RESEARCH PAPER

"HERBAL ANTIFUNGAL PRONIOSOMAL GELS: A NOVEL VESICULAR APPROACH FOR ENHANCED TOPICAL DRUG DELIVERY"

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ABSTRACT
Fungal infections, particularly superficial and cutaneous mycoses, represent a significant therapeutic challenge because of their recurrent nature, increasing antifungal resistance, adverse effects associated with conventional antifungal agents, and limitations in topical drug delivery. Herbal antifungal agents obtained from medicinal plants and essential oils have attracted considerable interest because of their diverse phytoconstituents and reported antifungal activity. However, their therapeutic application may be limited by poor aqueous solubility, instability, variable bioavailability, and inadequate penetration through the skin. Proniosomes are promising vesicular drug delivery systems composed primarily of non-ionic surfactants, cholesterol, and suitable carriers that generate niosomal vesicles upon hydration. They offer advantages such as improved stability, enhanced drug encapsulation, controlled release, and improved skin permeation. Incorporation of herbal antifungal agents into proniosomal gel systems may therefore provide an effective strategy for localized and sustained delivery at the site of infection. This review discusses the burden and major types of fungal infections, limitations of conventional antifungal therapy, and the therapeutic potential of herbal antifungal agents. The principles, composition, types, mechanisms, preparation methods, and advantages of proniosomes are also discussed, with particular emphasis on their application in topical and transdermal drug delivery. Furthermore, the formulation considerations, evaluation parameters, therapeutic applications, limitations, and future prospects of herbal antifungal proniosomal gels are reviewed. Available evidence indicates that proniosomal systems may improve drug stability, skin permeation, controlled release, and local therapeutic activity of herbal antifungal agents. However, variability in herbal extracts, formulation optimization, stability, scale-up, skin tolerability, and limited clinical evidence remain important challenges. Further systematic formulation studies and well-designed clinical investigations are required to establish the safety, efficacy, standardization, and translational potential of herbal antifungal proniosomal gels for the management of fungal skin infections**.**

Keywords: Herbal antifungal agents; Proniosomes; Proniosomal gel; Vesicular drug delivery; Topical drug delivery; Fungal skin infections; Skin permeation; Novel drug delivery system.
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FUNGAL INFECTIONS

Definition

Fungal infections are one of the deadliest infections acounting in excess of 1.5 million deaths annually worldwide. The main reason for fungal infection is neglected by the society. Over the past two decades, fungal infections have increased significantly in frequency and as causes of morbidity and mortality. Fungal infections are also called mycosis, is a skin disease caused by a fungus and a type of microorganisms. There are millions of species of fungi, fungi can live in the air, soil, water, plants and also live-in human body. They can also lead to skin problems like rashes or bumps. Fungal infections come in different forms like ringworm, athletes foot, yeast infections and jock itch. Some fungi like aspergillus can be dangerous and leads to life threatening disease. Fungal infections can be contagious and can be spread from one person to another person.[1]

TYPES OF FUNGAL ORGANISMS

Fungi can be divided into four classes

1. Yeasts: Cryptococcus neoformans
2. Yeast like fungi: It partly grows like yeast and partly as filaments (hyphae) and these types of fungi caused of Oral thrush, Vaginal thrush, Systemic Candidiasis. Example of these types of fungi is Candida albicans.
3. Dimorphic fungi: This type of fungi grows as filaments or as yeast and they caused Histoplasmosis,Coccidiomycosis, Blastomycoses,Sporotrichosis.Fungi species involved of this category is Histoplasma capsulatum, Coccidioides immitis, Blastomyces deramtides.
4. Moulds: Filamentous fungi reproduce by forming spores. This type of fungal organism caused Skin/ nail infections. Example:

Trichophyton sp, Microsporum sp., Epidermophyton sp.[2]

TYPES OF FUNGAL INFECTIONS

Fungal infections can be broadly divided into three main types based on how deeply they affect the body superficial, subcutaneous, and systemic infections.

1 **Superficial fungal infection**: affect your nails, skin and mucous membrane (like your mouth, throat or vagina). Athlete's Foot (Tinea pedis): Typically affects the feet, especially between the toes, causing itching, peeling, and sometimes burning. Ringworm (Tinea corporis): Presents as circular, red, scaly patches on the skin with clearer centres, giving a ring-like appearance. Fungal Nail Infection (Onychomycosis): Results in thickened, brittle, or discoloured nails, which may cause discomfort.

2 **Subcutaneous fungal infection**: Fungal infection under the surface of your skin (subcutaneous) if fungus gets into a cut or wound, usually through injury while working with plants (like a scratch from a thorn). They cause rashes, ulcers and other symptoms on your skin. Subcutaneous fungal infections are more common in tropical and subtropical areas of the world. Chromoblastomycosis: Causes wart-like skin lesions that develop slowly and can become chronic. Mycetoma: A chronic infection leading to swelling, nodules, and sometimes discharge of fungal material through the skin.

3 **Systemic fungal infections**: found in places in your body other than your skin, like your lungs, blood, urinary tract or brain. Some are opportunistic infections, meaning that they usually only cause disease in people with weakened immune systems. Aspergillosis: Caused by Aspergillus species, it often affects the lungs and sinuses, causing allergic or invasive disease. Cryptococcosis: Caused by Cryptococcus fungi, this infection can lead to severe lung disease or meningitis.[3]

SYMPTOMS OF FUNGAL INFECTION

Itching, Redness and inflammation,
Scaling, Rashes Cracking, Blistering, Skin discoloration and swelling, Painless nodules or papules at site of entry.

PREVALENCE OF FUNGAL INFECTIONS

Fungal infections affect millions of people worldwide every year. About 6.5 million people develop serious invasive fungal infections annually. Nearly 3.8 million deaths occur each year, with 2.5 million directly caused by fungal diseases.

Major Invasive Fungal Diseases

- **Invasive Aspergillosis**
  Affects >2.1 million people annually. Common in patients with lung disease, cancer, or ICU admission. Mortality rate ~85.2%.
- **Chronic Pulmonary Aspergillosis** Around 1.84 million cases each year. Causes about 340,000 deaths annually.
- **Candidiasis**
  About 1.57 million infections worldwide. Leads to ~1 million deaths per year.
  • Pneumocystis Pneumonia
  Affects ~505,000 people annually. Causes >214,000 deaths each year.
  • Cryptococcal Meningitis
  Around 194,000 cases annually. Responsible for ~147,000 deaths.
  • Fungal Skin Infections
  About 1.73 billion cases reported worldwide in 2021. Most common in children and older adults. Children aged 5–9 years show the highest number of cases.[4]

RISK FACTORS

Fungal infections can become severe or life-threatening in people with weakened immune systems. The immune system normally protects the body from fungi, but weakened immunity increases infection risk. Medical conditions increasing risk: Cancer, HIV/AIDS. Chronic lung disease Treatments and situations increasing risk: Long-term hospital stay, stem cell transplantation, Organ transplantation, Corticosteroid therapy, High-dose or prolonged antibiotic use. **People with cancer**: Chemotherapy and radiation reduce white blood cell count, weakening immunity and increasing fungal infection risk.

People with organ transplants: Need anti-rejection (immunosuppressive) drugs, which weaken the immune system. Higher risk in lung, liver, heart, and small bowel transplants.

People with stem cell transplants: Immune system is destroyed and rebuilt, increasing infection risk. Higher risk with donor stem cells. Risk of Graft-versus-host disease.

People in healthcare settings: Hospitalized patients may have temporarily weakened immunity. Wounds, surgeries, ventilators, and catheters can allow fungi to enter the body.[5]

ANTIFUNGAL AGENTS

Antifungal agents are drugs that eliminate fungal pathogens by targeting unique components of fungal cells, such as the ergosterol cell membrane, with minimal host toxicity. Major classes include Azoles (fluconazole), Polyenes (amphotericin B), Echinocandins (caspofungin), and Allylamines (terbinafine), used for infections ranging from topical skin issues to life threatening systemic diseases. Most antifungal drugs interfere with biosynthesis or integrity of ergosterol, the

major sterol in the fungal cell membrane. Others cause disruption of the fungal cell wall. Antifungal resistance poses a significant challenge in the management of fungal infections. Understanding the mechanisms of action of antifungal agents is crucial for developing effective treatment strategies.

MECHANISM OF ACTION

Polyene antifungals (like Amphotericin B and Nystatin) poke holes in the fungal cell membrane, causing its contents to leak out.

Azoles (like Fluconazole and Ketoconazole) block a specific protein, which stops the fungus from making ergosterol—a key building block of its membrane.

Echinocandins (like Caspofungin and Micafungin) stop the fungus from making \beta-(1,3)-D-glucan, which weakens its outer cell wall.

Allylamines (like Terbinafine and Naftifine) block the enzyme squalene epoxidase, causing lower ergosterol levels and a buildup of toxic squalene.

Pyrimidine analogues (like Flucytosine) turn into 5-FU inside the body, which stops the fungus from building its DNA and RNA.

ADVANTAGES OF CONVENTIONAL ANTIFUNGAL THERAPIES

1. Established Antifungal Efficacy Conventional antifungal drugs effectively treat a wide range of fungal infections by targeting fungal cell structures and metabolic pathways.

2. Proven Clinical Use

These drugs have long-standing clinical use and are widely available for treating common infections like onychomycosis and tinea pedis.

3. Known Safety Profile

Their safety, side effects, and drug interactions are well understood, allowing proper monitoring and dose adjustment.

4. Support for Combination Therapy They can be combined with other treatments and immunomodulatory therapies to improve outcomes and reduce resistance.

5.Cost-effective and Accessible Conventional antifungals are affordable, widely available, and come in well-established dosage forms suitable for routine treatment.[6]

LIMITATIONS OF CONVENTIONAL ANTIFUNGAL THERAPIES

1. Drug Toxicity

Amphotericin B: Causes nephrotoxicity and infusion-related reactions. Azoles: Can cause hepatotoxicity, visual disturbances, neurotoxicity, endocrine effects, and QT prolongation. Flucytosine: May cause myelosuppression, gastrointestinal, and liver toxicity. Echinocandins: Generally safer but still may cause mild adverse effects.

2. Drug Interactions

Azoles strongly interact with many drugs by inhibiting cytochrome P450 enzymes. Drugs like rifampin, carbamazepine, and phenytoin reduce azole effectiveness. Some interactions also occur with echinocandins.

3. Limited Antifungal Spectrum Some drugs are ineffective against certain fungi. Example: echinocandins are inactive against Cryptococcus and Mucorales. Some fungi show intrinsic resistance to specific antifungals.

4. Pharmacokinetic Limitations

Poor tissue penetration (e.g., limited CSF penetration). Biofilm formation reduces drug effectiveness. Some drugs have poor or variable oral absorption.

5. High Protein Binding

Reduces the amount of active free drug, especially in patients with low albumin.

6. Diagnostic Challenges

Nonspecific symptoms and slow culture results delay diagnosis. Limited availability and accuracy of antigen and molecular tests.[7]

APPLICATIONS OF CONVENTIONAL ANTIFUNGAL AGENTS

1. **Treatment of superficial fungal infections**

   Used for infections of skin, hair, and nails such as Tinea, Athlete's Foot, and Ringworm.

2. Management of mucosal infections Effective against infections of the mouth, throat, and genital tract such as Oral Candidiasis and Vaginal Candidiasis.

3. Treatment of systemic fungal infections

Used for severe infections affecting internal organs, such as Aspergillosis, Candidiasis, and Cryptococcosis.

4.Prophylaxis in immunocompromised patients

Given to prevent fungal infections in patients with weakened immune systems, such as those with HIV/AIDS, cancer, or organ transplants.

5. Treatment of opportunistic fungal infections

Helps control fungal diseases that occur in patients with chronic illnesses or long-term antibiotic use.

6. Management of hospital-acquired fungal infections

Used to treat fungal infections in intensive care or hospitalized patients.[8]

HERBAL ANTIFUNGAL AGENTS

*** Natural Source & Scope**: Bioactive plant compounds—such as those from Catharanthus roseus and other traditional medicinal plants—contain diverse constituents like alkaloids, flavonoids, terpenoids, and saponins that inhibit fungal growth.

* **Advantages over Synthetic Antifungals**: Conventional antifungal drugs face limitations including high toxicity, costs, and the rise of drug-resistant strains; plant extracts offer safer, effective alternatives.

* **Drug Discovery Potential**: Due to their unique structural diversity, natural products serve as valuable candidates for developing novel, selective antifungal treatments with minimal side effects.

HERBAL REMEDIES TO TREAT FUNGAL INFECTIONS

Garlic: It is one of the most potent antifungal and antimicrobial herbs. Those who take garlic regularly in their diet they are less susceptible to fungal infections. Crush garlic along with olive oil and make paste and apply to the infected area for 30minutes. Apply daily until the problem resolve and it is very beneficial with the ringworm infections.

Turmeric: It is a potent antimicrobial and anti-inflammatory agent which consists of curcuminoids. Curcuma longa rhizome is used as insect repellent. Mixture of curcumin with other antimicrobial agent is used for the development of skin gels and emulsions with improved skin protection and wound dressing properties which are used for the fungal infections on the body.

Aloe Vera: It is a natural remedy to cure any skin infections. It is not only used for the treatment of infections but also repairs skin damage. It is mainly beneficial for the skin and face.

Ginger: It has very good anti-fungal properties. Adding ginger in the tea helps to prevent and treat fungal infections like candida albicans. It is scientifically called as Zingiber officinale which belongs to the family Zingiberaceae.

Neem Leaves: It has antifungal properties and are extremely good for the skin. The infected area is washed with neem water to treat fungal infections. To make neem more effective it is boiled in water and then it is used for bath.

Apple Cider Vinegar: It has antifungal properties you could mix two tablespoons in warm water and drink it or dip a cotton ball and apply it on infected area. Apply thrice a day to show better results.

Oregano Oil: Mix few drops with normal oil and apply on the infected area. Even oregano oil capsules are available which can be taken orally. Oregano oil is a good antifungal agent.

Coconut Oil: It is simple agent which is used for skin soothing effect. It also has antifungal properties which is mostly used for the treatment of scalp ringworm.

Tea Tree Oil: It is naturally used as antifungal and antibacterial agents. It is mixed with coconut oil or olive oil and applied on the infected area for three to four times a day. It is most effective in treating fungal infections.

Yogurt: It contains high amount of lactobacillus which has strong antifungal properties which is used to treat different fungal infections.[13,14]

ADVANTAGES OF HERBAL ANTIFUNGAL AGENTS

Low toxicity, Lower risk of drug resistance , Minimal drug interactions, Reduced side effects, Suitable for topical formulations,Better patient compliance, Cost effective and ecofriendly[15]

DISADVANTAGES OF HERBAL ANTIFUNGAL AGENTS

Slower onset of action , Limited scientific and clinical evidence ,Difficulty in dose optimization , Poor stability and short shelf life , Risk of contamination and adulteration[16,17]

APPLICATIONS OF HERBAL ANTIFUNGAL AGENTS

a) **Skin and scalp care**
   Extracts from neem, tea tree oil, and turmeric are applied to treat dermatophytic infections like ringworm, eczema, psoriasis and dandruff.
b) **Oral and dental health**
   Herbal agents such as neem, clove and oregano are used in mouth washes and gels to combat Candida species responsible for oral thrush and denture stomatitis**.**
c) **Gynaecological care**
   Products containing herbal ingredients are used to treat vaginal candidiasis and bacterial vaginosis.
d) **Pharmaceutical formulations**
   Essential oils like lavender, peppermint, cinnamon and crude extracts are being formulated into creams and ointments to overcome the resistance developed against conventional synthetic antifungals.
e) **Agricultural and Food industry**
   Plant extracts are used as natural preservatives to inhibit fungal growth on produce and as antifungal coatings for food packaging to prevent post-harvest diseases.
f) **Medical device coatings**
   Propolis and other herbal extracts are being applied to catheters and medical materials to prevent the development of candida biofilms.[18,19]

NOVEL DRUG DELIVERY SYSTEM

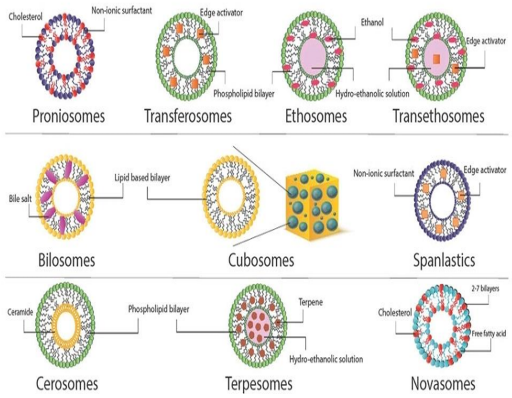
Novel Drug Delivery Systems (NDDS) represent an advanced and transformative area in pharmaceutical sciences that aim to optimize the delivery of therapeutic agents to achieve maximal efficacy and safety. Unlike conventional drug delivery methods, which

often face challenges such as poor solubility, rapid metabolism, systemic toxicity, and nonspecific distribution, NDDS are engineered to overcome these limitations through controlled, targeted, and sustained drug release mechanisms.[20]

Novel vesicular drug delivery systems aim to deliver the drug at a rate directed by need of body during the period of treatment, and channel the active entity to the site of action. Biologic origin of these vesicles was first reported in 1965 by 'Bingham' and has been given the name 'Bingham bodies'. A number of novel vesicular drug delivery systems have been emerged encompassing various routes of administration, to achieve targeted and controlled drug delivery.[21]

Vesicles are colloidal carriers formed using certain amphiphilic molecules such as phospholipids or surfactants surrounding an aqueous phase forming one or more concentric lipid bilayers. Vesicles can entrap hydrophilic and lipophilic drugs in the aqueous compartment or the lipid bilayer. They can reduce the risk of drug toxicity as they can deliver drugs to the targeted site of action hence lowering their concentration on other sites of the body

TYPES OF VESICULAR NOVEL DRUG DELIVERY SYSTEMS [22]



ADVANTAGES OF NOVEL DRUG DELIVERY SYSTEMS

Improved drug effectiveness, Better bioavailability, Controlled and sustained release, Targeted drug delivery, Reduced side effects, Less frequent dosing, Better patient compliance, Improved drug stability, Useful for herbal and biopharmaceutical drugs. [23]

DISADVANTAGES OF NOVEL DRUG DELIVERY SYSTEMS

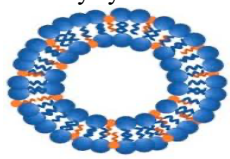
Difficult to make, Stability problems, Expensive, Approval is difficult, Not always accepted by patients, Possible side effects, Limited drug capacity, Hard to predict results.[24,25]

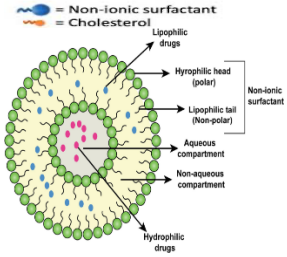
PRONIOSOMES

Proniosomes are vesicular drug delivery systems or vesicles that are composed of non-ionic surfactants, cholesterol and other additives. Proniosomes are anhydrous or dry formulations prepared by non-ionic surfactant coated carrier. Proniosomes are dry, free flowing, water soluble carrier particles coated with surfactant. They are hydrated just before use to form niosomes within minutes. The formed niosomes are similar to conventional niosomes but are more uniform in size.

The proniosomes are preferred over niosomes for its higher stability, appropriate release pattern and ease of packaging and transportation for its dry nature. The surfactants used in preparation of proniosomes act as important carrier/ ingredient in formulation as it enhances the drug permeation, biodegradable, non-toxic, amphiphilic and can encapsulate both hydrophilic and lipophilic drugs. Proniosomes are especially useful for transdermal drug delivery because they: Act as a drug reservoir for prolonged release,Enhance skinpermeation, Improve physical and chemical stability of drugs,Help drugs reach systemic circulation.

They overcome common problems of aqueous niosomal dispersions such as leakage, aggregation, and fusion. Proniosomes are stable during sterilization and storage, making them a promising and convenient novel drug delivery system.[26]





TYPES OF PRONIOSOMES

Proniosomes are classified on the basis of type of carrier and method of preparation. Proniosomes are classified into:

a) Dry Granular Proniosomes:

The dry granular proniosomes are classified into 2 types on the basis of method of preparation. These include:

1. Sorbitol Based Proniosomes: These are dry granular proniosomes prepared by addition of sorbitol (carrier) in non-ionic surfactants using simple agitation method.

2.Maltodextrins Based Proniosomes:

These are dry granular proniosomes prepared by addition of maltodextrin (carrier) in non-ionic surfactant by the method of fast slurry technique.

b) Liquid Crystalline Proniosomes: Proniosomal gel are semisolid liquid crystal gel that are prepared by dissolving surfactant in minimal quantity of solvent and hydrating with small amount of water to form gel. These gels are semisolid transparent, translucent or white physically stable formulations that can be used topically/ transdermally. These proniosomes act as reservoir in transdermal drug delivery system. The Proniosomal gel is placed onto the backing membrane of the transdermal patch and release the drug accordingly. The liquid crystalline proniosomes have exceptional benefits that make it the suitable choice for the pharmaceutical researchers in the field of provesicular drug delivery system.

These include: Higher stability, Higher entrapment efficiency, good penetration enhancer and easy to manufacture and economical.[27]

STRUCTURE OF PRONIOSOMES

Proniosomes are semisolid gel structures that are said to be mixture of phases of liquid crystal such as lamellar, cubic and hexagonal. Proniosomes are lamellar structures of microscopic range. The proniosomes are prepared from non-ionic surfactants and cholesterol. The hydrophobic part of non-ionic surfactant directs itself inwards whereas the hydrophilic part orients outwards and form bilayer. During incorporation of drug, the hydrophilic drugs are enclosed in the vesicles whereas hydrophobic drugs are embedded within the bilayer of proniosomes.[28]

COMPOSITION OF PRONIOSOMES

1.Non-ionic Surfactants

Non-ionic surfactants such as Tween (Tween 20, Tween 80) and Span (Span 60, Span 80) are the main components of proniosomes. They contain a hydrophilic head and a lipophilic tail, which allows them to form bilayer vesicles when hydrated. **2. Membrane Stabilizers**

Cholesterol or lecithin is added to stabilize the bilayer membrane. Cholesterol reduces membrane leakage, improves vesicle stability, and increases drug entrapment efficiency.

3. Carriers

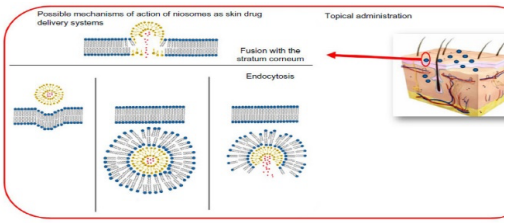
Carriers help in the formation of dry, free-flowing proniosomal powder and increase surface area for drug loading. Common carriers include sorbitol, mannitol, lactose, glucose, and sucrose stearate.

4.Solvents (Alcohols)

Alcohols such as ethanol, propanol, butanol, and isopropanol are used during preparation. The type of alcohol influences vesicle size and drug permeation, with ethanol generally producing larger vesicles.[29]

MECHANISM OF ACTION

The precise method by which a drug penetrates vesicles and enters the skin has not been fully explored yet. The extent of penetration depends on various factors such as the type and properties of the drug used, the formation of vesicles, and the temperature at which the proniosomes are converted to Niosomes. The lipids used in the preparation of proniosomes act as a carrier that forms a depot at the site of action, thereby prolonging the drug's effect. It is clear that proniosomes need to be hydrated to form niosomal vesicles before the drug can be released and permeate across the skin. Numerous scientists have proposed various theories and mechanisms. Vesicle skin interaction. There are various ways to enhance the absorption of hydrophobic drugs through the skin. These include: Disruption of stratum corneum lipid bilayer – modifies skin lipids and increases drug permeation,Nano-sized vesicles – smaller size improves transdermal penetration. Alteration of drug partitioning – improves the drug's distribution into different skin layers,Skin hydration and dilation of intercellular channels – niosomes hydrate the stratum corneum and loosen its structure, allowing easier drug release,Changing the permeation pathway of lipophilic permeants to follicular delivery. Non-ionic surfactants are an important part of this process as they act as penetration enhancers, entering the intercellular lipids through endocytosis. Non-ionic surfactants play a crucial role in improving the permeation of proniosome compared to conventional drug delivery systems. Their presence enhances the stability and solubility of the proniosomes, making them a more efficient drug delivery option.[30,31]



METHOD OF PREPARATION

a) Slurry method
b) Co-acervation phase separation method
c) Spray coating method

a) Slurry method

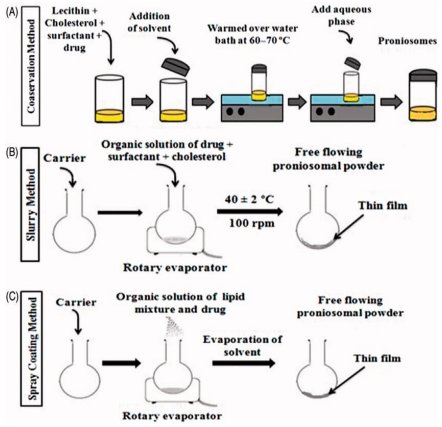
Proniosomes are a type of carrier system used to protect active ingredients and surfactants from hydrolysis. They can be prepared by adding a carrier and a surfactant solvent into a round bottomed flask, which is then attached to a rotary flash evaporator. A vacuum is applied to form a dry and free-flowing powder. The obtained formulation should be stored in a tightly closed container. The time required for proniosomes production is not dependent on the ratio of the surfactant solution and appears to be stable. This method has the advantage of producing a uniform coating on the carrier, which helps protect the active ingredients and surfactants.[32]

b) Co-acervation phase separation method

This is the widely used method to prepare proniosmal gel. Weighed quantities of drug, lipid and surfactants are taken in a dry wide-mouthed glass beaker followed by the addition of solvent. The ingredients are mixed well and warmed over water bath at 60–70^{0}C until the surfactant mixture dissolves completely. During the process care must be taken to prevent loss of any solvent due to evaporation. Finally, the aqueous phase is added to the mixture and warmed on water bath. The resultant solution is cooled overnight to obtain proniosomal gel.[33]

c)Spray – coating method

Proniosomes were produced by slurry method using maltodextrin as a carrier. The time required to produce proniosomes by this is independent of the ratio of surfactant solution to carrier material. In slurry method, the entire volume of surfactant solution is added to maltodextrin powder in a rotary evaporator and vacuum is applied until the powder appears to be dry and free flowing. Drug containing proniosomes-derived niosomes can be prepared in manner analogous to that used for the conventional niosomes, by adding drug to the surfactant mixture prior to spraying the solution onto the carrier (sorbitol, maltodextrin) or by addition of drug to the aqueous solution used to dissolve hydrate the proniosomes.[34,35]



ADVANTAGES OF PRONIOSOMES OVER CONVENTIONAL DRUG DELIVERY SYSTEMS

1.Bioavailability.

Proniosomes protect drugs from gastrointestinal degradation and act as reservoirs, thereby improving the bioavailability of poorly soluble drugs.

2.**Proniosomes vs Liposomes**

Proniosomes are more stable and cost-effective than liposomes, which suffer from high production cost, phospholipid instability, and strict storage requirements.

3.Biological Behaviour

Proniosomes/niosomes enhance drug circulation time, improve distribution and metabolic stability, and can reduce toxicity while maintaining therapeutic efficacy.

4.Effect of Cholesterol

The composition of the bilayer membrane, especially cholesterol content, influences drug entrapment efficiency in niosomes.

5.Advantages of Niosomes

Niosomes are stable, biocompatible vesicles capable of controlled drug release and can encapsulate both hydrophilic and lipophilic drugs.

6.Drug Delivery System

This system enables controlled drug delivery and reduces side effects, although oral administration may be affected by first-pass metabolism and surfactant-related irritation.[36,37]

LIMITATIONS AND CHALLENGES OF HERBAL PRONIOSOMAL ANTIFUNGAL GEL

•Formulation Complexity

Requires careful optimization of surfactants, cholesterol, and herbal extracts.Small changes can affect vesicle size, stability, and drug release.

•Stability and Storage Issues

Herbal components may degrade due to light, heat, and moisture.Risk of reduced shelf life and microbial contamination.

•Variability of Herbal Extracts

Differences in plant source and extraction methods cause variation in phytochemical content.Leads to

batch to-batch inconsistency in formulation performance.

•Drug Release and Skin Permeation Challenges

Difficult to balance rapid action and sustained drug release.skin penetration may vary depending on skin type and condition.

•Potential Skin Irritation

Surfactants or herbal components may cause irritation or allergic reactions.Enhanced penetration may increase risk of local toxicity.

•Scale-Up and Manufacturing Difficulties

Large-scale production requires specialized equipment and strict quality control. Maintaining uniform vesicle size and drug loading can be challenging.

•Limited Clinical Evidence

Most studies are laboratory or animal-based.More human clinical trials are needed to confirm safety and effectiveness.[38,39]

PHARMACEUTICAL GELS

Gels are semisolid preparations intended for application on the skin or the accessible mucous membranes like oral cavity. Gels are composed of two interpenetrating systems where the colloidal particles, also known as the gelator or gallant, are uniformly distributed throughout a dispersion medium or solvent forming a three-dimensional matrix known as the gel. The gels are prepared by adding a gelling agent (gelator) which could be natural, synthetic or semi-synthetic polymer or low molecular weight small molecules, into an organic, inorganic or aqueous solvent or solvent systems (Fig. 1). The polymer in gels acts as the backbone of the gel matrix. The polymeric meshwork gives gel its structural strength, increased adherence to the surface where applied and decreased permeation of the larger molecules hence making the retention possible.[40]

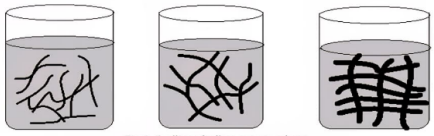
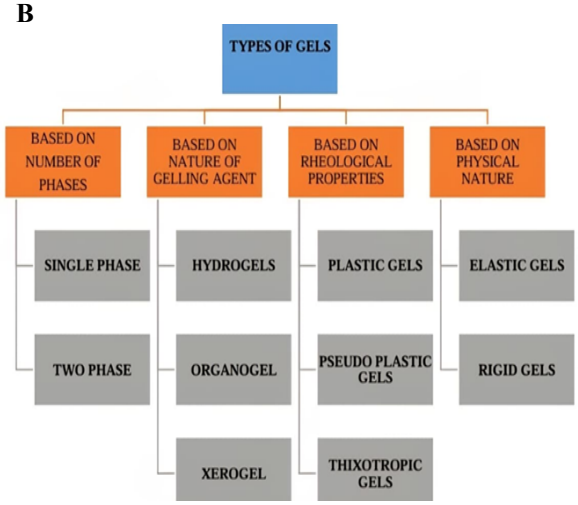


Fig. 1. Swelling of gelling agent in solvent.

CLASSIFICATION OF GELS

1. B



RE OF GELLING AGENT

a)Hydrogel (water-based): Hydrogels are networks of hydrophilic polymer chains in which water is the dispersing medium. These are highly absorbent natural or synthetic polymer networks. Due to their high-water content, they are also somewhat flexible.

b) Organogel: is a non-crystalline,nonvitreous thermoreversible solid consisting of a liquid organic phase trapped in a 3D cross-linked network. Fluid can be vegetable oil, organic solvent or mineral oil.

C)Xerogel: This is a dried solid gel that shrinks indefinitely. It generally retains high porosity (15-50%) and large surface area (m2/g).

2. BASED ON RHEOLOGICAL PROPERTIES

Generally, gels exhibit non-Newtonian flow properties.They are classified as:

a) Plastic gels: The Bingham body sees plastic flow as aluminum hydroxide, Flocculated suspensions, such as tragacanth gum, sodium alginate and sodium CMC dispersions, is the so-called plastic flow and the rheogram gives the results of the gel on which elastic Gel will deform and begin to flow.

b) Pseudoplastic gel: The viscosity of these gels decreases with increasing shear rate and has no yield value. The rheogram is given by cutting the length of the molecular chain of the linear polymer. As shear stress increases, solvent is released from the gel matrix as the chaotic molecules begin to align their long axes downstream.

c) Thixotropic Gels: The bonds between particles in these gels are so weak that can be broken by shaking. When particles collide and reconnect (reverse isothermal gel-sol-gel transition) the solution will return to the gel. This occurs in colloidal systems with aspherical particles to form scaffold-like structures. For example, kaolin, bentonite, agar etc.

3. BASED ON PHYSICAL STRENGTH:

They are divided into

a) Elastic gels: gels of agar, pectin, guar gum and alginates exhibit elastic behavior.fiber molecules are connected at points by weak forces such as hydrogen bonds and dipole attraction. If the molecule has a free -COOH group, additional associations occur between two adjacent chains of a -COO-X-COO type salt bridge.

For example, Alginate and Carbopol.

b) Rigid Gels: This can be formed from macromolecules to which framework is bound by primary bonds. For example, in silica gel, silicic acid molecules are

attached to by Si-O-Si-O bonds, giving a polymer structure with a pore network.[41]

ADVANTAGES OF GEL FORMULATIONS

Some of the major advantages of gel formulations over other semisolid dosage forms are as follows.

Gels are easy to formulate as compared to other semisolid dosage forms.

- A gel is an elegant non-greasy formulation.
- It can be used as controlled release formulation by entwining the polymer more than once.
- Gels have good adherence property to the site of application.
- They are biodegradable and biocompatible.
- They have excellent tolerability to certain stress conditions.
- They are washable and nontoxic in nature.
- They provide excellent spreadibility and cooling effect because of solvent evaporation.

DISADVANTAGES OF GEL FORMULATIONS

In spite of a number of advantages, gel formulations also have some disadvantages or limitations such as .

- The effect of gels is comparatively slower and sustained.
- The additives or the gelators may induce irritation.
- The water content may increase the chances of microbial or fungal attack in gels.
- Syneresis (expulsion of solvent from the gel matrix) may occur in gels during storage.
- Solvent evaporation from the formulation may result in drying of the gel.
- Covalent bonds present in some gels may render them unbreakable thus sealing the medicament inside the gel matrix.
- Flocculation in some gels may produce an unstable gel.
- Rheology of some gels may alter due to the effect of temperature, humidity and other environmental factors.
- Some drugs may degrade in gel formulation due to the presence of polymers.[42]

EVALUATION PARAMETERS OF HERBAL ANTIFUNGAL PRONIOSOMAL GEL

1. **Physical Appearance and Homogeneity**

The gel is evaluated for color, uniformity, texture, and smoothness to ensure it is homogeneous and free from lumps or particles, which helps maintain uniform drug distribution.

2. **pH Measurement**

The pH of the gel is measured to ensure compatibility with skin or mucosal surfaces and to avoid irritation. Proniosomal gels usually have a pH between 5–7, close to the natural skin pH.

3. **Viscosity, Spreadability, and Extrudability**

These properties determine the ease of application and handling of the gel. Suitable viscosity allows the gel to spread easily on the skin while remaining at the site of application.

4. **Drug Content and Entrapment Efficiency**

This evaluates the amount of drug present in the formulation and the percentage of drug encapsulated within the vesicles. Higher entrapment efficiency supports controlled drug release and better antifungal activity.

5. **In Vitro Drug Release and Permeation**

Drug release studies determine how the drug is released from the gel over time. Permeation studies evaluate the ability of the drug to penetrate biological membranes and reach the target site.

6. **Microbiological Evaluation**

Tests are performed to confirm that the formulation is free from microbial contamination and to evaluate its antifungal activity against fungi such as Candida albicans using methods like zone of inhibition and MIC.

7. **Stability and Compatibility Studies**

Stability studies assess changes in pH, viscosity, drug content, and appearance during storage. Compatibility studies (such as FTIR analysis) ensure that the drug and excipients do not interact negatively.

8. **Vesicle Characterization**

The vesicles formed after hydration are evaluated for size, morphology, stability, and zeta potential, as these factors influence drug encapsulation, penetration, and controlled release.[43,44]

APPLICATIONS OF HERBAL ANTIFUNGAL PRONIOSOMAL GELS

1. **Improved Skin Penetration**

Proniosomal gels form niosomal vesicles on hydration, which enhance drug penetration through the stratum corneum and improve drug delivery to deeper skin layers.

2. **Controlled and Sustained Drug Release**

These gels provide slow and controlled release of herbal antifungal agents, maintaining effective drug levels and reducing the frequency of application.

3. **Enhanced Antifungal Activity and Safety**

Herbal proniosomal gels show strong antifungal activity against fungi such as Candida albicans and Aspergillus Niger and are generally safe with minimal skin irritation.

4. **Stable and Effective Formulation**

They are prepared using non-ionic surfactants, cholesterol, and gelling agents like carbopol, providing good stability, spreadability, and high drug encapsulation.

5. **Broad Therapeutic Applications**

These formulations are useful in treating various fungal infections such as candidiasis and other superficial fungal skin infections.[45]

ADVANTAGES IN THERAPEUTIC APPLICATION

1. **Sustained and Controlled Drug Release**

Proniosomal gels provide sustained release of antifungal agents, maintaining effective drug concentration at the infection site for a longer time. This reduces dosing frequency and improves patient compliance.

2. **Improved Stability and Permeation**

Proniosomes enhance the stability of poorly soluble drugs and improve their penetration through skin or mucosal barriers, allowing better drug retention and therapeutic effect.

3. **Compatibility with Herbal Antifungal Agents**

Proniosomal gels can incorporate herbal extracts and essential oils such as eugenol, oregano, clove, lavender, and betel leaf. These natural agents show good antifungal activity with fewer side effects.

4. **Enhanced Antifungal Activity**

Combining multiple herbal extracts in proniosomal gels can produce synergistic antifungal effects, reduce the required drug concentration and improve treatment effectiveness.[46,47]

FUTURE PROSPECTS OF HERBAL PRONIOSOMAL ANTIFUNGAL GELS

The future of herbal proniosomal antifungal gels is very promising because people are looking for natural, safe, and effective alternatives to chemical antifungal medicines. Proniosomal gels are special drug delivery systems that improve the stability of medicines, provide slow and controlled release, and deliver the drug directly to the infected area. This helps in better treatment of fungal infections like candidiasis.

1. **Better Antifungal Effect**

Herbal antifungal agents such as eugenol have shown strong activity against Candida albicans, which commonly causes oral fungal infections. When these herbal ingredients are added to proniosomal gels, the medicine is released slowly for a longer time. This improves drug absorption, reduces the number of applications needed, and increases patient comfort and treatment effectiveness.

2. **Fewer Side Effects and Reduced Drug Resistance**

Conventional antifungal medicines may cause side effects and sometimes become less effective because of drug resistance. Herbal proniosomal gels use natural plant extracts like Sesamum indicum, Origanum vulgare, and Syzygium aromaticum, which have good antifungal properties with fewer side effects. Some herbal oils also work well against drug-resistant fungal strains, especially when used together in gel formulations.[48]

3. **Use of Different Herbal Extracts**

Many herbal plants such as Tulsi (Ocimum sanctum), betel leaf (Piper betle), aloe vera, Datura stramonium, Cassia alata, Calendula officinalis, and lavender (Lavandula angustifolia) have been used successfully in antifungal gels. These herbal gels show good stability, spreadability, and antifungal action similar to standard medicines. Combining these herbal extracts with proniosomal technology may further improve their effectiveness and drug delivery.

4. **Need for Clinical Research**

Although laboratory and animal studies show positive results, more clinical studies in humans are needed to confirm the safety and effectiveness of herbal proniosomal antifungal gels. Future research should focus on proper testing, standard manufacturing methods, and regulatory approval so that these formulations can be widely used in medical practice.

5. **Increasing Market Demand**

Nowadays, many people prefer herbal and natural skincare products because they are considered safer and have fewer side effects. Herbal proniosomal antifungal gels are easy to apply, stable, and effective, making them a good option for treating fungal infections of the skin and mouth. Therefore, these formulations have strong future market potential in both developing and developed countries.[49]

CONCLUSION

Fungal skin infections remain a common health problem due to their frequent occurrence, recurrence, and increasing resistance to conventional antifungal drugs. Although synthetic antifungal agents are widely used, their long-term use may cause side effects, toxicity, and reduced effectiveness. Herbal antifungal agents from medicinal plants offer a safer alternative because of their natural origin, lower toxicity, and broad antifungal activity. However, their therapeutic effectiveness is often limited by poor solubility and low skin penetration.

Proniosomal gel systems help overcome these limitations by improving drug stability, enhancing skin permeation, and providing controlled drug release. Incorporating herbal antifungal agents into proniosomal formulations can enhance therapeutic efficacy and patient compliance. Therefore, herbal-based proniosomal nanocarriers show great potential for the effective treatment of fungal skin infections, though further clinical studies are needed to confirm their safety and effectiveness

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