16). (45)

II. Zeta Potential (Surface Charge)

• Stability Indicaton: Zeta potential values generally range from -10 mV to -25 mV.

• Negative Charge: The particles usually exhibit a negative charge, which is attributed to fatty acid residues or the non-ionic surfactant used, providing electrostatic repulsion that prevents aggregation.

III. Entrapment Efficiency (EE) and Drug Loading (DL)

• High Entrapment: Itraconazole is highly lipophilic, allowing for excellent encapsulation, with efficiency values often reported >90% (some as high as 98.78%).

• Lipid Choice: Stearic acid often provides higher entrapment efficiency for Itraconazole compared to other lipids due to its higher affinity for the drug.

IV. Morphological Analysis (TEM/SEM)

• Spherical Shape: Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) images confirm that the SLNs are spherical in shape and uniformly distributed.

• Structural Integrity: TEM imaging shows a distinct lipid coat around the drug core.

V. Solid State Characterization (DSC and XRD)

• Amorphous Conversion: Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) studies confirm that the crystalline, raw Itraconazole is converted into an amorphous or molecularly dispersed form within the solid lipid matrix.

• Absence of Drug Peak: DSC thermograms typically show the disappearance of the endothermic melting peak of pure Itraconazole, indicating it is successfully entrapped.

VI. Fourier Transform Infrared Spectroscopy (FTIR)

• Compatibility: FTIR analysis is used to confirm the absence of chemical interactions between the drug and the lipid/surfactant components.

• Key Peaks: Characteristic peaks of Itraconazole, such as those for C=O stretching (ketone) in the triazole ring (around 1697 cm^{-1}), are analyzed to ensure chemical stability.

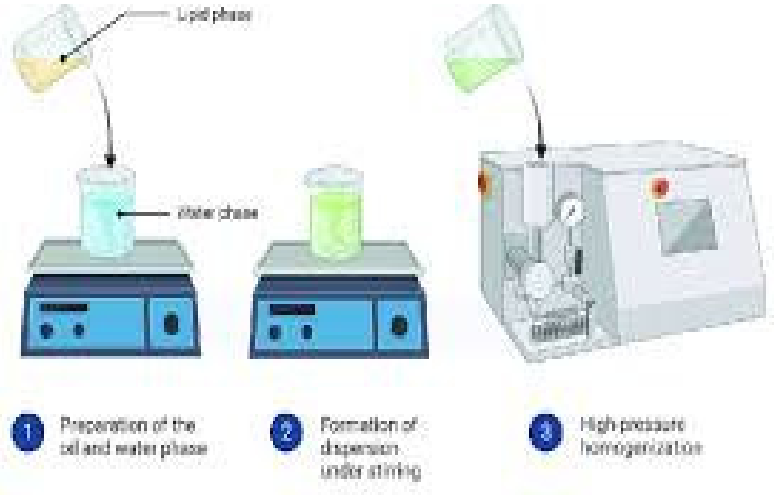
VII. In Vitro Drug Release

• Biphasic Release: In vitro studies demonstrate a characteristic biphasic release profile: an initial, fast burst release (representing surface-associated drug) followed by a slow, sustained, or controlled release over 12–24 hours.

• Improved Dissolution: The SLNs show a significant increase in the dissolution rate compared to pure, crystalline Itraconazole. (46).

4. METHODS OF PREPARATION

4.1. High-Pressure Homogenization Method



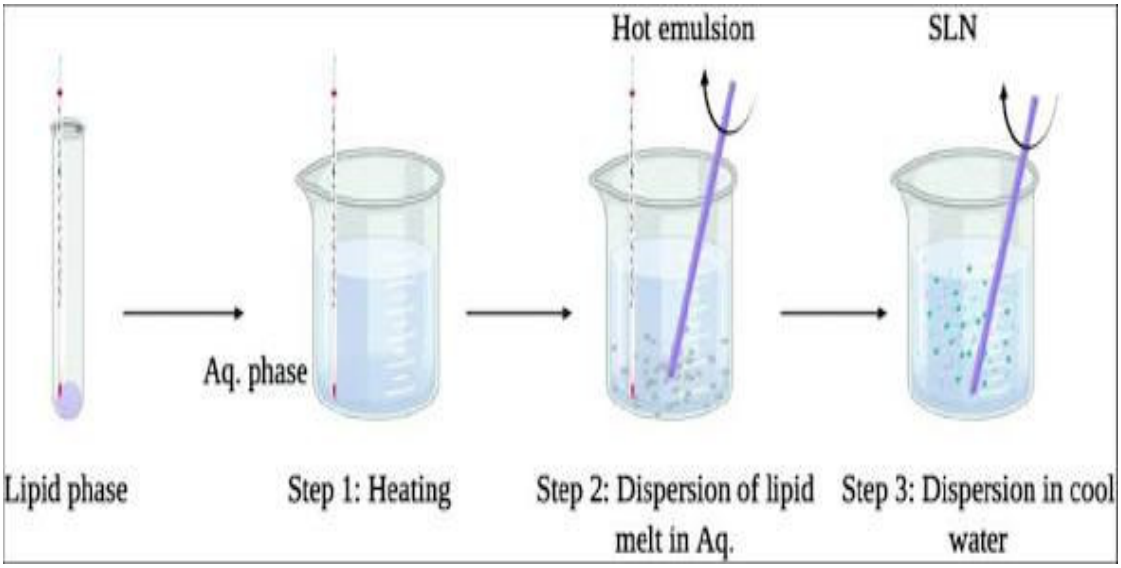
One of the most common methods for making itraconazole-loaded SLNs is high-pressure homogenization. The drug-containing lipid phase is melted and dispersed in an aqueous surfactant phase to create a pre-emulsion in this process. The mixture is then treated with a homogenizer under high pressure to produce a nanoemulsion by reducing particle size. The lipid recrystallizes and produces solid lipid nanoparticles as it cools.

Procedure

- A suitable solid lipid such as tristearin or glyceryl monostearate is heated above its melting point.
- Itraconazole is dissolved or dispersed in the molten lipid phase.
- An aqueous phase containing surfactant (Tween 80, Poloxamer 188, etc.) is heated to the same temperature as the lipid phase.
- The hot aqueous phase is added to the molten lipid phase with continuous stirring to form a coarse pre-emulsion.
- The pre-emulsion is passed through a high-pressure homogenizer (100–2000 bar) for several cycles.
- The obtained nanoemulsion is cooled to room temperature.
- Cooling leads to solidification of lipid droplets, forming itraconazole-loaded solid lipid nanoparticles.(47,48)

4.2. Microemulsion Dispersion Technique

The microemulsion technique is another important method for preparing itraconazole-loaded SLNs. It is based on the formation of a hot microemulsion containing lipid, surfactant, co-surfactant and water. When this microemulsion is dispersed into cold water, rapid crystallization of lipid occurs and forms nanoparticles.

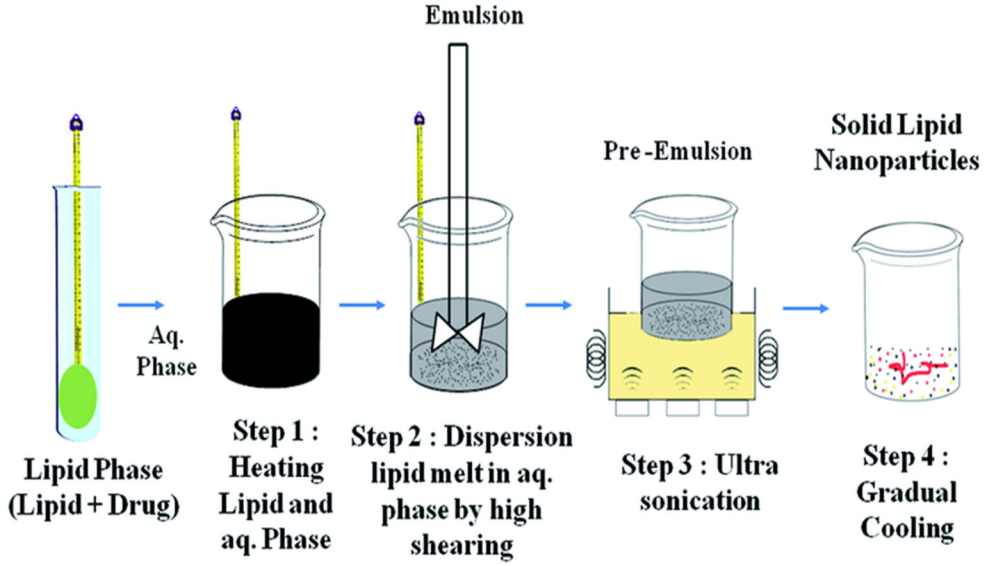


Procedure:

- The lipid (such as palmitic acid or stearic acid) is melted at a temperature above its melting point.
- Itraconazole is dissolved or dispersed in the molten lipid.
- Surfactant and co-surfactant (for example Tween 80, butanol or lecithin) are added to the lipid phase.
- Warm distilled water is added slowly with gentle stirring to form a transparent microemulsion.
- The hot microemulsion is then rapidly dispersed into cold water (2–10 °C) with continuous stirring.
- Sudden cooling causes precipitation and crystallization of lipid droplets.
- This results in the formation of solid lipid nanoparticles containing itraconazole.(49)

4.3. Melt-Emulsification and Ultrasonication Method

In this method, itraconazole-loaded SLNs are prepared using melt emulsification followed by ultrasonication. Sonication helps reduce droplet size and produce nanoparticles with uniform distribution.



Procedure

A lipid such as stearic acid or glyceryl monostearate is melted above its melting point.

Itraconazole is dissolved in the molten lipid phase.

The aqueous phase containing an emulsifier (such as polyvinyl alcohol or Tween 80) is heated to the same temperature.

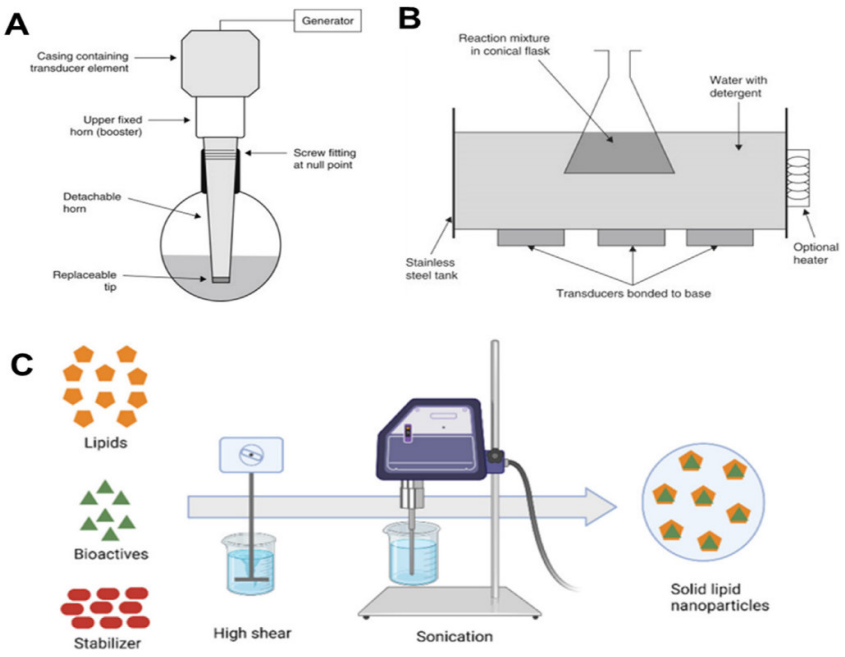
The hot aqueous phase is added to the molten lipid with continuous stirring to form a coarse emulsion.

The emulsion is subjected to probe ultrasonication for several minutes to reduce particle size.

The resulting nanoemulsion is cooled at room temperature.

Upon cooling, the lipid phase solidifies and forms itraconazole-loaded solid lipid nanoparticles (50).

4.4. High-Shear Homogenization Method



High-shear homogenization is another commonly reported technique for preparing itraconazole-loaded SLNs. This method uses mechanical energy to reduce particle size and produce nanoscale lipid particles.

Procedure

The lipid phase containing itraconazole is melted above its melting temperature.

An aqueous surfactant solution (such as Poloxamer or Tween 80) is prepared separately and heated to the same temperature.

The molten lipid phase is slowly added to the hot aqueous phase with continuous stirring.

The mixture is subjected to high-shear homogenization using a high-speed homogenizer (10,000–20,000 rpm).

Homogenization produces a fine oil-in-water nanoemulsion.

The nanoemulsion is allowed to cool gradually.

Cooling results in solidification of lipid droplets, producing itraconazole SLNs.(51)

5. MECHANISM OF ACTION

Itraconazole Solid Lipid Nanoparticles (SLNs)

⬇

Inhibition of fungal enzyme – 14-α demethylase

⬇

Block in ergosterol synthesis

⬇

Damage to fungal cell membrane

⬇

Fungal cell death

Encapsulation of itraconazole in SLNs

⬇

Enhanced solubility of drug

⬇

Improved bioavailability

⬇

Better skin penetration

⬇

Sustained and targeted drug release

⬇

Minimized side effects

6. ADVANTAGES OF ITRACONAZOLE SOLID LIPID NANOPARTICLES

- Improved Solubility and Bioavailability
- Enhanced Skin Penetration
- Sustained and Controlled Release
- Reduced Side Effects and Toxicity (52, 53, 54)

7. Conclusion

Itraconazole-loaded solid lipid nanoparticles represent a promising strategy for improving antifungal therapy in aspergillosis. SLNs enhance drug solubility, bioavailability, and targeted delivery while reducing toxicity. The use of lipid-based nanocarriers has demonstrated significant potential in overcoming limitations associated with conventional itraconazole formulations. Continued research in nanotechnology-based drug delivery systems is expected to lead to improved treatment options for invasive fungal infections such as aspergillosis.

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