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Review Article

Nanotechnology-Based Transdermal Systems for Antifungal Therapy: Emphasis on Transferosomal Gels

Rohan Patil*, Sanika Jagadale, Omkar Yadav, Sakshi Vibhute

Annasaheb Dange College of B Pharmacy, Ashta, Sangli, Maharashtra, India

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ABSTRACT

This study focuses on improving the delivery and effectiveness of antifungal medications through the skin using novel transdermal formulations. The skin, being the body's largest organ, serves as a natural barrier that limits drug penetration. To overcome this, advanced systems like transferosomes ultra-flexible lipid vesicles are explored for their ability to transport drugs deeply and efficiently across skin layers. The project reviews current challenges in topical antifungal therapy, including poor drug permeability and resistance, and highlights the advantages of Transdermal Drug Delivery Systems (TDDS) such as enhanced bioavailability, avoidance of first-pass metabolism, and controlled release. Transferosomal gels, in particular, show promise due to their biocompatibility, high deformability, and ability to deliver both hydrophilic and lipophilic drugs. A series of evaluation tests including pH, spreadability, drug content, diffusion, stability, and skin irritation studies were performed to ensure safety, uniformity, and sustained drug release. The report also discusses the role of pharmacists in dermatological care and the growing influence of Artificial Intelligence (AI) in diagnostics and treatment. In conclusion, the project demonstrates that transferosome based transdermal systems offer a safe, efficient, and patient friendly approach for antifungal therapy, representing a significant step toward next-generation skin drug delivery.

INTRODUCTION

INTRODUCTION TO SKIN

The skin biggest organ of the human body. It covers and protects everything inside us. It works like a shield to stop germs, dirt, chemicals, and harmful things from entering the body[1].

***Corresponding Author:** Rohan Patil

Address: Annasaheb Dange College of B Pharmacy, Ashta, Sangli, Maharashtra, India.

Email ✉: patil.rohanadcbp@gmail.com

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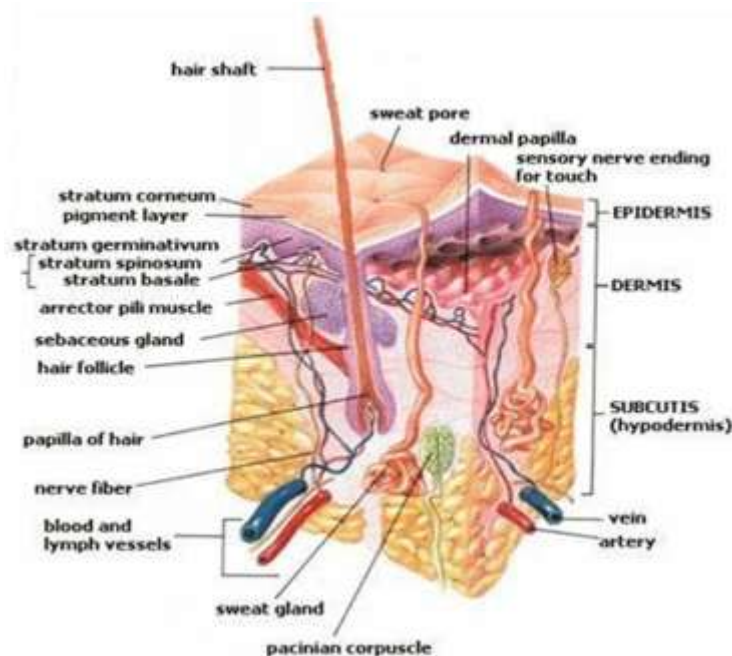


Fig 1. Cross sectional area of skin

It consists of three main structural layers:

Skin Layers	Description
Epidermis	Outermost layer, avascular, made of 5 distinct sublayers (stratum layers).
Dermis	Lies beneath the epidermis, provides structural support, elasticity, and contains blood vessels and nerves.
Hypodermis	Subcutaneous layer, composed mainly of adipose tissue, connective tissue, and blood vessels, providing cushioning and insulation.

1) Epidermis

The epidermis is avascular and varies in thickness depending on the body location. It is thinnest on the eyelids and thickest on the heels. Areas exposed to constant friction (such as fingertips or soles) develop thicker layers. Although devoid of true nerves, free nerve endings from the dermis extend into the mid-epidermis.

Layer (Superficial Deep)	Key Features
Stratum corneum	15–30 layers of dead keratinocytes (corneocytes), rich in keratin,

	providing a waterproof barrier. Cells are continuously shed and replaced (cell cycle ~30 days).
Stratum lucidum	Found only in thick skin (palms, soles). Composed of 2–3 non-living keratinocyte layers.
Stratum granulosum	Contains the highest concentration of free nerve endings. Last living cell layer of the epidermis.
Stratum spinosum	Contains Langerhans cells and lymphocytes; important for immune defense.
Stratum basale	Basal layer; only layer undergoing continuous mitosis. Produces keratinocytes which migrate outward.

2) Dermis

The dermis provides structural support and nourishes the epidermis. It is highly vascular and innervated.

- **Papillary Layer:** Interdigitates with the epidermis, forming fingerprints. Contains fibroblasts that produce collagen and elastin, giving strength and elasticity.

- **Reticular Layer:** Lies between the papillary dermis and hypodermis. Contains dense collagen fibers, blood vessels, nerves, immune cells, hair follicles, and glands. Hair follicle stem cells aid in wound healing.

3) Hypodermis

The hypodermis (subcutaneous tissue) is composed of adipose tissue and loose connective tissue. It is well vascularized and innervated. Functions include:

- a. Anchoring skin to muscle and bone
- b. Providing insulation
- c. Acting as cushioning and an energy reservoir[2].

Functions of the Skin

- **Secretion:** Secretion of sweat and sebum .Sweat removes waste from the skin and also helps control body temperature.
- **Heat regulation:** Skin allows the body to either lose heat or retain it.
- **Absorption:** The skin cannot absorb a lot of substances as it is a waterproof layer, essential oil, drugs and creams can be absorbed via pores.
- **Protection:** Skin is natural layered barrier against entry of bacteria.
- **Elimination:** Toxins such as salts ,urea and wastewater are lost through sweat glands of skin[3].

AIM & OBJECTIVES:

Aim

To investigate novel formulation strategies that enhance the bioavailability and sustained release of antifungal agents through the skin.

Objectives

1. To review the current challenges in topical antifungal therapy, including drug resistance and poor skin penetration.
2. To analyze the latest innovations in transdermal delivery systems for antifungal agents.
3. To evaluate the role of nanotechnology (e.g., nanoparticles, liposomes) in enhancing antifungal drug delivery.
4. To assess the impact of novel excipients and permeation enhancers on transdermal absorption of antifungal drugs.
5. To compare the efficacy and safety profiles of conventional versus advanced topical antifungal formulations.

LITERATURE REVIEW

1. Alhajj, M., Bansal, P., & Goyal, A, November 2022

Studied the information carried out in this review is about the anatomy and physiology of the skin and various permeation factors of the skin

2. Cohen, B., & Hull, K. (2019)

Studied the information is carried out in this review about the skin and barriers of the skin

3. Eisha Ganju, Bhaskar Gupta ,Rakhi Dixit , Oct 2022

Transferosomes are ultra-flexible lipid vesicles designed to deliver drugs through the skin more effectively than traditional creams or liposomes Topical gels, when combined with transferosomes, enhance drug stability, absorption, and patient comfort..

4. Sanjay Satya - Akunuri Koka and Craig G. Burkhardt , March 2023



Studied the information about what are the advancements in the dermatology and the role of the AI in advancement.

5. Namrata Matharoo , Hana Mohd , Bozena Michniak – Kohn Aug 2023

Delivering drugs through the skin is appealing because it avoids needles or a pill's journey through the gut – but the skin's outer layer (the stratum corneum) is a formidable barrier. This review focuses on a clever solution: transferosomes, which are ultra-flexible lipid vesicles designed to squeeze through skin pores and deliver a wide variety of therapeutics (even big ones like proteins and nucleic acids) rather than only small lipophilic drugs.

6. Roderick J.Hay MD , FRCP May – June 2006

Studied the information carried out in this review is about the introduction to fungal infection and types of the fungal infections like superficial , subcutaneous and systemic mycoses.

7. John M.Goldsmid and Wayne Melrose

Studied about the various skin infections mainly about the parasitic infections of the skin.

8. Jane C. Sterling Oct 2016

Studied about the information carried in this review is about skin diseases mainly about viral skin infections .

9. Fransesco Branda ,Nicola Petrosillo , et.al Aug 2025

Studied the information about the antifungal agents in 21st century its Advances, Challenges and future perspectives and various perspectives

about the resistance of the antifungal agents , limitations of the current antifungal agents.

10. Alhaj M ,Bansal P , Goyal A .Nov 2020

Studied the information carried out in this review is about the anatomy and physiology of the skin and different layers of the skin and permeation through the various layers of the skin.

11. Saji Ahmed and G Harini Kumari 2025

Fungal infections are a growing global concern, especially among people with weakened immune systems. Conventional antifungal creams often fail to deliver sufficient drug concentrations through the skin's tough outer layer, the stratum corneum. To address this, researchers have developed transferosomes—ultra-flexible lipid vesicles that can squeeze through tiny skin pores and deliver drugs more effectively

12. Koka, S. S.-A., & Burkhart, C. G. (2023)

Artificial Intelligence (AI) is rapidly transforming healthcare by improving diagnostic accuracy and efficiency, especially in fields like dermatology. AI-powered image analysis systems can now detect and classify skin conditions such as melanoma, eczema, and ulcers with high precision—sometimes outperforming dermatologists.

13. Parveen, S., & Mittapally, S. (2018).

Transdermal drug delivery is an effective alternative to oral or injectable routes but is limited by the skin's barrier layer. Transferosomes, flexible lipid vesicles made with phospholipids and surfactants, overcome this issue by enhancing drug penetration.

INTRODUCTION TO TDDS:



Drug administration via skin has effective approach in drug delivery .transdermal drug delivery is innovative term in pharmaceutical field of drug administration. Large dose is required and larger regimen to get therapeutic effects in Conventional drug delivery system, it has major side effects due to longer regimen which effects on patient compliance , patient may be skip the dose fluctuation in drug plasma level may occur due to avoid such kind of complications transdermal drug delivery system is used in drug administration.

TDDS is improved delivery of many pharmacological activities such as drugs, hormones , therapeutic agents, proteins and RNA based therapeutics which can degraded in GIT due to acidic environment. TDDS gives vital contributions in medicine field to achieve full potential

Transdermal delivery of particle is largely limited for SC lipids. It mainly depends upon molecular size and hydrophobicity / hydrophilicity of drug various methods developed to overcome this problem such as use of penetration enhancer, electrical impules , ultrasound etc.

TDDS delivers the solutes by following three routes:

1. The Trans- appendageal route (shunt route)
2. Transcellular route (Intracellular route)
3. Intercellular route

1. Trans-appendageal route (shunt route)

- The drug passes through tiny openings in the skin like hair follicles and sweat glands.
- These act like small tunnels that bypass the tough outer skin layer.
- Factors like sweating or oil (sebum) can affect how much drug goes through.

- Since hair follicles cover only about 0.1% of the skin surface, this route helps very little overall.

2. Intracellular (Transcellular) route

Here, the drug passes through the skin cells (called corneocytes) in the outer layer.

- These cells are filled with water and keratin (a protein), making this a good route for water- loving (hydrophilic) drugs.
- But because the cells are surrounded by fat (lipid layers), the drug has to keep switching between watery and fatty areas as it moves through, which is complicated.

3. Intercellular route

- In this case, the drug moves between the skin cells through the fatty (lipid) layers.
- As the drug moves downward, it passes through areas with different water content, so it must keep adjusting (partitioning and diffusing) until it finally reaches the deeper skin layers and then the blood[4].

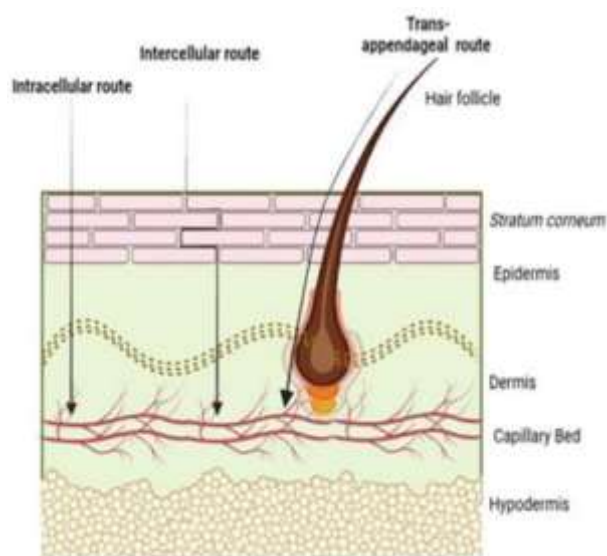


Fig 2. Permeation routes of TDDS

Advantages of TDDS:

- Avoid first pass metabolism
- Improved skin penetration
- Enhanced bioavailability
- Wide drug compatibility

- oxidative degradation
- Ingredient purity
- High production costs
- Potential skin irritation[5].

Disadvantages of TDDS:

Various formulations permeation through TDDS:

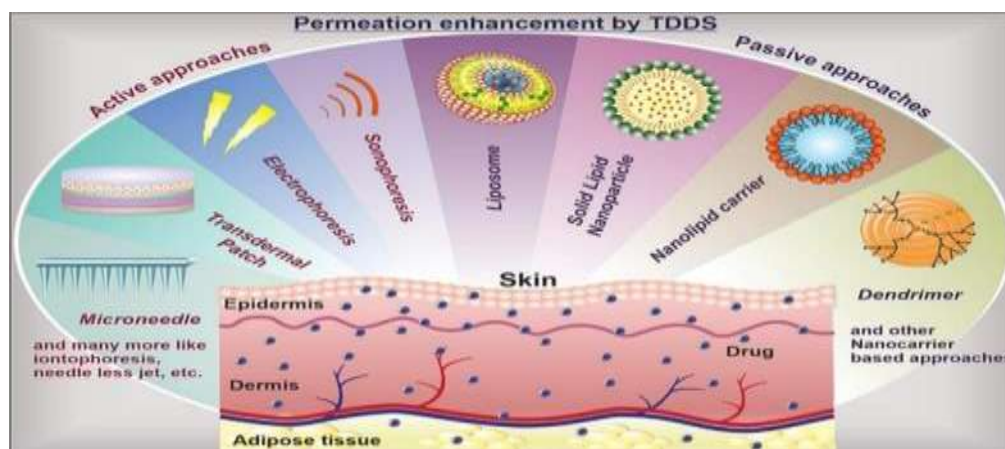


Fig 3.Overcoming skin barrier through TDDS[5].

Skin Diseases

Extrinsic Diseases

• Parasitic infections:

Caused by parasites. In parasitic infections it involves the skin and subcutaneous tissues. Depending on the species of then its involvement is transient, the parasite passing through the skin and migrates into the blood stream and at the specific site of the targeted organ or infection may get localized to skin [6].

• Viral infections:

Caused by viruses. Skin diseases due to the viruses occurs they may be primary infection of the epidermis or may arises as the secondary infections to the skin . It depends on the viruses they may cause necrotic damage of the infected cells.

• Bacterial infections:

Caused by bacteria. Also called as pyoderma this disease often commonly start as primary skin problem like impetigo or they appear as secondary in places where skin is already damaged .The main bacteria responsible are streptococci and staphylococcus aureus it can also cause folliculities (infection of hair roots).

• Fungal infections:

Caused by fungi. They are most common everywhere .They include ringworm (dermatophytosis), candidiasis, infections from malassezia (like pityriasis versicolor and other fungal infections such as scytalidium that often affects on feet. A common example is athelets foot (tinea pedis)[7].

Intrinsic Skin Diseases

- Eczema (Atopic Dermatitis)
- Psoriasis
- Seborrheic dermatitis

- Lichen planus
- Pityriasis rosea
- Secondary syphilis

Fungal Infections

Definition: Fungal infections (mycoses) are caused by fungi, either molds or yeasts. They commonly affect the skin and nails but may also involve the mouth, throat, lungs, urinary tract, or internal organs.

Fungi Characteristics:

- Separate biological category (not plants or animals).
- Spread by spores.
- Some fungi live naturally in human microbiota but can overgrow under certain conditions (immune suppression, antibiotics, diabetes) [8].

Need of focusing on fungal infections:

Before the medical advances severe fungal infections are less common. This rise of invasive and skin fungal infections are due to:

- Use of anti-inflammatory steroids
- Use of immunosuppressive drugs
- Overuse of broad-spectrum antibiotics

Antifungal resistance is also a one of the consequences. It is an escalating health concerns contributes to invasive fungal infections [9].

Types of Fungal Infections

1. Tropical Superficial Mycoses

Superficial fungal infections are common everywhere, but they occur more often in hot and humid climates. These conditions make the skin more prone to infections like dermatophytosis or Malassezia. The exact reason is not clear, but higher levels of carbon dioxide (Pco₂) on the skin surface may help fungi grow and invade. Examples include tinea Pedis (athlete's foot) and tinea infections in other body areas.

2. Subcutaneous Mycoses

These infections mainly occur in tropical and subtropical regions. They are called implantation mycoses because the fungi enter the body through the skin, usually after a minor injury. The fungi are normally found in soil or plants and get into the skin or tissue under the skin when pricked, often by thorns. Many patients do not remember the injury that caused the infection.

3. Systemic Mycoses

Systemic fungal infections affect deep organs such as the lungs, liver, and spleen. They can also spread through the blood to the skin and mucous membranes, causing widespread or localized disease [10].

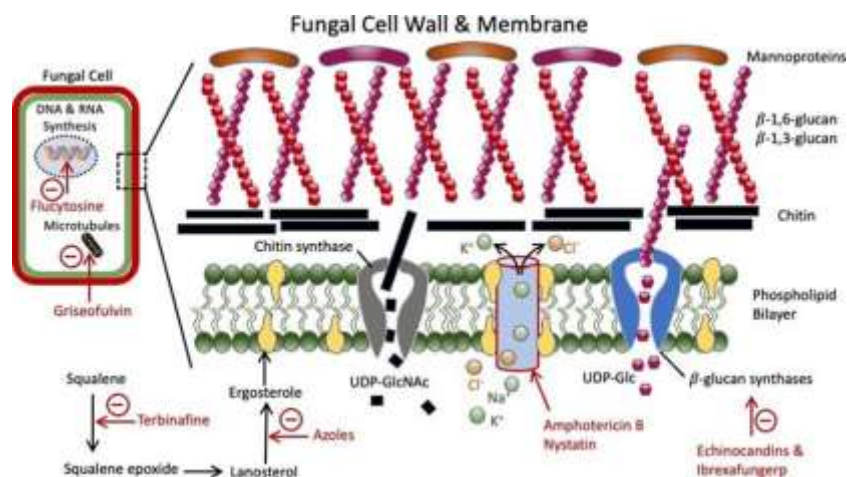


Fig 4.Mechanism of antifungal agents

Management and Treatment :

Vary depending on the site and severity of infection:

Form	Administration	Use
Oral (tablets/capsules)	Systemic treatment	Skin/ nail infections
IV therapy	Hospital setting	Severe systemic infections
Lotions, creams, powders	Topical treatment	Local skin mycoses
Mouthwash/lozenges	Oral cavity infections	Oral thrush
Eye drops	Ophthalmic fungal infections	Keratitis, endophthalmitis
Shampoo	Scalp infections	Tinea capitis, seborrheic dermatitis

Antifungal medications:

Based on their chemical structures:

Antifungal agents	Drugs	Mode of action
Azoles	Econazole, voriconazole, itraconazole, ketoconazole, cotrimazole, econazole	Inhibition of lanosterol 14α-demethylase
Echinocandins	Caspofungin, micafungin	Inhibition of 1,3 β – glucan

		synthase
Polyenes	Amphotericin B, nystatin	Binding to ergosterol
Pyrimidine analogues	Flucytosine	Inhibition of DNA /RNA/ Protein synthesis

Various formulations:

1. Cream
2. Lotion
3. Ointment
4. Liposomes
5. Transferosomes

Transferosomes:

Transferosomes are ultra-flexible vesicles developed in the 1990s to improve drug delivery through the skin. They are made from phospholipids, cholesterol, and special surfactants called edge activators, which make them highly deformable and able to pass easily through the skin barrier. Unlike regular liposomes or solid lipid nanoparticles, transferosomes can carry both water-loving and fat-loving drugs, including small and large molecules. Their flexibility allows them to deliver higher amounts of drugs deep into the skin and even into the bloodstream. They are especially useful for controlled and targeted drug delivery [11].

Advantages:

1. **Can carry many types of drugs:** Transferosomes have both water-loving (hydrophilic) and fat-loving (hydrophobic) parts, so they can deliver drugs that dissolve in either type.
2. **Can squeeze through skin easily:** They are very flexible and can pass through tiny gaps in the skin that are much smaller than their size.
3. **Works for skin and body delivery:** Their flexibility helps drugs move through the skin without losing much of the carrier, so they can be used for both local and whole-body treatments.
4. **Can carry different kinds of drugs:** Transferosomes can hold drugs of different sizes, shapes, and properties.
5. **Safe for the body:** Made from natural materials, they are biodegradable and biocompatible.
6. **Can deliver many types of medicines:** They can carry proteins, insulin, steroids, painkillers, anti-cancer drugs, and even herbal medicines.
7. **Long-lasting effect:** They can release drugs slowly over time, keeping the effect for longer [12].

Disadvantages:

1. **Chemical instability:** Transferosomes formulations can easily break down due to oxidative stress. This means they can react with oxygen and lose effectiveness.
2. **Phospholipid purity issue:** It is hard to get completely pure natural phospholipids for making transferosomes. Because of this, synthetic phospholipids can be used instead [13].

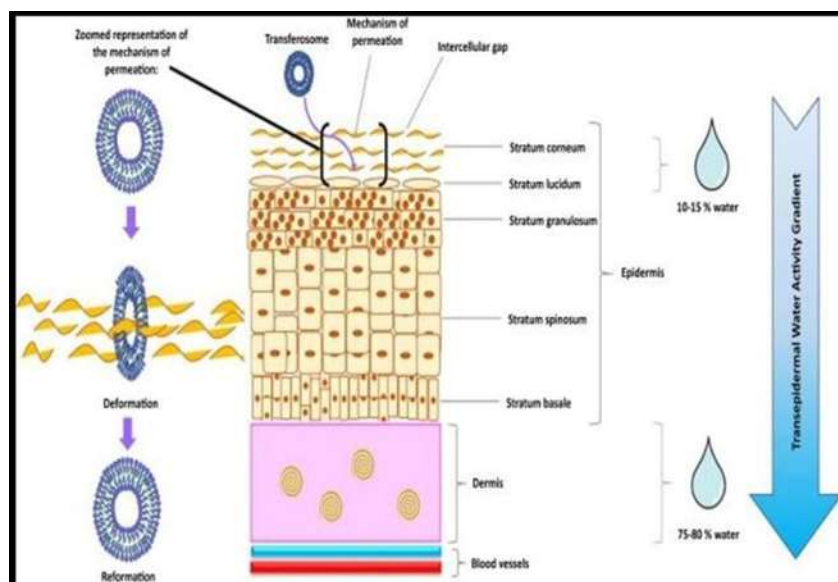


Fig 5. Mechanism of permeation through transferosomes

Basic components of transforesome gel:

- Drug
- Polymer matrix
- Penetration enhancers



- Gelling agent
- PH adjuncts
- Preservatives
- Solvent [14].

1. Drug:

Sr. no	Parameters	Properties
1	Molecular weight	Less than 500 Daltons
2	Lipophilicity	Log P between 1 & 3
3	Melting point	Less than 200
4	Pka	5.5 to 6.5
5	Skin reaction	Not irritating, not sensitizing

2. Components:

Sr. no	Class	Example	Use
1	Phospholipids	Egg Phosphatidyl Choline, Soya Phosphatidyl choline, di palamitoyl phosphatidyl choline	Vesicle forming compound
2	Solvent	Ethanol, methanol, isopropyl alcohol, chloroform	As a solvent
3	Surfactant	Sod. Chelate, Sod. Deoxycholate, Tween- 80, Span 80, Tween 20	Edge activator
4	Buffering agent	Saline phosphate, phosphate buffer	As a hydrating medium

METHODS OF PREPARATION:

1. Rotary Film Evaporation Method.

The drug (API), lecithin, and edge activator are mixed in equal parts of chloroform and ethanol

and shaken manually at a temperature higher than the lipid's melting point.

The mixture is left to evaporate, removing the organic solvents and leaving a thin lipid film overnight

The lipid film is then hydrated by rotating it at 60 RPM for 1 hour at room temperature using a pH 6.5 buffer.

The remaining vesicles are allowed to swell for 2 hours at room temperature

Finally, small vesicles are made by sonication of the swollen vesicles at room temperature

2. Reverse Phase Evaporation Method .

Lipids and organic solvents are mixed in a round-bottom flask while purging with nitrogen.

The drug is added to either a fat-loving (lipophilic) or water- loving (hydrophilic) medium, depending on its solubility

The mixture is sonicated and then left for 30 minutes to form a uniform Mixer

The organic solvents are removed under low pressure.

The remaining mixture turns into a thick gel, which forms the vesicles.

3. Vortex or Sonication Method.

Phospholipids and edge activators are mixed by continuous swirling in phosphate buffer. This forms a milky suspension.

The suspension is then sonicated in a sonicator bath.



Finally, it is passed through polycarbonate membranes to form uniform vesicles.

4. Ethanol Injection Method.

This method is considered better than others.

The drug and water are warmed at a constant temperature with continuous stirring.

Phospholipids and edge activators are mixed in ethanol.

Then added to the aqueous drug solution They react together to form the vesicles.

5. Modified Handshaking method.

In this process, the organic solvent, lipophilic drug, phospholipids, and edge activator are added into a round- bottom flask.

All these ingredients are mixed until a clear solution is formed.

Instead of using a vacuum evaporator, the solvent is removed by shaking the flask by hand.

The flask is placed in a warm water bath (about 40–60°C). As the solvent evaporates, a thin layer of lipids forms on the inner wall of the flask.

The flask is then kept overnight to let the solvent fully evaporate. The next day, the thin lipid film is gently shaken and hydrated with a suitable buffer solution at a temperature above its phase transition point

Evaluation tests:

1) pH Determination of Transfersosomal Gel :

P^H tells us whether the gel is acidic, neutral, or basic.

P^H meter is used because it gives a very accurate value. Before checking the gel, the pH meter is calibrated using standard solutions (pH 4, 7, 9). This makes sure the reading is correct. The electrode of the pH meter is dipped into the gel sample. Wait for the reading to become stable, then write it down observations. This test is done 3 times (triplicates) on different samples to avoid error. Final P^H is reported as the average of the 3 readings. Skin pH is around 5.5, so gels should ideally be close to skin P^H to avoid irritation ^[16].

2) Spreadability Test of Gel :

Spreadability means how easily the gel spreads on the skin. Good spreadability helps in better drug absorption and patient comfort. Gel is placed between the slides. Weight pulls the upper slide, and the gel spreads. The distance the slide moves and time taken is measured.

Spreadability is calculated using the formula:

$$S = m \times l \div t$$

Where:

- S = Spreadability
- m = Weight used
- l = Distance travelled (cm)
- t = Time taken (sec)

The test is repeated 3 times and the average is taken as final value.

Higher S value = Gel spreads faster. It is better patient application

Too runny gel = poor retention on skin

Too thick gel = difficult to apply

3) Drug Content in Gel



To check how much drug is actually present in the gel, we first calculate the amount of drug that should be in one normal dose. Then, we take at least 6 gel samples from different places (because gel is thick and can be uneven) to make sure the drug is spread evenly. These samples are then tested using a proper laboratory method (like UV-spectroscopy or HPLC) to confirm the correct drug content.

4) In-Vitro Diffusion / Drug Release Study

The drug release from the gel is tested in the lab using a Franz diffusion cell.

A dialysis membrane is placed between: Donor compartment in transferosome gel (one dose) & Receptor compartment in phosphate buffer (pH 7.4), which acts like body fluid. The setup is kept at 32°C (similar to skin temperature) and stirred at 50 rpm to mimic real skin conditions. Samples are taken from the receptor compartment at different time intervals through a side tube. Each sample is then analyzed to check how much drug has passed through the membrane.

5) Skin Irritation Test:

Guinea pigs (400–500 g) were used to check whether the gel causes irritation on the skin. They were kept under normal lab conditions with proper food and water. Hair from the back of each animal was shaved, and two small areas (4 cm² each) were marked. One for the test gel and the other as control (no gel). The gel (500 mg per animal) was applied twice daily for 7 days. The skin was checked regularly to see if there were any signs of irritation such as:

- Slight redness
- Patchy or moderate redness
- Severe redness
- Swelling (edema)

This helps determine if the gel is safe and non-irritating for topical use.

6) Grittiness Test

All gel samples were checked under a light microscope to ensure there were no visible particles or rough materials in them. A good gel should feel smooth on the skin, so being free from grit or particles

7) Stability Studies

To check if the transferosomal gel remains stable during its shelf life, it is stored under accelerated conditions (higher temperature and humidity). At specific time intervals, important parameters are tested again, such as:

- Vesicle size → to ensure transferosomes do not break or grow too big
- Zeta potential → to confirm stability against aggregation
- Drug diffusion/release behavior → to ensure the gel still releases the drug properly over time

These tests help confirm that the formulation remains effective and unchanged during storage.

8) Extrudability Study

This test checks how easily the gel comes out of its tube. The gel is packed in collapsible tubes, and pressure is applied to squeeze out the gel. The weight (in grams) needed to push out a 0.5 cm strip of gel in 10 seconds is recorded.

A good gel should:

- Come out smoothly
- Not require too much force
- Maintain a uniform ribbon.^[16]



Role of Pharmacists in Dermatology

- **Education & Counseling:** Guidance on medication use, adherence, side effects, skincare routines, and lifestyle.
- **OTC & Prescription Medication:** Provide safe access to moisturizers, corticosteroids, antifungals, and monitoring therapy effectiveness. ^{[17], [18]}.

Advancements in Dermatology

- **Artificial Intelligence (AI)** is revolutionizing dermatology by improving diagnostic accuracy and treatment efficiency.
- **Imaging & Analysis:** AI-powered tools can detect and differentiate skin cancers, ulcers, and psoriasis via lesion analysis.
- **Wound Assessment:** AI can map wound boundaries to monitor healing.
- **Teledermatology:** Enables remote diagnosis and monitoring of skin conditions using photographs and AI-support systems ^[19], ^[20].

CONCLUSION

This report details a project aiming to enhance the delivery and sustained release of antifungal agents through the skin using novel formulations. It begins with an overview of the skin's anatomy and physiology, highlighting the skin as the body's largest organ, which acts as a protective barrier. The skin is composed of three main layers: the Epidermis (the avascular, outermost layer with the waterproof Stratum corneum), the Dermis (providing structural support, containing blood vessels and nerves), and the Hypodermis/Subcutis (a subcutaneous layer primarily made of adipose tissue for cushioning and insulation). The report then addresses the major health concern of fungal

infections (mycoses), which are increasing in prevalence and often face challenges like antifungal resistance. These infections can be superficial, subcutaneous, or systemic, and current treatments involve various forms such as oral tablets, topical creams, and IV therapy. To overcome the limitations of conventional therapy, the report focuses on the Transdermal Drug Delivery System (TDDS), an innovative approach that avoids first-pass metabolism and improves bioavailability. Finally, the report outlines a comprehensive set of evaluation tests essential for confirming the quality and safety of the final transferosomal gel formulation.

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