

Liposomal Gel Systems for Herbal Antifungal Therapy: Formulation Strategies and Therapeutic Outcomes

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ABSTRACT

Fungal infections are a major global health concern, and conventional antifungal therapies often face challenges such as drug resistance, systemic toxicity, and poor bioavailability. Herbal antifungal agents, derived from medicinal plants such as *Cassia alata*, offer promising therapeutic potential due to their natural origin, broad-spectrum activity, and reduced side effects. However, limitations including poor solubility, instability, and inadequate skin penetration restrict their clinical efficacy. Liposomal gel systems have emerged as advanced topical delivery platforms that combine the advantages of nanocarriers and semisolid formulations. Liposomes can encapsulate hydrophilic and lipophilic herbal constituents, improving stability, enhancing skin permeation, and allowing controlled release at the target site. Incorporation into gel matrices further increases residence time, patient compliance, and localized antifungal activity. This review discusses current strategies for the formulation of liposomal herbal gels, their physicochemical characterization, in vitro and in vivo antifungal performance, therapeutic outcomes, challenges in development, and future perspectives. The integration of nanotechnology with herbal therapy holds considerable promise for improving the efficacy and safety of topical antifungal treatments..

KEYWORDS: Liposomal Gel, Skin Penetration, Gelling agent, Formulation Strategies.

I. INTRODUCTION

Burden of Fungal Infections and Limitations of Conventional Antifungal Therapy Fungal infections are among the most common cutaneous and systemic infections worldwide, affecting millions of individuals, especially in tropical and subtropical regions [1].

Conventional antifungal therapies, including topical creams and systemic drugs, often suffer from poor skin penetration, frequent dosing

requirements, and the development of resistant fungal strains, limiting their therapeutic effectiveness[2].

Additionally, systemic adverse effects, drug interactions, and low localized drug concentration further compromise the efficacy of standard antifungal treatments [3].

Role of Herbal Antifungal Agents in Modern Medicine

Herbal antifungal agents derived from medicinal plants are increasingly recognized due to their broad-spectrum activity, lower toxicity, and higher patient acceptability [4].

Phytochemicals such as flavonoids, alkaloids, tannins, and terpenoids have demonstrated potent antifungal activity against *Candida*, *Trichophyton*, and *Aspergillus* species [5].

Medicinal plants like *Cassia alata* have been traditionally used for the treatment of dermatophytic infections due to their bioactive components [6].

However, herbal extracts face challenges such as poor solubility, rapid degradation, and limited skin penetration, which restrict their clinical application [7].

Rationale for Liposomal Gel-Based Delivery Systems

Liposomal gel systems combine the advantages of vesicular nanocarriers and semisolid gels to improve topical drug delivery [8].

Liposomes can encapsulate both hydrophilic and lipophilic herbal constituents, protecting them from degradation and improving their stability [9].

Incorporation into gel matrices increases residence time on the skin, enhances controlled release, and improves localized antifungal efficacy [10].

The combination of liposomes and gels addresses many limitations of conventional formulations, including poor penetration, rapid drug clearance, and suboptimal therapeutic outcomes [11].

Herbal Antifungal Agents: An Overview Common Medicinal Plants with Antifungal Activity

Medicinal plants have been widely explored for antifungal potential against human pathogenic fungi [12].

Plant extracts from species such as *Lawsonia inermis*, *Pelargonium graveolens*, *Camellia sinensis*, and *Mentha piperita* exhibited significant inhibitory effects against *Candida albicans* [13].

Traditional herbs such as *Azadirachta indica* (Neem), *Allium sativum* (Garlic), *Melaleuca alternifolia* (Tea Tree), and *Curcuma longa* (Turmeric) are known for their antifungal efficacy against dermatophytes and yeast strains [14].

Other plants like *Catunaregum spinosa*, *Solanum virginianum*, and *Syzygiumcumini* also demonstrate inhibitory effects on fungal growth [15].

Phytochemical Constituents Responsible for Antifungal Effects

The antifungal activity of plant extracts is primarily due to bioactive phytochemicals such as phenolics, flavonoids, terpenoids, tannins, and saponins [16].

Phenolic compounds such as gallic acid, thymol, and catechin can disrupt fungal cell walls and inhibit fungal growth [17].

Flavonoids like rutin, kaempferol, and quercetin interfere with fungal enzymes involved in cell membrane synthesis, showing significant antifungal activity [18].

Essential oils and their constituents, such as terpinen-4-ol from tea tree and eugenol from clove, disrupt fungal membrane integrity, causing leakage of intracellular contents and cell death [19].

Challenges Associated with Herbal Extract Delivery

Despite promising activity in vitro, herbal extracts face formulation challenges that limit their therapeutic use [20].

Variability in extract composition due to differences in plant species, harvesting time, and extraction methods leads to inconsistent antifungal performance [21].

Lack of standardization and quality control protocols makes reproducibility difficult and complicates regulatory approval as medicinal products [22].

Many herbal compounds also have limited solubility, instability under physiological conditions, and poor penetration through biological barriers, which necessitates advanced delivery systems for clinical efficacy [23].

II. LIPOSOMAL DRUG DELIVERY SYSTEMS

Structure and Classification of Liposomes

Liposomes are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core, capable of encapsulating both hydrophilic and lipophilic drugs [24].

They are classified based on size, lamellarity, and preparation method into small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), multilamellar vesicles (MLVs), and multivesicular vesicles (MVs) [25].

Additionally, liposomes can be conventional, sterically stabilized (“stealth”), cationic, or ligand-targeted, depending on their surface properties and functionalization [26].

Advantages of Liposomes for Topical Drug Delivery

Liposomes enhance drug solubility, protect bioactive compounds from degradation, and provide controlled or sustained release [27].

They can improve localized delivery to the skin while reducing systemic absorption and potential side effects [28].

Liposomes also allow co-delivery of multiple compounds, including herbal extracts, increasing therapeutic efficacy against fungal infections [29].

The biocompatibility and biodegradability of phospholipids used in liposome preparation make them suitable for repeated topical application [30].

Stability and Skin Penetration Mechanisms

Liposomes can improve the chemical and physical stability of encapsulated drugs by protecting them from oxidation, hydrolysis, and enzymatic degradation [31].

Their flexible bilayer structure and small size facilitate penetration through the stratum corneum via intercellular, transcellular, or follicular routes [32].

Surface modification, such as PEGylation or incorporation of edge activators, can further enhance skin permeation and vesicle stability [33].

Liposomes may also act as penetration enhancers by fluidizing skin lipids, temporarily disrupting the barrier and promoting drug diffusion [34].

III. LIPOSOMAL ENCAPSULATION OF HERBAL EXTRACTS :

Selection of Lipids and Surfactants

The choice of lipids significantly influences liposome stability, encapsulation efficiency, and release profile of herbal extracts [35].

Phospholipids such as phosphatidylcholine, phosphatidylserine, and hydrogenated soy phosphatidylcholine are commonly used for their biocompatibility and ability to form stable bilayers [36].

Surfactants, including Tween 80, Span 60, and bile salts, are often incorporated to modify membrane fluidity, improve solubility of hydrophobic phytochemicals, and enhance skin penetration [37].

The lipid-to-surfactant ratio is a critical parameter, affecting vesicle size, zeta potential, and overall encapsulation efficiency [38].

Encapsulation Techniques for Plant Extracts

Various techniques exist for loading herbal extracts into liposomes, including thin-film hydration, reverse-phase evaporation, ethanol injection, and freeze-thaw methods [39].

Thin-film hydration is widely preferred due to simplicity and the ability to encapsulate both hydrophilic and lipophilic plant constituents [40].

Reverse-phase evaporation produces larger unilamellar vesicles with high encapsulation efficiency, suitable for heat-sensitive plant bioactives [41].

Other methods like microfluidization and supercritical fluid-assisted techniques offer controlled particle size and scalable production for industrial applications [42].

Factors Affecting Entrapment Efficiency and Vesicle Size

Entrapment efficiency depends on lipid composition, lipid-to-drug ratio, surfactant type, and the solubility of the herbal extract [43].

Vesicle size is influenced by sonication, homogenization, extrusion, and the hydration method used during preparation [44].

pH, temperature, and ionic strength of the hydration medium can also impact vesicle stability and size distribution [45].

The presence of cholesterol or sterols in the lipid bilayer enhances membrane rigidity, reducing leakage and increasing the retention of phytochemicals [46].

IV. LIPOSOMAL GEL FORMULATIONS Rationale for Incorporating Liposomes into Gel Bases

Incorporating liposomes into gel bases combines the benefits of vesicular carriers with the advantages of semisolid topical formulations [47].

Liposomal gels improve drug retention at the application site, prolong release, and enhance localized therapeutic efficacy [48].

The gel matrix stabilizes liposomes against aggregation and fusion, reducing leakage of encapsulated herbal compounds [49].

Topical gels also improve patient compliance due to ease of application, non-greasy texture, and minimal irritation [50].

Types of Gelling Agents Used

Natural gelling agents such as carbomers, xanthan gum, and guar gum are frequently used for their biocompatibility and rheological properties [51].

Synthetic polymers like hydroxypropyl methylcellulose (HPMC), poloxamers, and sodium alginate offer controlled viscosity and improved drug release characteristics [52].

Combination of natural and synthetic polymers can optimize spreadability, adhesiveness, and consistency for topical delivery [53].

Some gelling agents, like chitosan, provide additional bioactive benefits, including antimicrobial and wound-healing properties [54].

Influence of Gel Composition on Drug Release and Stability

Gel composition affects the viscosity, water activity, and pH, which in turn influence liposome stability and drug release kinetics [55].

Higher polymer concentration increases viscosity, slowing drug diffusion but improving retention on the skin [56].

The interaction between liposomes and gelling agents can affect vesicle integrity, potentially altering encapsulation efficiency [57].

Incorporation of humectants, preservatives, and antioxidants in the gel can

further enhance stability and shelf-life of herbal liposomal formulations [58].

V. ANTIFUNGAL EVALUATION OF LIPOSOMAL HERBAL GELS

In Vitro Antifungal Activity Studies

In vitro antifungal testing of liposomal herbal gels is typically performed using methods such as disk diffusion, broth microdilution, and agar dilution to determine minimum inhibitory concentration (MIC) [59].

Studies have shown that liposomal gels containing herbal extracts like *Cassia alata*, *Azadirachta indica*, and *Allium sativum* exhibit potent activity against *Candida albicans* and dermatophytes [60].

The vesicular encapsulation of phytochemicals enhances their stability and bioavailability, resulting in higher antifungal activity compared to unencapsulated extracts [61].

Time-kill assays indicate sustained antifungal effects of liposomal gels over prolonged periods, suggesting controlled release from the vesicular system [62].

Comparative Efficacy with Conventional Formulations

Liposomal herbal gels often demonstrate superior antifungal efficacy compared to conventional creams, ointments, or gels containing the same herbal extract [63].

This improvement is attributed to enhanced skin penetration, better retention at the site of infection, and protection of active compounds from degradation [64].

Clinical and preclinical studies have reported faster reduction of fungal load and improved patient outcomes with liposomal formulations [65].

Additionally, reduced systemic absorption minimizes the risk of side effects, making liposomal gels a safer alternative to conventional topical antifungals [66].

Mechanisms of Enhanced Antifungal Performance

Liposomal encapsulation facilitates deeper penetration of herbal phytochemicals through the stratum corneum and hair follicles, enhancing local drug concentration [67].

The vesicles may fuse with fungal cell membranes, delivering bioactive compounds directly into the pathogen and disrupting membrane integrity [68].

Liposomes also provide sustained release, maintaining inhibitory concentrations of antifungal compounds for extended durations [69].

Synergistic effects of encapsulated multiple phytochemicals can further enhance antifungal efficacy by targeting different cellular pathways simultaneously [70].

VI. THERAPEUTIC OUTCOMES AND CLINICAL POTENTIAL

- 1. Improved Bioavailability and Skin Retention:** Liposomal gel systems enhance localized drug delivery by improving skin penetration and increasing drug retention within the epidermis and dermis compared to conventional gel formulations, leading to enhanced bioavailability at the target site[71].
- 2. Safety and Biocompatibility Considerations:** Liposomal gel formulations are generally well-tolerated and biocompatible, often resulting in reduced skin irritation and lower systemic side effects due to their controlled release and localized action relative to non-vesicular systems[72].
- 3. Patient Compliance and Therapeutic Benefits:** The sustained release behavior, ease of topical application, and potential for reduced dosing frequency in liposomal gel systems contribute to improved patient compliance and enhanced therapeutic outcomes in treating dermatological conditions, including fungal infections[72].

Challenges and Limitations

- 1. Scale-up and Manufacturing Issues:** Scaling up liposomal gel formulations from the laboratory to industrial production poses significant technical challenges, including maintaining consistent particle size, encapsulation efficiency, and batch-to-batch reproducibility due to the complexity of multi-step processes and sensitive formulation parameters [73].
- 2. Stability and Shelf-Life Concerns:** Liposomal systems are prone to physical and chemical instability, such as aggregation, fusion, lipid oxidation, and drug leakage, which can compromise product integrity and reduce shelf life unless advanced stabilization strategies (e.g., lyophilization or cryoprotectants) are applied [74].
- 3. Regulatory and Quality Control Aspects:** The regulatory approval of liposomal gel products is demanding, requiring exhaustive

physicochemical characterization, rigorous quality control protocols, and comprehensive documentation to satisfy stringent guidelines from agencies like the FDA and EMA, which can extend development timelines and increase costs [75].

VII. FUTURE PERSPECTIVES (SUMMARY PARAGRAPH)

Herbal nanocarrier systems are rapidly advancing, with multifunctional and stimulus-responsive designs that improve the delivery, controlled release, and therapeutic efficacy of plant-derived antifungal compounds. Nanocarrier technologies also enable personalized and targeted antifungal therapies, allowing site-specific drug delivery, minimizing off-target effects, and supporting precision medicine approaches. Moreover, preclinical studies demonstrate that these formulations, including liposomal gels, have strong potential for clinical translation and commercialization, provided that regulatory, manufacturing, and quality control challenges are adequately addressed.

VIII. CONCLUSION

Liposomal gel systems have emerged as promising carriers for herbal antifungal therapy due to their ability to enhance bioavailability, improve skin retention, and provide sustained release of plant-derived antifungal compounds. These formulations are generally safe and biocompatible, minimizing local irritation and systemic side effects compared to conventional topical treatments, while also improving patient compliance through convenient application. Despite these advantages, several challenges remain, including difficulties in large-scale manufacturing, maintaining stability during storage, and navigating complex regulatory requirements, which can impact shelf-life, product consistency, and market translation. Nonetheless, ongoing advancements in nanocarrier technology, including multifunctional and stimulus-responsive liposomes, are addressing these limitations, enabling more targeted and personalized antifungal therapies that reduce off-target effects and improve therapeutic efficacy. Emerging trends in herbal nanocarrier research also focus on integrating novel targeting ligands, responsive release mechanisms, and improved formulation strategies to optimize drug delivery and clinical outcomes. With increasing preclinical evidence supporting their efficacy, safety, and patient acceptability,

liposomal gel systems hold significant potential for clinical translation and commercialization, bridging the gap between laboratory research and therapeutic applications. Overall, these systems represent a versatile and effective strategy for enhancing the treatment of fungal skin infections using herbal agents, combining advanced delivery technology with improved safety, therapeutic benefits, and patient-centered care.

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