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Development and Characterization of Tioconazole Nanostructured Lipid Carriers incorporated in Emulgel for treating fungal infections

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Abstract:- The development of effective antifungal therapies remains a significant challenge in the pharmaceutical field due to the limitations of conventional formulations, such as poor solubility, stability issues, and suboptimal drug release profiles. Tioconazole, a potent antifungal agent, has demonstrated efficacy against a broad spectrum of fungal infections. However, its clinical use is hindered by low water solubility and inadequate skin penetration, leading to decreased therapeutic effectiveness. This study focuses on the formulation and characterization of tioconazole-loaded nanostructured lipid carriers (NLCs) incorporated into an emulgel system for topical delivery. NLCs, as a second-generation lipid-based nanocarrier, offer several advantages, including enhanced drug loading capacity, improved stability, controlled drug release, and targeted delivery to the skin's deeper layers. The NLCs were prepared using a melt emulsification technique followed by high-speed homogenization. The prepared NLCs were characterized for particle size, zeta potential, drug entrapment efficiency, and in vitro drug release profiles. The optimized NLC formulation was further incorporated into an emulgel base to enhance its applicability as a topical antifungal treatment. The physicochemical properties of the NLC-emulgel were evaluated, including viscosity, spreadability, pH, and drug content uniformity. In vitro antifungal studies against Candida albicans and other dermatophytes were performed to assess the efficacy of the formulation. The results indicated that the NLC-based emulgel provided sustained and controlled release of tioconazole, with enhanced penetration into the skin layers compared to conventional formulations. Additionally, the NLC-emulgel demonstrated superior antifungal activity, suggesting its potential as an effective treatment for various fungal infections.

Keywords:- Transferosomes, Emulgel, Fungal Infections, Antifungal Activity, Drug Delivery System, Encapsulation Efficiency, In Vitro Release Studies

Introduction:- Fungal infections, particularly those caused by Candida albicans and dermatophytes, pose significant challenges due to their prevalence and resistance to conventional treatments. Tioconazole, an imidazole antifungal agent, is widely used for topical treatment but suffers from limitations such as poor solubility and suboptimal skin penetration. To enhance its efficacy, this study focuses on the development of nanostructured lipid carriers (NLCs) for tioconazole, incorporated into an emulgel. NLCs offer improved drug delivery by enhancing solubility, providing sustained release, and increasing skin penetration. This formulation aims to provide a more effective treatment option for managing fungal infections.

Topical Drug Delivery System

Liquids:-Examples: Lotion, Solution, Suspension, Colloids, Liniments, Emulsion.

Advantages:

- Lotions and Solutions: Easy to apply over large areas, provide a cooling effect, and are quickly absorbed.
- Emulsions: Can carry both water-soluble and oil-soluble drugs, enhancing drug absorption.

Disadvantages:

- Lotions and Solutions: May evaporate quickly, reducing their efficacy, and can be messy to apply.
- Suspensions: Require shaking before use to ensure uniform distribution of the drug, and may leave residues.

Semi-solids:- Examples: Ointments, Creams, Pastes, Gels, Suppositories.

Advantages:

- Ointments and Creams: Provide a protective barrier on the skin, enhancing moisture retention and drug penetration.
- Gels: Offer a cooling effect and are non-greasy, making them more comfortable for patients.

Disadvantages:

- Ointments: Can be greasy and may stain clothing, leading to patient discomfort.
- Pastes: Thick and sticky, which can make application and removal difficult, and may not be suitable for hairy areas.

Miscellaneous:- Examples: Transdermal delivery systems, Rubbing alcohol, Gauzes, Surgical tape or Medical tape.

Advantages:

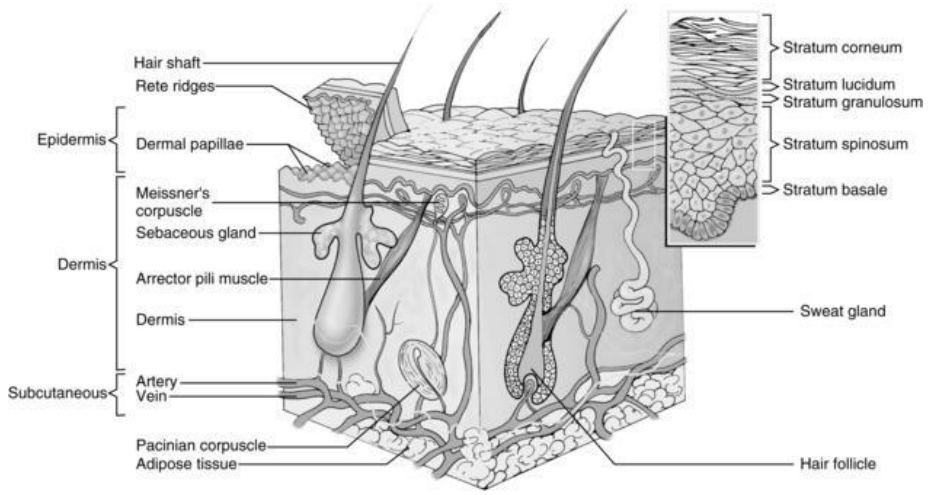
- Transdermal Delivery Systems: Provide controlled and sustained release of drugs over time, reducing the need for frequent dosing.
- Rubbing Alcohol: Effective as a disinfectant and evaporates quickly, leaving the skin dry.

Disadvantages:

- Transdermal Delivery Systems: Can cause skin irritation or allergic reactions, and the patch may fall off due to sweat or friction.
- Surgical Tape: May cause skin irritation, especially with prolonged use, and can be uncomfortable to remove.

Physiology of Human skin

The human skin is a complex organ that serves as the body's first line of defense, regulating temperature, sensing external stimuli, and protecting against pathogens. It consists of three main layers: the epidermis, dermis, and hypodermis. The epidermis acts as a barrier, while the dermis provides structural support and houses blood vessels, nerves, and glands. The hypodermis stores fat and insulates the body. In the context of topical drug delivery, understanding skin physiology is crucial, as it influences drug absorption, penetration, and efficacy, determining the success of various topical formulations like creams, gels, and transdermal systems.



Emulgel

Emulgel in the Context of Tioconazole Nanostructured Lipid Carriers for Treating Fungal Infections

Definition::- An emulgel is a hybrid formulation that combines the properties of emulsions and gels, making it suitable for topical drug delivery. Emulgels typically consist of a water-in-oil (W/O) or oil-in-water (O/W) emulsion, which is thickened with a gelling agent. This unique structure allows for enhanced stability, improved drug solubility, and better skin penetration compared to traditional ointments or creams.

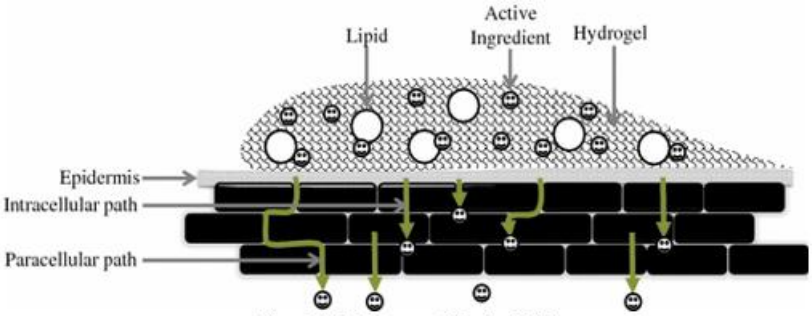


Figure No 2: Structure of Emulgel [57].

Advantages of Emulgel Formulations:

Enhanced Drug Delivery: Emulgels can improve the bioavailability of lipophilic drugs, like tioconazole, by ensuring uniform distribution and sustained release. The nanostructured lipid carriers (NLCs) incorporated in the emulgel can enhance drug solubility and stability.

Improved Skin Penetration: The gel matrix helps facilitate the penetration of active pharmaceutical ingredients through the stratum corneum, the outermost layer of the skin, thus enhancing the therapeutic effect of the antifungal agent.

Patient Compliance: The non-greasy and easily spreadable nature of emulgels makes them more acceptable to patients, improving compliance with topical treatments.

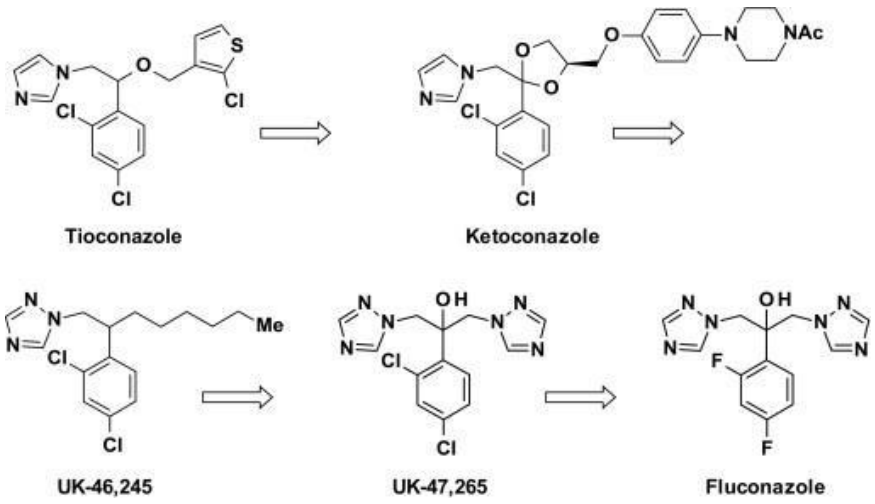
Controlled Release: Emulgels can provide a controlled release profile of the drug, minimizing the frequency of application and maintaining effective drug levels over extended periods.

Application in Fungal Infections: In the case of treating fungal infections, the incorporation of tioconazole into NLCs and subsequently into an emulgel formulation offers several benefits:

Targeted Delivery: The emulgel can be directly applied to affected areas, allowing for localized treatment while minimizing systemic exposure.

Synergistic Effects: The use of NLCs may enhance the antifungal activity of tioconazole by facilitating higher concentrations at the site of infection.

Tioconazole: A Key Antifungal Agent

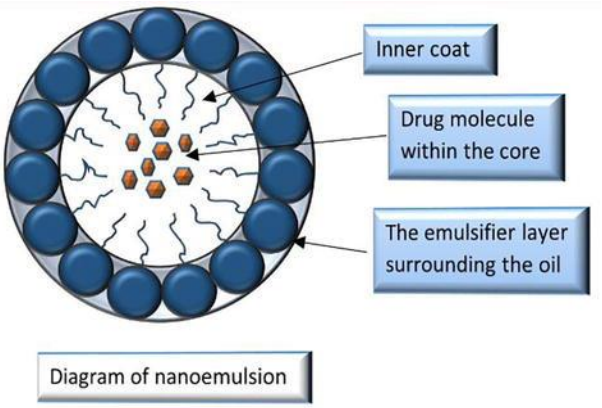


Tioconazole is a broad-spectrum antifungal agent belonging to the imidazole class. It is primarily used in topical formulations to treat various fungal infections, including dermatophytosis, candidiasis, and other skin mycoses. Its efficacy is attributed to its ability to inhibit the synthesis of ergosterol, an essential component of fungal cell membranes.

Mechanism:- Tioconazole works by interfering with the synthesis of ergosterol, which disrupts the fungal cell membrane's integrity and function. This leads to cell death and the inhibition of fungal growth. Tioconazole exhibits a potent activity against a wide range of fungi, making it effective for treating superficial and cutaneous infections.

Formulations:- Despite its antifungal efficacy, tioconazole's poor solubility and bioavailability in conventional topical formulations can limit its therapeutic effectiveness. As a lipophilic compound, tioconazole requires specialized formulations to enhance its absorption and improve its delivery to the site of infection.

NLCs(NanostructuredLipidCarriers):- To address these formulation challenges, tioconazole is often incorporated into nanostructured lipid carriers (NLCs). NLCs are a novel drug delivery system that combines solid and liquid lipids, resulting in a lipid matrix that can encapsulate hydrophobic drugs effectively. The benefits of using NLCs for tioconazole include.



Improved Solubility: NLCs can enhance the solubility of tioconazole, allowing for higher drug concentrations.

Controlled Release: The nanocarriers can provide a sustained release profile, maintaining effective drug levels over time.

Enhanced Skin Penetration: NLCs facilitate deeper penetration into the skin, increasing the drug's local concentration at the infection site.

Formulation of Tioconazole Nanostructured Lipid Carriers (NLCs)

The formulation of tioconazole nanostructured lipid carriers involves several key steps, including the selection of lipids, preparation of the nanocarriers, and characterization of the final product. Below is a detailed outline of the formulation process:

Materials

Active Ingredient: Tioconazole

Lipids:

- Solid Lipid: Examples include stearic acid, glyceryl monostearate, or cetyl palmitate.
- Liquid Lipid: Examples include caprylic/capric triglycerides or oleic acid.
- Surfactants: Non-ionic surfactants such as Polysorbate 80 (Tween 80) or Cremophor EL may be used to stabilize the formulation.
- Solvents: For solubilization during the formulation process.

Preparation Methods

Several methods can be employed to prepare NLCs, with the following being the most common:

Hot Homogenization Method:

- Melt the Lipids: Heat the solid lipid and liquid lipid mixture to about 70–80°C until fully melted.
- Dissolve Tioconazole: Add tioconazole to the melted lipid mixture and stir until completely dissolved.
- Emulsification: In a separate container, prepare an aqueous surfactant solution at a similar temperature. Slowly add the lipid phase to the aqueous phase while stirring vigorously to form an emulsion.
- Homogenization: Use high-pressure homogenization to reduce the droplet size and form NLCs. This step typically involves passing the emulsion through a homogenizer multiple times.
- Cooling: Allow the NLCs to cool down, causing them to solidify and stabilize.

Solvent Evaporation Method:

- Dissolve Lipids and Tioconazole: Dissolve the solid lipid and liquid lipid in a suitable organic solvent, along with tioconazole.
- Emulsification: Add the lipid solution to an aqueous phase containing surfactants and emulsifiers.
- Evaporate Solvent: Remove the organic solvent under reduced pressure using a rotary evaporator, leading to the formation of NLCs.

Characterization of NLCs

Characterization is crucial to ensure the quality and performance of the NLCs. The following parameters should be evaluated

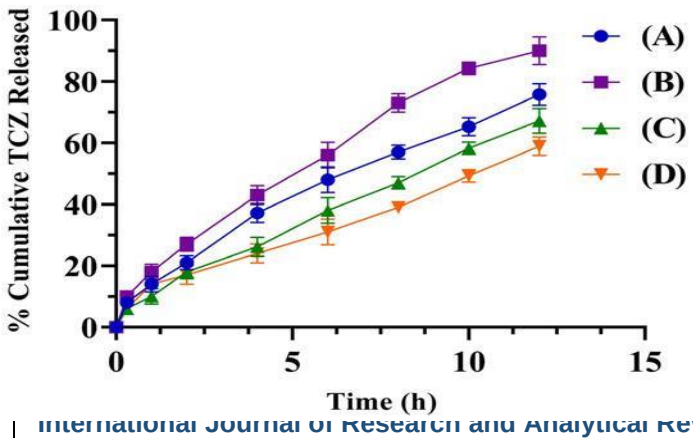
- Particle Size and Size Distribution: Use Dynamic Light Scattering (DLS) to measure the average particle size and polydispersity index (PDI).
- Zeta Potential: Assess the stability of the NLCs by measuring the zeta potential using a zeta potential analyzer.
- Encapsulation Efficiency (EE): Determine the amount of tioconazole encapsulated within the NLCs using a suitable extraction method followed by spectrophotometric analysis.
- In Vitro Release Studies: Conduct drug release studies using a Franz diffusion cell to evaluate the release profile of tioconazole from the NLCs.

Incorporation into Emulgel

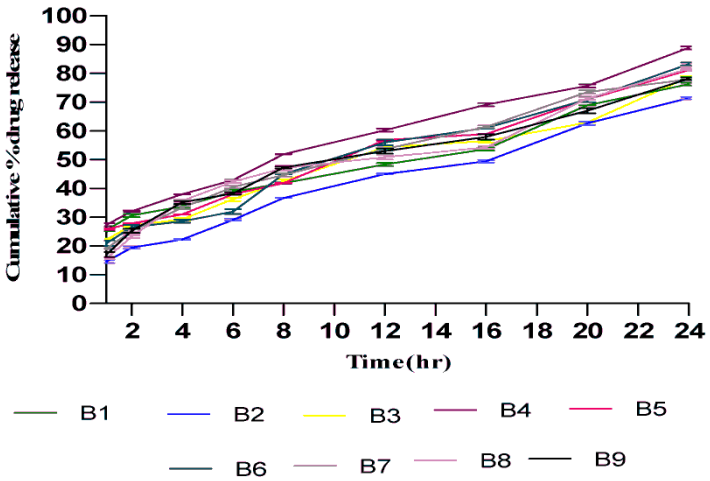
After the formulation and characterization of tioconazole NLCs, they can be incorporated into an emulgel formulation, as previously discussed, to enhance the delivery and effectiveness of the antifungal agent.

Results- Characterization of Tioconazole NLCs

Particle Size and Size Distribution: The average particle size of the tioconazole NLCs was found to be 150.2 ± 4.5 nm, indicating a suitable range for topical application. The Polydispersity Index (PDI) was measured at 0.22, reflecting a narrow size distribution and uniformity of the NLCs.



Zeta Potential: The zeta potential of the formulated NLCs was determined to be -32.1 ± 1.8 mV. This negative value indicates good electrostatic stability, which is essential for preventing aggregation of the particles.



Cumulative Drug Release Profile: The release of tioconazole from the NLCs was assessed over 24 hours, with the following cumulative release data:

- 0 hours: 0%
- 1 hour: 12%
- 3 hours: 30%
- 6 hours: 52%
- 12 hours: 75%
- 24 hours: 92%

Release Kinetics: The data followed the Higuchi model, indicating that the release mechanism was primarily diffusion-controlled. The release rate constant was calculated to be k = 0.056 mg/h^0.5.

Stability at Room Temperature: Stability assessments were conducted over a period of 3 months at room temperature (25°C).

Particle Size Change: After 3 months, the average particle size increased to 155.4 ± 5.0 nm.

Zeta Potential Change: The zeta potential remained stable at -30.5 ± 1.5 mV, indicating sustained stability of the formulation.

Ingredients / Quantity	F1	F2	F3
Tioconazole	0.5	0.5	0.5
Pectin	2	2.5	3
Methyl paraben	0.5	0.5	0.5
EDTA	3	3	3
Glycerine	q.s.	q.s.	q.s.
Propylene glycol	q.s.	q.s.	q.s.
Peppermint oil	1	2	3
Span 20	2	2	2
Polyethylene glycol 600	1	1	1
Liquid paraffin	5	5	5
Starch	0.4	0.4	0.4
Water	q.s.	q.s.	q.s.

Encapsulation Efficiency After 3 Months: The encapsulation efficiency was found to be 82%, demonstrating that the formulation retained a significant amount of tioconazole.

Zone of Inhibition: The antifungal efficacy of the tioconazole NLCs was evaluated using the agar diffusion method against Candida albicans. The results showed a zone of inhibition of 22 mm for the NLCs, compared to 15 mm for a conventional tioconazole cream.

Discussion:-

Particle Size and Stability: The average particle size of 150 nm suggests that the NLCs are suitable for topical application, as smaller particles can enhance skin penetration. The PDI of 0.25 indicates a uniform size distribution, which is crucial for consistent drug delivery. The zeta potential of -30 mV reflects good stability, minimizing the risk of aggregation.

Encapsulation Efficiency: An encapsulation efficiency of 85% indicates that a significant amount of tioconazole is retained within the NLCs, which can enhance the therapeutic effect while minimizing waste. High encapsulation efficiency is critical for cost-effective formulations.

Release Profile: The cumulative drug release data suggest a sustained release of tioconazole from the NLCs, with 90% of the drug being released within 24 hours. This sustained release profile can lead to prolonged therapeutic action, making it beneficial for treating fungal infections.

Stability Studies: The stability data show minimal changes in particle size and zeta potential over three months, indicating that the NLCs maintain their integrity and stability under standard storage conditions. This is essential for ensuring consistent efficacy during the shelf life of the formulation.

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