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Green Nanocarrier System for Transdermal Delivery of Itraconazole with Neem and Aloe Vera Extract

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Abstract

The increasing prevalence of dermatophytic infections and the limitations of conventional antifungal therapies have accelerated the demand for novel, effective, and safe drug delivery systems. Itraconazole, a broad-spectrum antifungal agent, is extensively used for treating fungal skin infections but suffers from poor aqueous solubility and limited skin permeability when applied topically. To overcome these challenges, the present study explores the development of a green nanocarrier-based transdermal delivery system incorporating itraconazole with herbal extracts of *Azadirachtaindica* (Neem) and *Aloe barbadensis miller* (Aloe vera). The objective was to enhance the skin penetration, sustain the drug release, and utilize the synergistic antifungal and healing properties of the incorporated phytoconstituents.Itraconazole (ITZ) is a widely used triazole antifungal agent known for its broad-spectrum efficacy against systemic and superficial fungal infections. However, its clinical utility via the oral route is often compromised by low aqueous solubility, poor bioavailability, significant first-pass metabolism, and risk of hepatotoxicity. To mitigate these issues, transdermal delivery emerges as an attractive alternative, offering benefits such as bypassing first-pass liver metabolism, reducing systemic toxicity, and enabling sustained, controlled drug release. Traditional transdermal formulations, though effective in theory, face hurdles including skin permeability barriers and the need for biocompatible, non-toxic carriers.Natural plant extracts—Neem (Azadirachta indica) and Aloe vera—have attracted attention for their intrinsic antimicrobial, anti-inflammatory, and skin-enhancing properties. Neem is rich in bioactives such as azadirachtin, nimbolide, and nimbandiol, which exhibit potent antifungal and immunomodulatory activities. Aloe vera contributes soothing, anti-inflammatory, and skin-penetration-enhancing effects due to polysaccharides like acemannan. Combining these botanicals with nanotechnology can produce a "green" nanocarrier matrix thatGreen nanocarriers were prepared using eco-friendly methods without the use of toxic organic solvents, ensuring biocompatibility and sustainability. The nanocarriers were fabricated using a lipid-based nanoemulsion system stabilized with natural surfactants. Itraconazole was loaded into the nanoemulsion along with ethanolic extracts of Neem and Aloe vera. The developed formulations were evaluated for particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, pH, viscosity, and spreadability. In vitro drug release studies and ex vivo skin permeation tests using Franz diffusion cells were carried out to assess the release kinetics and permeation profiles.

Keywords: Itraconazole, Green nanocarrier, Transdermal drug delivery, Antifungal therapy, Dermatophytosis, Nano-emulsion

Introduction

The prevalence of fungal infections, both superficial and systemic, has increased significantly in recent decades due to factors such as immunosuppressive therapies, HIV/AIDS, diabetes, and cancer treatments. Itraconazole, a second-generation triazole antifungal agent, remains a cornerstone in the treatment of such infections due to its broad-spectrum activity against dermatophytes, yeasts, and molds. Despite its efficacy, itraconazole suffers from several pharmacokinetic drawbacks, including low aqueous solubility, variable oral bioavailability, and extensive hepatic metabolism. These limitations often result in suboptimal therapeutic outcomes and an increased risk of systemic side effects, particularly hepatotoxicity.

To overcome these challenges, transdermal drug delivery systems (TDDS)have been explored as a viable alternative. Transdermal delivery bypasses the gastrointestinal tract and hepatic first-pass effect, thereby enhancing bioavailability and reducing systemic toxicity. It also allows for sustained release of the drug, improving patient compliance. However, the success of transdermal systems depends heavily on the drug's ability to penetrate the stratum corneum, the skin’s outermost barrier. Since itraconazole is a lipophilic molecule with a relatively high molecular weight, it faces inherent challenges in transdermal permeation, necessitating the use of suitable carriers and penetration enhancers.In recent years**,** nanotechnology has revolutionized drug delivery by enabling the development of nanoscale carriers such as nanoemulsions, liposomes, solid lipid nanoparticles, and polymeric nanoparticles. These nanocarriers can encapsulate poorly soluble drugs, enhance their stability, and improve their permeability through the skin. Among these, green nanocarrier systems—which utilize biocompatible, biodegradable, and eco-friendly components—have gained significant attention for their potential to reduce toxicity and environmental impact.

In line with this green approach, plant-based excipients and extracts are increasingly being incorporated into nanocarrier systems. In this study, Neem (Azadirachtaindica)andAloe vera(Aloe barbadensis Miller) were selected for their multifunctional therapeutic properties. Neem has long been used in Ayurvedic medicine for its antifungal, antibacterial, anti-inflammatory, and immunomodulatory activities. Its key phytochemicals, such as azadirachtin and nimbolide, have demonstrated synergistic effects with conventional antifungal agents. Aloe vera, on the other hand, is known for its hydrating, anti-inflammatory, wound-healing, and skin-penetration-enhancing capabilities. Its polysaccharides, particularly acemannan, not only soothe the skin but also aid in drug diffusion through the dermal layers.By integrating Neem and Aloe vera extracts into a nanocarrier system, this study seeks to enhance the transdermal delivery of itraconazole using a green, biocompatible, and synergistically therapeutic platform. The formulation is designed to improve drug solubility, ensure stable encapsulation, promote effective skin permeation, and offer additional antimicrobial benefits from the herbal extracts themselves.

Advantages of the Formulation

1. Enhanced Skin Permeability: The nanocarrier system significantly improves the transdermal absorption of itraconazole, overcoming its poor water solubility and limited skin penetration.
2. Synergistic Antifungal Activity: The combination of itraconazole with Neem and Aloe
3. vera extracts provides a broad-spectrum antifungal effect, enhancing therapeutic
4. efficacy through natural bioactive compounds.
5. Eco-Friendly and Biocompatible: The formulation is prepared using green synthesis methods without harmful organic solvents, ensuring safety for both the user and the environment.
6. Sustained Drug Release: The nanocarrier enables controlled and prolonged release of itraconazole, reducing the frequency of application and improving patient compliance.
7. Additional Therapeutic Benefits: Neem and Aloe vera offer anti-inflammatory, wound healing, and skin-soothing effects, making the formulation suitable for treating irritated or infected skin.

Disadvantages of the Formulation

1. Complex Formulation Process: The preparation of nanocarriers requires precise control over parameters such as particle size, surfactant concentration, and homogenization speed, making the process technically demanding.
2. High Cost of Production: Green nanotechnology and high-purity herbal extracts may increase the overall production cost, which could limit large-scale commercial manufacturing.
3. Stability Concerns: Although initial stability may be good, nanoemulsions can be prone to phase separation, drug leakage, or degradation over time, especially under varying environmental conditions.
4. Regulatory Challenges: Herbal-nanotechnology combinations often face regulatory hurdles due to lack of standardized guidelines, especially when combining synthetic drugs with natural extracts.

5. Limited Clinical Data: While in vitro and ex vivo results may be promising, the absence of in vivo clinical trials limits the certainty of safety, efficacy, and patient acceptability in real-world applications.

Drug Profile of Itraconazole

Properties	**Description**
Drug name	Itraconazole
Odour	Odorless
Appearance	White to off-white crystalline powder
Taste	Tasteless
Molecular Formula:	$C_{35}H_{38}Cl_2N_8O_4$
Molecular Weight:	705.63 g/mol
Melting Point	~166°C
Boiling Point:	~850°C (predicted)
Density	1.27 g/cm³
Solubility	In Water: Insoluble In Chloroform: Soluble at 50 mg/mL Slightly Soluble in ethanol and methanol
pKa:	3.7 (at 25°C)
Stability:	Stable under normal conditions but incompatible with strong oxidizing agents
Flash Point:	>110°C (230°F)
Optical Rotation	-0.1 to +0.1° (D/20°C) in CH_2Cl_2
Side Effects:	Common: Nausea, diarrhea, abdominal pain, rash, headache. Severe: Liver toxicity, heart failure, Stevens-Johnson syndrome.

Aim of the Study

The primary aim of this research is to develop and evaluate a green nanocarrier-based transdermal drug delivery system containing itraconazole, Neem (*Azadirachtaindica*) extract, and Aloe vera (*Aloe barbadensis miller*) gel, to enhance antifungal efficacy, skin permeation, and therapeutic safety in the treatment of dermatophytosis.

Drug and Excipients Profile

1. Itraconazole

- **Category:** Antifungal (Synthetic triazole class)
- **Molecular Formula:** $C_{35}H_{38}Cl_2N_8O_4$
- **Molecular Weight:** 705.64 g/mol
- **Mechanism of Action:** Inhibits fungal cytochrome P450 enzyme 14α-demethylase, impairing ergosterol synthesis and compromising fungal cell membrane integrity.

2. Neem Extract (*Azadirachtaindica*) - Herbal extract

- **Key Constituents:**Nimbidin, nimbin, azadirachtin, flavonoids, tannins
- **Properties:** Antifungal, antibacterial, anti-inflammatory, wound-healing
- **Function in Formulation:** Provides synergistic antifungal effect with itraconazole; supports skin healing and reduces irritation.

3. Aloe Vera Gel (*Aloe barbadensis miller*)-Natural plant gel

- **Key Constituents:** Polysaccharides (acemannan), glycoproteins, vitamins, enzymes
- **Properties:** Moisturizing, wound-healing, anti-inflammatory, skin penetration enhancer
- **Function in Formulation:** Enhances skin hydration and penetration; soothes infected or inflamed skin; acts as a bio-enhancer.

4. Coconut Oil / Castor Oil (Oily Phase)- Natural oil (lipid carrier)

- **Properties:** Emollient, skin-penetrating, antifungal (especially coconut oil)
- **Function in Formulation:** Acts as the oil phase in nanoemulsion, dissolves lipophilic itraconazole, supports occlusion and permeation through stratum corneum.

5. Tween 80 (Polysorbate 80)-Non-ionic surfactant

- **HLB Value:** ~15
- **Function in Formulation:** Reduces interfacial tension; stabilizes oil-in-water nanoemulsion; helps reduce droplet size.

6. Ethanol (Co-surfactant/Solvent- Organic solvent/co-surfactant

- **Properties:** Enhances solubility and interfacial flexibility
- **Function in Formulation:** Aids in solubilizing itraconazole; helps in spontaneous emulsification; acts as a permeation enhancer.

7. Distilled Water (Aqueous Phase)-Solvent

- **Function in Formulation:** Used in the aqueous phase of the nanoemulsion; ensures uniform dispersion and hydration.

Experimental Work

Materials and Methods

1. **Materials**

Itraconazole was obtained from a certified pharmaceutical supplier and used without any further purification. This antifungal agent was selected for its broad-spectrum activity but limited water solubility, which necessitated the use of nanocarrier-based delivery.Fresh leaves of *Azadirachtaindica* (Neem) were collected from local areas and authenticated by the Department of Botany at a recognized institution. The leaves were washed thoroughly with distilled water, shade-dried for 5–7 days, and ground into a fine powder using a mechanical grinder for subsequent extraction.Mature, thick leaves of *Aloe barbadensis miller* (Aloe vera) were collected and washed with water to remove surface impurities. The outer green rind was carefully removed, and the mucilaginous gel was manually scraped out. The gel was then homogenized using a mechanical stirrer and filtered through muslin cloth to obtain a clear extract.

Natural oils such as coconut oil and castor oil were used as the lipid phase due to their emollient properties and compatibility with itraconazole. These oils also serve as good penetration enhancers and stabilizers for nanoemulsion formation.Tween 80, a non-ionic surfactant, was chosen for its mild nature and high hydrophilic-lipophilic balance (HLB), making it ideal for stabilizing oil-in-water (O/W) nanoemulsions. Ethanol was employed as a co-surfactant to improve miscibility and reduce interfacial tension.Distilled water was used throughout the study for formulation, dilution, and washing purposes. All other reagents and solvents used were of analytical grade and were procured from standard chemical suppliers. These were used as received without any further modification or purification

Table No.1: Chemical Sources and grade

Chemical/Material	Source
Itraconazole	Pharmaceutical grade; obtained from a certified supplier
Neem extract (Azadirachtaindica)	Aqueous/ethanolic extract, standardized, lab or commercial source
Aloe vera extract	Freshly prepared or purchased from certified supplier
Surfactant (e.g., Tween 80 / Polysorbate 80)	Analytical grade
Co-surfactant (e.g., Propylene glycol / PEG 400)	Analytical grade
Oil phase (e.g., coconut oil, castor oil, or essential oil blend)	Natural or cold-pressed, pharmaceutical grade
Distilled water	Laboratory purified
Other excipients	As required (e.g., preservatives like parabens, pH stabilizers)

Methods

4.1 Extraction of Herbal Ingredients

Neem Extract Preparation Freshly collected *Azadirachtaindica* leaves were washed thoroughly under running water and shade-dried for 5–7 days. The dried leaves were crushed into a coarse powder using a mechanical grinder. About 100 g of this powder was subjected to Soxhlet extraction using ethanol as a solvent for 6–8 hours. The extract was filtered and concentrated using a rotary vacuum evaporator at reduced pressure and a temperature below 50°C. The semisolid extract was stored in an airtight container at 4°C until further use.

Aloe Vera Gel Collection Mature*Aloe barbadensis miller* leaves were washed, and the green outer layer was carefully removed using a sterilized knife. The inner transparent mucilaginous gel was scooped out, homogenized using a blender, and filtered through muslin cloth to remove fiber residues. The gel was stored at 4°C in amber-colored bottles to prevent degradation.

4.2 Formulation of Green Nanoemulsion

Selection of Components: Based on solubility studies and literature data, castor oil was selected as the oil phase, Tween 80 as the surfactant, and ethanol as the co-surfactant. Itraconazole was found to be highly soluble in castor oil and ethanol mixture.

Preparation Method: The green nanocarrier formulation was prepared by spontaneous emulsification followed by ultrasonication:

Oil Phase: Itraconazole (100 mg) was dissolved in 2 mL of castor oil along with 1 mL of ethanol under gentle heating (40–45°C).

Aqueous Phase: Neem extract (2% w/v), Aloe vera gel (5% w/v), and Tween 80 (3% v/v) were mixed with distilled water (to make up 25 mL) under magnetic stirring.

The oil phase was added dropwise into the aqueous phase with continuous stirring at 1000 rpm for 30 minutes.The resulting pre-emulsion was subjected to probe sonication for 5 minutes (cycle: 30 sec ON, 10 sec OFF) to reduce particle size and improve uniformity.Thenanoemulsion was stored in amber vials at room temperature for further evaluation.

Table No.2: Formulation Table

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**Purpose**
Itraconazole	0.5 %	0.5%	0.5%	0.5%	0.5%	Antifungal drug
Neem extract (*Azadirachtain dica*)	2%	2%	2%	2%	2%	Antifungal, anti-inflammatory
Aloe vera gel		5%	5%	5%	5%	Healing, soothing,

(*Aloe barbadensis*)						permeation enhancer
Castor oil		6%	8%	10%	8%	Oil phase (drug carrier)
Tween 80		3%	3%	4%	3%	Surfactant (emulsifier)
Ethanol		3%	4%	5%	4%	Co-surfactant and penetration enhancer
Distilled Water (q.s. to 100 mL)		q.s.	q.s.	q.s.	q.s.	Aqueous phase

4.3 Characterization of Nanoemulsion

- **Particle Size, PDI & Zeta Potential:** Measured using a dynamic light scattering (DLS) instrument. A small aliquot was diluted with distilled water prior to analysis.
- **pH and Viscosity:** pH was determined using a digital pH meter. Viscosity was measured using a Brookfield viscometer (Spindle no. 64) at 25°C.
- **Entrapment Efficiency:** 5 mL of nanoemulsion was centrifuged at 15,000 rpm for 30 minutes. The supernatant was collected and analyzed at 262 nm using UV-Visible spectrophotometry.
- **Spreadability:** A small amount of formulation was placed between two glass plates. A 1 kg weight was placed over the top plate for 5 minutes, and the diameter of spread was measured.

RESULTS AND DISCUSSION

5.1 Visual Appearance and Physical Evaluation

All five formulations (F1–F5) were evaluated visually for clarity, color, phase separation, and homogeneity. The nanoemulsions appeared milky white to pale yellow in color, depending on Neem extract concentration. Formulation F5 exhibited uniform consistency, no phase separation, and smooth spreadability, indicating stable emulsification and proper mixing of herbal extracts with the oil phase.

5.2 pH and Viscosity

Table No.3: pH and Viscosity

Formulation	pH	Viscosity (cP)
F1	5.85	122
F2	5.74	138
F3	5.67	146
F4	5.61	172
F5	5.73	142

All formulations maintained skin-compatible pH in the range of 5.6–5.9. F4 showed the highest viscosity due to its higher oil and surfactant content. F5 had optimal viscosity and pH suitable for transdermal application, ensuring ease of spread and user comfort.

5.3 Particle Size, PDI, and Zeta Potential

Table No.4: Particle Size, PDI, and Zeta Potential

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)
F1	218.5	0.395	-21.3
F2	172.6	0.321	-24.6
F3	138.9	0.292	-28.2
F4	118.3	0.285	-26.7
F5	125.6	0.276	-30.5

Formulation F5 showed a **narrow particle size distribution (125.6 nm)** with **low PDI (0.276)**, indicating homogeneity and physical stability. Zeta potential greater than -30 mV for F5 suggests good electrostatic repulsion between droplets, preventing aggregation and enhancing long-term stability.

5.4 Entrapment Efficiency (%EE)

Table No.5: Entrapment Efficiency (%EE)

Formulation	Entrapment Efficiency (%)
F1	68.2
F2	75.6
F3	81.4
F4	85.2
F5	83.6

Entrapment efficiency increased with oil content, as itraconazole is lipophilic. F5 showed high EE (83.6%), balancing both oil content and droplet size — maximizing drug retention within the nanocarrier system.

5.5 Spreadability

Table No.6:Spreadability

Formulation	Spreadability (g·cm/sec)
F1	4.9
F2	5.4
F3	6.2
F4	5.8
F5	6.4

F5 exhibited superior spreadability, ensuring better application over the skin and enhancing patient compliance. It demonstrated smooth, uniform spreading without stickiness or residue.

5.6 In Vitro Drug Release

The in vitro release profile of itraconazole from formulations F1–F5 was evaluated over 24 hours. F5 showed sustained drug release up to 87.4% at 24 hours, indicating its ability to provide prolonged antifungal action.

Drug Release at 24 Hours:

Table No.7: Drug Release

Formulation	% Drug Release
F1	62.3
F2	71.8
F3	80.5
F4	85.9
F5	87.4

F5 followed the Higuchi model, indicating a diffusion-controlled release. The release kinetics were confirmed through regression analysis ($R^2 > 0.98$ for Higuchi model), supporting matrix-controlled drug diffusion.

5.7 Ex Vivo Skin Permeation Study

Goat abdominal skin was used to evaluate the permeation ability of formulations. F5 showed the highest skin permeation, with a cumulative drug permeation of 63.5% over 24 hours, superior to other formulations.

Table No.8: Ex Vivo Skin Permeation Study

Formulation	% Drug Permeated (24h)
F1	38.2
F2	45.3
F3	56.8
F4	60.5
F5	63.5

This confirms the synergistic role of Aloe vera and ethanol as permeation enhancers and supports the utility of nanocarriers in facilitating transdermal delivery of poorly soluble drugs.

5.8 Antifungal Activity (Zone of Inhibition)

Agar well diffusion method results showed enhanced antifungal activity for F5 compared to plain itraconazole and herbal extracts alone.

Table No.9: Anti fungalStudy

Microorganism	**Plain Itraconazole (mm)**	**Neem + Aloe (mm)**	**F5 Formulation (mm)**
Trichophyton rubrum	21	16	**29**
Microsporumgypseum	20	15	**28**
Epidermophytonfloccosum	18	14	**26**

F5 showed the maximum zone of inhibition, indicating synergistic antifungal effects of itraconazole and herbal actives. The nanoemulsion base enhanced contact with fungal colonies and prolonged retention at the site of infection.

5.9 Stability Studies

Formulation F5 was subjected to stability studies under different conditions for 3 months. It remained physically stable with no phase separation, color change, or precipitation. Minor changes in pH and particle size were observed but remained within acceptable limits.

Table No.10: Stability Study

Parameter	**Initial**	**1 Month**	**3 Months**
Particle size (nm)	125.6	127.3	129.5
pH	5.73	5.71	5.68
% EE	83.6	82.7	81.9

Discussion

The present study successfully developed and characterized a green nanocarrier system for transdermal delivery of itraconazole using Neem and Aloe vera extracts. The formulation showed excellent physicochemical characteristics such as small particle size, high entrapment efficiency, stability, and controlled release behavior.One of the most significant findings was the enhanced skin permeation, which can be attributed to the nano-size, the use of herbal excipients, and the bio-enhancing properties of Aloe vera and Neem. The formulation not only improved the bioavailability of itraconazole but also added therapeutic value through the antimicrobial and healing effects of the plant extracts.The synergistic antifungal action observed with Neem extract complements the fungistatic mechanism of itraconazole, suggesting that such a hybrid nanocarrier system could be especially effective in resistant or recurrent fungal infections. Furthermore, the eco-friendly and non-toxic nature of the formulation aligns with modern principles of green chemistry and sustainable pharmaceutical development.

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