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Glycerosomes as advanced vesicular drug delivery systems for topical antifungal therapy: Formulation strategies and therapeutic potential

Veenu Choudhary* | Azhar Khan | Shweta Shekhedwal | Bhupendra Chauhan | Ranjit Singh

Topical antifungal therapy is often ineffective because the drugs don't penetrate deeply enough into the skin, don't remain at the site of infection long enough, or cause irritation. Glycerosomes, a new type of liposome-based vesicular carrier with high levels of glycerol in the aqueous phase, are receiving increasing attention because they can overcome these problems. This review critically evaluates glycerosomes as sophisticated vesicular drug delivery systems for topical antifungal therapy, focusing on their structural attributes, formulation methodologies, and mechanistic benefits compared to traditional liposomes and other deformable vesicular systems. We talk about important formulation parameters like phospholipid composition, glycerol content, vesicle size, lamellarity, surface charge, and drug encapsulation efficiency in relation to vesicle stability, skin interaction, and permeation performance. The function of glycerol in augmenting vesicle deformability, enhancing stratum corneum hydration, and enabling regulated drug deposition within epidermal and dermal layers is emphasized. A comprehensive evaluation of recent *in vitro, ex vivo,* and *in vivo* studies indicates that glycerosomal formulations provide enhanced antifungal efficacy, extended drug retention, and decreased dosing frequency compared to traditional topical formulations and other vesicular carriers. In general, this review shows that glycerosomes could be a useful liposome-derived platform for making topical antifungal treatment more effective.

Keywords: Glycerosomes, Liposomes, Vesicular drug delivery systems, Fungal treatment, Topical antifungal therapy, Antifungal agents

INTRODUCTION

Significant dermatological morbidity worldwide is caused by fungal infections of the skin and related tissues[1,7,9,45]. Because of the protective stratum corneum, traditional topical formulations (creams, gels, and ointments) frequently experience poor therapeutic outcomes and problems with patient compliance because they are unable to deliver adequate drug quantities into deeper epidermal layers[2,3]. To get around these restrictions, researchers have looked into using nanovesicular carriers like ethosomes, glycerosomes[106], transfersomes, and liposomes[105]. Because of their distinct composition and functional characteristics, glycerosomes are becoming one of the most advanced carriers designed for topical and transdermal applications. The stratum corneum barrier, poor drug penetration, and systemic side effects continue to be obstacles to topical antifungal therapy[4-6].

Because of their improved permeation, entrapment, stability, and therapeutic efficacy, glycerosomes, a novel class of glycerol-enriched vesicular carriers, have shown

Adarsh Vijendra Institute of Pharmaceutical Sciences, Shobhit University, Gangoh, Saharanpur, U.P., India

***Corresponding Author** Veenu Choudhary (veenuchoudhary828@gmail.com)

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great promise as systems for better topical drug delivery. With a particular focus on antifungal therapy, this review addresses the formulation techniques, mechanistic aspects, characterization parameters, and therapeutic potential of glycerosomes. To offer a thorough understanding of glycerosomal systems, recent developments, such as optimization strategies and clinical significance, are examined. A revolutionary development in drug delivery technology is represented by glycerosomes[7]. When compared to traditional liposomes, glycerosomes, which are made up of glycerol, phospholipids, and water, provide better drug stability, penetration, entrapment efficiency, fluidity, and viscosity[8].

Glycerosomes

A new class of vesicular drug delivery systems called glycerosomes was created especially for topical and systemic uses[9]. These sophisticated carriers are distinguished by their distinct makeup, which consists of water, phospholipids, and high glycerol content (usually 20-40%)[10]. High glycerol concentrations are especially important because they improve vesicle stability and flexibility, which in turn promotes drug penetration[11,12]. The internal and external layers make up the skin. The epidermis is the outermost layer, while the dermis is the inner (deeper) layer[13]. The stratum corneum is found between the numerous layers that make up the external layer[14] (Fig. 1).

It is a barrier for the majority of drug substances because it functions as a challenging membrane for drug penetration[15-17]. The thickness of the two layers varies. The external epidermal layer is 50-150 µm thick, while the inner layer, which is made up of hair follicles and connective tissues, ranges in thickness from 0.3 to 4 mm. A hydrolipidic layer made up of water, sweat, and sebum extends it. This film serves as a protective sheath to shield the skin from microorganisms[18-21]. Glycerosome carriers are suitable for extremely sensitive skin because, like other vesicular systems, they are safe and generally accepted for topical treatments.

This is due to the fact that they don't contain any toxic substances, such as ethanol, as a structural element[22]. Glycerosomes represent a revolutionary development in medication delivery technology. When compared to traditional liposomes, glycerosomes, which are composed of glycerol, phospholipids, and water, provide better drug stability, penetration, entrapment efficiency, fluidity, and viscosity[23].

Structural and physicochemical basis of glycerosomes

The main advantage of Glycerosome over traditional topical formulations is their capacity to deliver deeper into the layers of the skin. Free drugs would typically not be able to reach the deeper layers of skin as well as these noninvasive carriers[24,67]. Treating fungal infections, which frequently reside in deeper dermal and subdermal layers, requires this improved penetration capability. Furthermore, glycerosomes are adaptable carriers for a range of antifungal agents[26,27] due to their ability to encapsulate hydrophilic and lipophilic medications while shielding them from degradation[25,99].

At the structural level, glycerol forms hydrogen bonds with the polar head groups of phospholipids, changing the bilayer packing, increasing membrane fluidity, and lowering the lipid phase transition temperature. Increased vesicular deformability is provided by these interactions

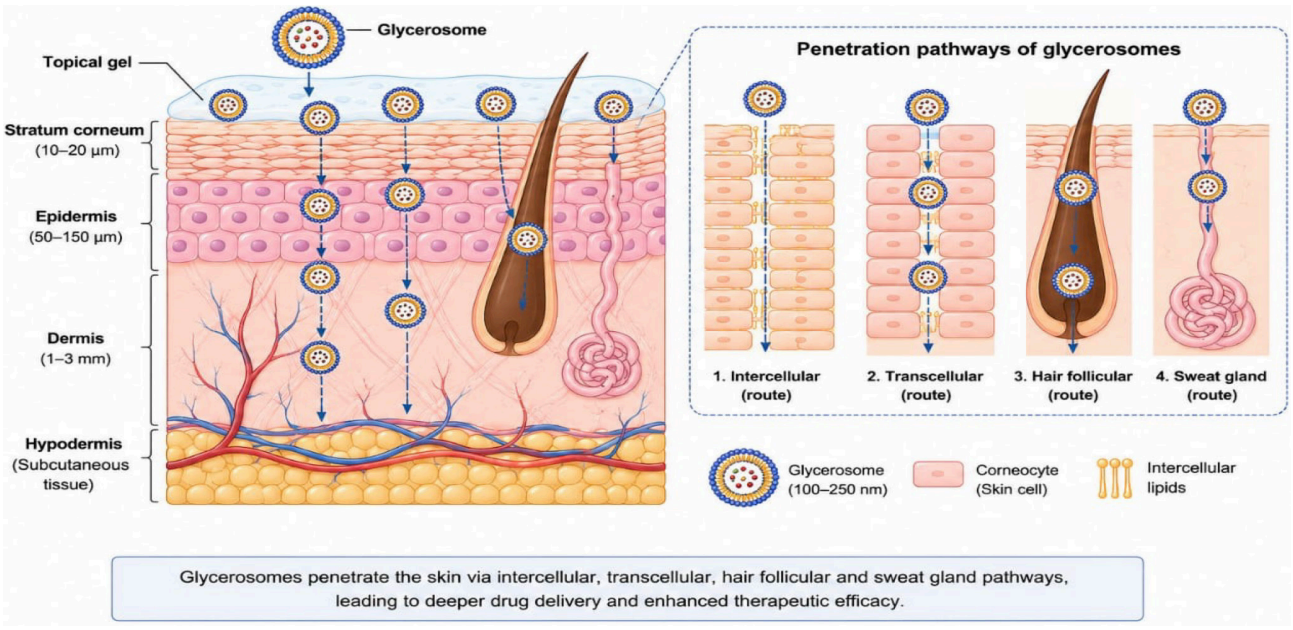

Figure 1. Skin structure and penetration pathway of glycerosomes

while maintaining the integrity of the bilayer, which is essential for efficient skin penetration[28].

When compared to standard liposomes, glycerosomes show better colloidal stability, a narrower size distribution, and less vesicle rigidity from a physicochemical standpoint. Glycerol contributes to steric stability and resistance to aggregation during storage by strengthening the hydration shell around vesicles[134,135]. Furthermore, glycerol functions as a humectant, encouraging temporary lipid disordering and stratum corneum hydration, both of which work in concert to improve vesicle-skin interactions[29].

Glycerol content, lipid composition, and vesicle lamellarity all have a major impact on the encapsulation efficiency of both hydrophilic and lipophilic antifungal drugs. Optimized glycerosomal systems minimize systemic absorption by exhibiting prolonged drug release profiles and enhanced drug retention within epidermal layers[30]. Glycerosomes' exceptional effectiveness as liposome-derived carriers for topical antifungal therapy is supported by their distinct structural organization and physicochemical characteristics[109].

Comparative evaluation of Glycerosomes with other vesicular carriers

Glycerosomes share several characteristics with other lipid-based vesicular carriers; however, their unique glycerol-enriched composition provides distinct advantages for topical antifungal delivery. Conventional liposomes exhibit good biocompatibility but often suffer from limited skin penetration because of rigid bilayer structures. Transfersomes possess excellent deformability due to edge activators, enabling efficient penetration through narrow skin pores, although their long-term stability may be compromised. Ethosomes, enriched with ethanol, demonstrate enhanced permeation but may cause irritation or vesicle leakage during storage. Niosomes offer improved chemical stability and cost-effectiveness but generally show lower flexibility compared with glycerosomes. In contrast, glycerosomes combine improved deformability, enhanced hydration-mediated penetration, higher entrapment efficiency, and superior patient tolerability, making them highly suitable for topical antifungal therapy. The balanced physicochemical properties of glycerosomes position them as promising alternatives to existing vesicular carriers[109] (Table 1).

Composition and mechanism of action

Biocompatible phospholipids, like phosphatidylcholine or hydrogenated phospholipids, are the main parts of glycerosomes. They are spread out in a water phase that has a lot of glycerol in it[31]. Controlled amounts of cholesterol or other membrane stabilizers can be added to change the rigidity, permeability, and stability of vesicles. The vesicle's size, lamellarity, deformability, and drug encapsulation efficiency depend on the relative amounts of phospholipid, glycerol, and stabilizing agents. Lipophilic antifungal agents preferentially integrate into the lipid bilayer, while hydrophilic drugs are sequestered within the glycerol-enriched aqueous core, facilitating adaptable drug-loading methodologies[32].

The mechanism of action of glycerosomes in topical antifungal therapy is multifaceted and transcends mere passive drug diffusion. When applied to the skin, glycerol is a powerful humectant that makes the stratum corneum more hydrated and breaks up the ordered lipid domains of corneocytes[33]. This hydration-induced lipid fluidization reduces the skin's barrier resistance, making it easier for vesicles to come into contact with the skin and change shape. At the same time, the flexible glycerosome bilayer lets vesicles that are whole or only slightly deformed move through intercellular pathways, which helps them penetrate deeper into the epidermis. As glycerosomes move through the skin, they slowly and carefully release the antifungal drug they contain. This increases the amount of drug that gets to the infection site while reducing the amount of drug that gets into the rest of the body[34].

The superior antifungal efficacy and prolonged therapeutic action of glycerosomal formulations are attributable to the synergistic effects of optimized composition and glycerol-mediated penetration enhancement.

Phospholipids

Glycerosomal bilayers are mostly composed of phospholipids, which create ordered lamellar structures that enclose and shield antifungal agents[35]. Phospholipid type and acyl chain composition have a significant impact on vesicle properties such as size, lamellarity, bilayer fluidity, mechanical flexibility, and encapsulation efficiency. In comparison to traditional liposomes, glycerosomes exhibit improved vesicle deformability due to the interaction of phospholipid bilayers with glycerol, which results in hydrogen bonding at the headgroup region and a modest alteration of the phase transition temperature (Tm). When compared to ordinary liposomes, vesicles with a higher glycerol content are more elastic and have a better ability to penetrate skin intercellular channels. This is demonstrated by the improved transport of model pharmaceuticals into epidermal layers. Glycerosomal superiority for topical antifungal deployment is supported by these molecular characteristics[36].

Glycerol

Glycerol acts as both a structural modifier and penetration enhancer by interacting with phospholipid head groups through hydrogen bonding[37]. This interaction improves bilayer fluidity, vesicle deformability, and stratum corneum hydration, collectively enhancing skin permeation while maintaining vesicular integrity.

Table 1. Comparative evaluation of Glycerosomes with other vesicular carriers for dermal drug delivery

Parameter	Glycerosomes	Liposomes	Transfersomes	Ethosomes	Niosomes
Vesicle flexibility	Very high	Low to moderate	Very high	High	Moderate
Membrane fluidity	High	Moderate	Very high	Very high	Moderate
Typical vesicle size (nm)	100-250	100-1000	70-300	80-400	100-500
Entrapment efficiency	High, especially for lipophilic drugs	Moderate to high	High	Moderate to high	High
Skin hydration effect	Excellent (due to glycerol)	Limited	Moderate	Moderate	Limited
Skin penetration ability	Excellent	Limited	Excellent	Excellent	Moderate
Stratum corneum interaction	Hydration + lipid fluidization	Surface deposition	Deformation through narrow pores	Lipid extraction/ fluidization	Adsorption and diffusion
Follicular targeting potential	High	Moderate	High	High	Moderate
Drug retention in skin	Excellent	Moderate	High	High	Moderate
Suitability for lipophilic drugs	Excellent	Good	Excellent	Excellent	Good
Suitability for hydrophilic drugs	Good	Excellent	Good	Good	Excellent
Physical stability	High	Moderate	Moderate	Moderate	Highç
Aggregation tendency	Low	Moderate to high	Moderate	Moderate	Low
Leakage during storage	Minimal	Moderate	Moderate	Moderate	Low
Scalability	High	High	Moderate	Moderate	High
Cost of formulation	Moderate	Moderate	High	High	Low to moderate
Regulatory familiarity	Emerging	Well established	Growing	Growing	Well established
Best application area	Chronic dermal therapy, sustained topical delivery	Conventional topical delivery	Deep skin/ transdermal delivery	Rapid dermal penetration	Stable topical formulations

Cholesterol

Cholesterol is routinely combined with glycerosomes to improve bilayer stability and permeability[137]. Cholesterol improves packing order and mechanical strength by intercalating between phospholipid acyl chains, eliminating excess fluidity that could jeopardise vesicle integrity during storage and application. Cholesterol content optimization improves encapsulation efficiency and controls drug release kinetics by lowering bilayer permeability. However, mechanistic investigations show that an excessive amount may counteract glycerol-induced flexibility, potentially lowering vesicle deformability. As a result, the phospholipid-cholesterol ratio must be carefully tuned to strike a compromise between rigidity and flexibility, achieving increased stability without significantly reducing penetration potential[38,74,138].

Formulation strategies

The thin film hydration method is commonly used to construct glycerosomes because it enables regulated composition and the production of stable, nanoscale drug-loaded vesicles[39]. To investigate the effects of varying composition parameters on drug loading, entrapment efficiency, and particle size, central composite design has been utilized[40]. According to studies, numerical optimization can show that composition alterations have a remarkable impact on particle size and entrapment effectiveness, allowing researchers to create highly optimized formulations. Glycerosomal performance is influenced by a number of formulation parameters.

Preparation methods

Thin film hydration method

Because of its ease of use and versatility in handling a variety of lipid compositions, the thin film hydration

process is the most popular and repeatable approach for creating glycerosomes[41]. To create a homogeneous, thin lipid film, phospholipids and other lipophilic substances are dissolved in a volatile organic solvent and then evaporated under low pressure. Vesicles occur spontaneously when the film is subsequently hydrated with an aqueous phase that contains a certain concentration of glycerol. In comparison to traditional liposomes, the addition of glycerol during hydration significantly affects bilayer structure, leading to increased membrane flexibility and decreased vesicle stiffness[42].

Vesicle size, lamellarity, and drug encapsulation efficiency are all significantly influenced by process variables such as hydration temperature, glycerol content, and post-hydration size reduction methods (extrusion or sonication). This technique enables precise control over the physicochemical properties of glycerosomes and is especially well suited for adding lipophilic antifungal drugs.

Reverse phase evaporation method

In glycerosomal systems, the reverse phase evaporation approach is particularly useful for obtaining high encapsulation efficiency of hydrophilic antifungal drugs. This method creates a stable water-in-oil emulsion by dissolving phospholipids in an organic phase and then emulsifying them with an aqueous phase that contains glycerol[43]. Emulsion droplets give way to vesicular structures with a sizable interior aqueous compartment when the organic solvent is gradually removed under lower pressure. The resultant bilayers have better flexibility and stability, and the glycerol-enriched core improves drug solubilization and vesicle deformability[44]. This technique produces glycerosomes that are suited for prolonged drug release and improved skin deposition since they usually exhibit bigger vesicle sizes and unilamellar or oligolamellar structures. To preserve vesicle integrity and reduce residual solvent, careful optimization is necessary.

Detergent removal method

A regulated approach to creating glycerosomes with a consistent lamellarity and a restricted size distribution is provided by the detergent removal procedure[45]. This method creates mixed micelles by first solubilizing phospholipids in the presence of an appropriate detergent. Glycerosomes self-assemble when the detergent is gradually removed, usually by dialysis or adsorption onto hydrophobic resins, while an aqueous phase containing glycerol is present. By stabilizing intermediate structures and encouraging flexible bilayer assembly, glycerol regulates the vesicle formation kinetics[46,55,136]. This technique allows for exact control over the composition of the vesicles and is especially helpful for delicate antifungal compounds that might break down in severe processing environments. The method's operational complexity and scalability restrictions make it less popular despite its benefits[139].

Solvent injection method

A quick and scalable method for producing glycerosomes, the solvent injection method may be used in both industrial and laboratory settings. This technique involves injecting a lipid solution in a water-miscible organic solvent into an aqueous phase that contains glycerol while being carefully stirred[47]. Lipid precipitation and vesicle formation result from instantaneous solvent diffusion. The presence of glycerol in the aqueous phase inhibits vesicle aggregation during formation and encourages flexible bilayer construction. This method is especially useful for heat-sensitive antifungal medications and usually produces tiny, unilamellar glycerosomes with a very homogeneous size distribution. However, injection rate, solvent choice, and lipid content all have a significant impact on formulation results, therefore meticulous process optimization is required to provide repeatable vesicle properties[48].

Optimization parameters

The efficacy of glycerosomes as advanced vesicular carriers is greatly reliant on the careful adjustment of formulation and manufacturing parameters[49]. Unlike ordinary liposomes, glycerosomes have glycerol as a crucial structural and functional component, which has a considerable impact on vesicle flexibility, bilayer packing, drug encapsulation, and skin penetration behavior. Systematic adjustment of glycerol content, phospholipid-cholesterol ratios, and processing factors is required to create repeatable, stable, and therapeutically effective glycerosomal formulations for topical antifungal treatment[50].

Glycerol concentration

Glycerol concentration is an important factor influencing glycerosome architecture and functional effectiveness. Glycerol, which is typically present at a concentration of 10-30% v/v, interacts with the polar head groups of phospholipids via hydrogen bonding, resulting in increased bilayer fluidity and deformability. At ideal quantities, glycerol serves as a softener, lowering the gel-liquid crystalline transition temperature of the lipid bilayer and increasing vesicle flexibility while maintaining structural integrity[51]. An increase in glycerol content reduces vesicle size, improves homogeneity, and increases entrapment efficiency for both lipophilic and moderately hydrophilic antifungal drugs. Glycerol interrupts inter-lipid hydrogen bonding, resulting in transitory aqueous channels inside the bilayer that enable drug accommodation.

Furthermore, glycerol's humectant and hygroscopic properties help to improve skin moisture, which increases stratum corneum permeability and enables deeper medication penetration[52]. However, excessive glycerol

levels (>30%) might destabilize vesicles, causing bilayer instability, drug leakage, and decreased physical stability. As a result, an optimal glycerol content is required to maintain vesicle flexibility, drug retention, and long-term formulation stability[53].

Phospholipid-cholesterol ratios

The phospholipid-cholesterol ratio regulates glycerosomal membrane stiffness, permeability, and resistance to vesicle fusion or aggregation. Phospholipids are the structural backbone of glycerosomes, and cholesterol influences bilayer packing density by intercalating between phospholipid acyl chains[54].

An adjusted cholesterol content improves membrane stability by minimizing bilayer permeability and limiting medication leakage during storage and application. In glycerosomal systems, cholesterol counterbalances glycerol's fluidizing impact, ensuring structural cohesiveness under mechanical stress. The typical phospholipid-to-cholesterol ratio ranges from 7:3 to 9:1, depending on the encapsulated drug's physicochemical qualities[55].

Low cholesterol levels may produce too flexible vesicles with poor stability, whereas high cholesterol levels can stiffen the bilayer, lowering vesicle deformability and restricting epidermal penetration. For topical antifungal administration, an ideal balance is required to guarantee enough membrane elasticity for transdermal transport while retaining vesicular integrity and regulated drug release at the target location[56,107].

Process variables

Process factors have a substantial impact on glycerosome production, size distribution, encapsulation efficiency, and repeatability. Hydration temperature, hydration period, organic solvent removal rate, sonication or homogenization intensity, and stirring speed all play important roles in vesicle formation[57,131].

The hydration temperature must be kept above the lipid phase transition temperature to guarantee homogeneous bilayer formation and full vesicle swelling[132]. Prolonged hydration durations improve effective drug entrapment, but they may potentially increase vesicle size due to excessive bilayer relaxation[58,133]. Mechanical energy input by probe sonication or high-pressure homogenization is widely used to reduce vesicle size and polydispersity; however, too much energy can induce vesicle breakage and drug leakage[140-143].

Furthermore, regulated solvent evaporation and progressive aqueous phase addition are required for consistent glycerosome synthesis, especially in scalable production techniques. The optimization of these factors results in uniform vesicle shape, high entrapment efficiency, and predictable *in vitro* and *in vivo* performance[59].

For antifungal medications to be delivered topically effectively, glycerosomal formulations must be optimized. Glycerosomes can perform better than traditional vesicles by optimizing composition and processing parameters, improving skin permeability and therapeutic results. The best vesicle features may be attained by utilizing design-of-experiments techniques like factorial design or central composite design, opening the door for cutting-edge topical treatments[60].

Glycerosomes' therapeutic efficacy in topical antifungal administration depends on the formulation and process factors being strategically optimized[141]. This study highlights the potential of glycerosomes as a flexible platform for improved skin delivery by clarifying these crucial elements, making them an appealing substitute for traditional vesicular systems in the treatment of fungal diseases.

Characterization of glycerosomes

To determine glycerosomes' stability, drug-loading ability, and appropriateness for topical antifungal administration, a thorough physicochemical characterization is necessary[61]. Important factors that affect skin penetration, residence time, and therapeutic efficacy include particle size, polydispersity index, zeta potential, entrapment efficiency, and vesicular shape (Fig. 2).

Particle size and polydispersity index (PDI)

Glycerosomal penetration into the stratum corneum and deeper skin layers is significantly influenced by particle size. The usual nanoscale vesicle diameters of glycerosomes range from 100 to 300 nm, contingent on the manufacturing method and formulation composition. Compared to traditional liposomes, the inclusion of glycerol results in reduced vesicle size due to increased membrane fluidity[62]. Vesicles that are consistently distributed and smaller have a greater surface area, which improves medication dispersion across cutaneous barriers and allows for intimate contact with the skin.

The homogeneity of the vesicle size distribution is reflected in the polydispersity index (PDI). It is thought that a restricted size distribution and consistent formulation are indicated by PDI values less than 0.3. Reproducible drug delivery and long-term formulation stability depend on effective vesicle production and low aggregation, which are shown by low PDI values in glycerosomal systems[63]. PDI and adjusted particle size work together to provide consistent antifungal activity and better skin deposition.

Zeta potential

The zeta potential indicates the surface charge and electrostatic stability of glycerosomal dispersions. Glycerosomes have moderate to high negative zeta potential values due to the ionization of phospholipid head groups and the impact of glycerol inside the vesicular bilayer[64].

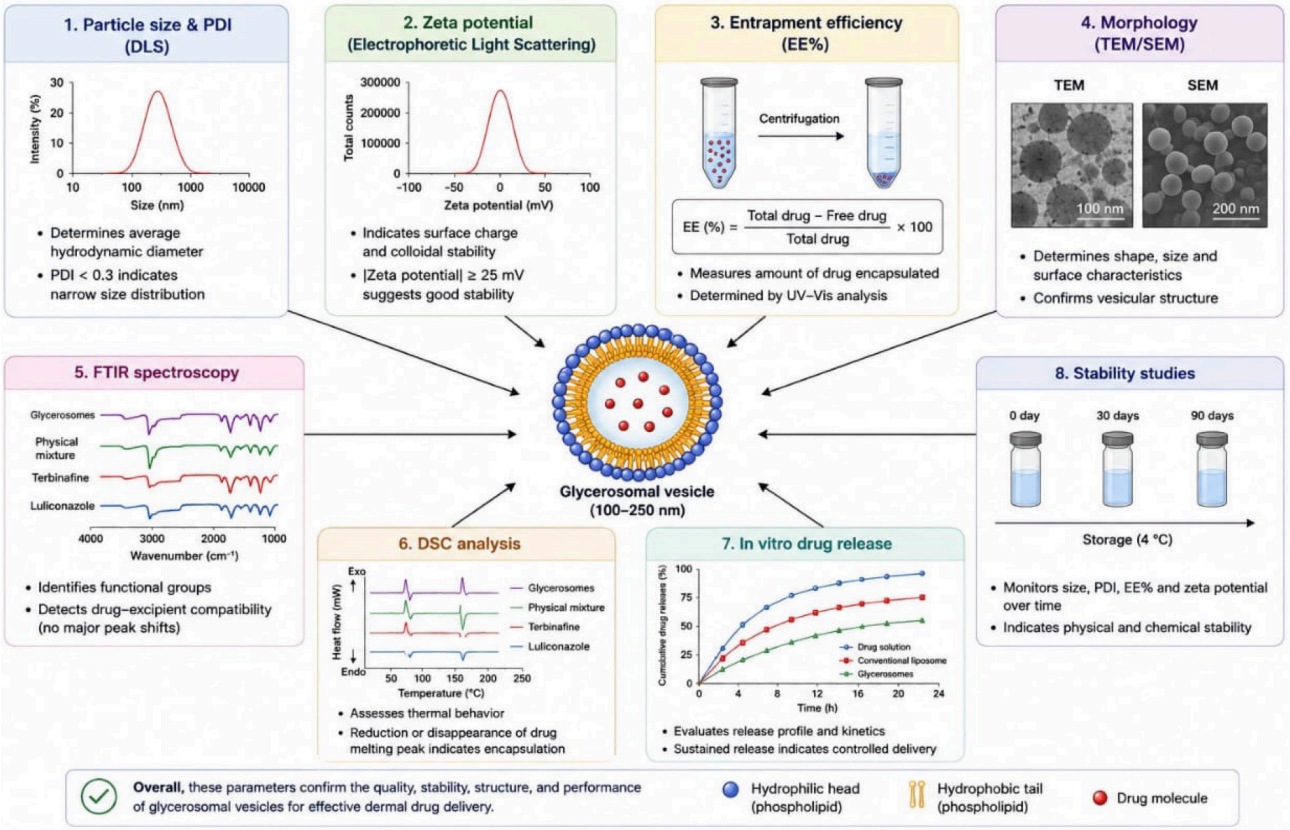

Figure 2. Characterization parameters of glycerosomal vesicles

Electrostatic repulsion inhibits vesicle aggregation during storage, hence values over ±30 mV frequently indicate improved colloidal stability.Surface charge modulates vesicle-skin interactions during topical administration. Negatively charged glycerosomes have been shown to interact favorably with skin lipids, resulting in longer residence duration at the application site. As a result, zeta potential not only determines physical stability but also influences cutaneous retention and therapeutic efficacy of glycerosome-based formulations[65].

Entrapment efficiency

Entrapment efficiency measures glycerosomes' capacity to encapsulate and hold drug molecules within their vesicular structure[154]. The unusual bilayer design of glycerosomes, along with the presence of glycerol, provides for better accommodation of both lipophilic and moderately hydrophilic medicines[66]. Glycerol enhances bilayer flexibility and internal aqueous volume, resulting in more drug entrapment than typical liposomes. High entrapment efficiency is especially beneficial for topical antifungal treatment because it assures enough drug availability at the target location while reducing drug loss and systemic exposure. Efficient drug encapsulation also promotes prolonged medication release, lowering dose frequency and enhancing patient compliance[67].

Morphology

Morphological assessment confirms vesicle production and structural integrity of glycerosomes. Transmission electron microscopy (TEM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) are standard methods for examining vesicle form, lamellarity, and surface properties[142,144]. Glycerosomes are often well-defined, spherical or near-spherical vesicles that have smooth surfaces.

Glycerol helps to build flexible and pliable vesicular membranes, which distinguishes glycerosomes[145-148]. Such deformability allows vesicles to pass across tight intercellular gaps in the stratum corneum without rupture. Consistent shape with little vesicle fusion or collapse indicates formulation resilience and suggests good efficacy in topical drug delivery applications[68].

Overall, the physicochemical characterisation of glycerosomes sheds light on their stability, skin contact potential, and drug delivery effectiveness, highlighting their expanding importance as advanced vesicular carriers for topical antifungal treatment. Glycerol incorporation often improves vesicle deformability and drug trapping as compared to liposomes.

Therapeutic advantages

Glycerosomes have emerged as a viable vesicular drug

delivery mechanism for topical antifungal treatment due to their distinct composition and improved interaction with the skin barrier[142,149]. Glycerosomes, which incorporate high quantities of glycerol into phospholipid vesicles, have improved flexibility, hydration capacity, and drug-carrier performance, resulting in considerable therapeutic benefits over standard topical formulations.Glycerosomes have various therapeutic advantages for topical antifungal treatment.

Enhanced skin penetration

One of the most notable therapeutic benefits of glycerosomes is their increased ability to permeate the stratum corneum. Glycerol is a potent humectant and penetration enhancer that increases skin moisture and loosens the stratum corneum's densely packed lipid architecture[150]. Simultaneously, the flexibility and deformability of glycerosomal vesicles allow them to pass via tight intercellular routes without structural damage[70]. This dual method allows for greater medication penetration and increased drug accumulation inside the epidermal and dermal layers, which is especially useful for treating fungal infections in deeper skin strata. High glycerol concentrations provide flexibility that allows for deeper skin penetration, which is crucial for treating dermatological fungal infections[71] (Fig. 3).

Antifungal drugs (e.g., terbinafine, tolnaftate, miconazole) exhibit increased dermal accumulation when administered via glycerosomes, which is due to glycerol-induced bilayer fluidization and stratum corneum hydration. This increase in local concentration around infection sites improves fungicidal action.

Improved efficacy and safety

Improved skin penetration directly correlates with higher antifungal activity of glycerosome-based formulations. Glycerosomes provide fast fungal clearance and extended therapeutic effect by delivering larger quantities of the antifungal drug directly to the site of infection[72,135,151]. Simultaneously, targeted drug administration reduces drug exposure to healthy adjacent tissues, lowering the likelihood of local irritation, erythema, and other cutaneous side effects often associated with traditional topical antifungals. This customized delivery method improves the therapeutic index while balancing efficacy and safety. In contrast to typical formulations, glycerosomal carriers:

- Improve drug retention in dermatological areas.
- Minimize systemic exposure and negative effects.
- Maintain medication release, potentially reducing dose frequency.
- Computational and preclinical models offer promise, but clinical validation requires further study.

Drug protection

Glycerosomes form a safe milieu for encapsulated antifungal drugs, sheltering them from destruction caused by external variables such as light, oxygen, and enzymatic activity[110,135]. The phospholipid bilayer functions as a physical barrier, keeping the medicine stable throughout storage and after topical administration. This safeguard is especially critical for antifungal medications that are chemically unstable or susceptible to oxidative destruction. Enhanced drug stability guarantees consistent therapeutic effectiveness and increases the formulation's shelf life. Both lipophilic and hydrophilic antifungal drugs are protected from degradation in the vesicle environment[73].

Minimal systemic absorption

Topical antifungal treatment tries to increase medication concentrations at the site of infection while minimizing systemic exposure. Glycerosomes efficiently localize the medication inside the skin's layers, decreasing transdermal drug absorption into the systemic circulation[155]. This localized retention reduces the possibility of systemic adverse effects and drug-drug interactions, making glycerosomal formulations ideal for long-term treatment for patients who require repeated or extended antifungal medication. Glycerosomes provide for targeted distribution, potentially lowering systemic adverse effects associated with oral antifungal medication[74,135].

Versatility

Glycerosomes are extremely versatile as drug delivery vehicles. They may encapsulate a diverse spectrum of antifungal medicines, including lipophilic, hydrophilic, and amphiphilic medications. Furthermore, glycerosomal formulations can be used in a variety of topical dose forms, including gels, creams, lotions, and ointments, without affecting vesicle integrity[114]. This flexibility allows formulation customisation based on the drug's physicochemical qualities and the therapeutic needs of various fungal infections[75]. Multiple studies have shown that glycerosomes may successfully encapsulate a variety of antifungal medicines, including terbinafine, natamycin, and natural antimicrobial extracts.

Biocompatibility

Glycerosome components, most notably phospholipids and glycerol, are biocompatible and readily tolerated by the skin. These ingredients are closely related to natural skin lipids, which reduces the possibility of immunogenic or harmful reactions. Glycerol's moisturizing function improves patient comfort by avoiding skin dryness and irritation, which are prevalent during antifungal medication[76]. High biocompatibility allows for the safe and recurrent use of glycerosome-based topical preparations in clinical practice.Glycerol, phospholipids, and cholesterol are completely safe and suitable constituents for topical medicinal formulations.

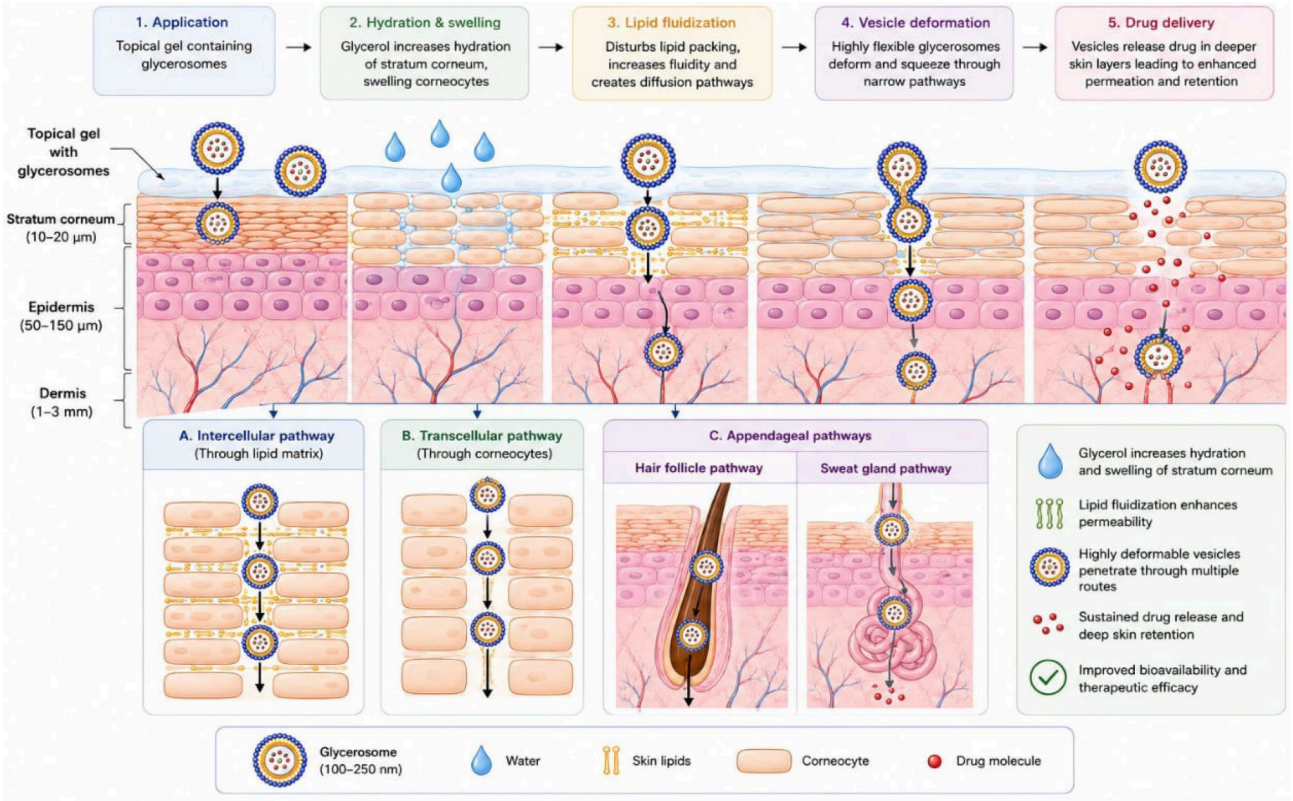

Figure 3. Mechanism of glycerosome-mediated skin permeation

Recent advances and case studies

Although particular glycerosomal antifungal formulations are a relatively new concept, current research suggests that additional topical medicines may show promise[113]. For example, glycerosomal gels containing a topical anti-inflammatory increased penetration flow by more than twofold when compared to traditional ointments[77]. In recent years, there has been substantial progress in the development and assessment of glycerosome-based delivery methods for topical antifungal treatment. Advances in formulation strategies, processing techniques, and preclinical assessment models have reinforced glycerosomes' therapeutic rationale, establishing them as the next-generation vesicular carriers for cutaneous fungal infections[115].

Recent advances in Glycerosome-based antifungal delivery

One of the most significant advancements is the adjustment of glycerol concentrations within the vesicular system to balance membrane flexibility, vesicle stability, and skin penetration efficiency[116]. According to studies, increasing glycerol concentration increases bilayer fluidity and deformability, resulting in enhanced transdermal penetration and longer drug retention inside the epidermis[108]. This has resulted in the invention of glycerosomes that can carry antifungal drugs more effectively than traditional liposomes and other elastic vesicular systems[78].

Technological advancements in preparation methods, including improved thin-film hydration, probe sonication, and high-pressure homogenization, have resulted in glycerosomes with smaller particles, narrower size distributions, and higher entrapment efficiency. These enhancements improve repeatability and scalability, overcoming previous constraints associated with vesicular drug delivery systems.

Another significant innovation is the incorporation of glycerosomes into secondary topical dose forms, including gels and hydrogel matrices[79]. Glycerosomal gels have been found to increase spreadability, extend skin residence duration, and provide sustained drug release characteristics[117]. These hybrid systems combine the penetration-enhancing capabilities of glycerosomes with the patient-friendly characteristics of semisolid formulations, making them ideal for chronic and recurring fungal infections[80].

Case Studies and Preclinical Evidence

Several *in vitro* and *in vivo* investigations have found persuasive evidence for the therapeutic superiority of glycerosome-based antifungal formulations[81]. *In vitro* antifungal studies revealed increased fungistatic and fungicidal efficacy against common dermatophytes, which

was ascribed to better drug availability at the site of action. Skin permeation and deposition investigations using excised animal or human skin models have repeatedly shown that glycerosomes improve medication retention in the epidermal and dermal layers[82]. Preclinical *in vivo* investigations in fungal infection models have supported similar findings, demonstrating quicker lesion regression, lower fungal load, and better histopathology outcomes than traditional topical formulations[104]. Importantly, glycerosome-treated groups experienced minor skin irritation and no evidence of systemic toxicity, demonstrating the safety and acceptability of these systems[99].

Comparative case studies comparing glycerosomes to other advanced vesicular carriers such as ethosomes, transfersomes, and niosomes have revealed a unique advantage in terms of hydration-induced penetration enhancement and biocompatibility. These findings indicate that glycerosomes provide a balanced profile of effectiveness, safety, and formulation simplicity[118].

Translational significance and future prospects

An increasing collection of experimental and comparative evidence supports glycerosomes' translational promise in topical antifungal treatment. While most current studies are still in the preclinical stage, their consistent results suggest high clinical promise. Future research is planned to concentrate on clinical validation, long-term stability tests, and scale-up feasibility, which are crucial for regulatory approval and commercialization[83].

Advantages and Limitations of Glycerosomes in Topical Antifungal Therapy

Glycerosomes are an innovative vesicular drug delivery technology with significant therapeutic and formulation benefits for topical antifungal applications[84]. However, despite their promising performance, several constraints must be addressed in order for effective clinical translation and large-scale utilization.

Advantages

One of the key benefits of glycerosomes is their improved skin penetration[98]. High glycerol concentration improves stratum corneum hydration and bilayer flexibility, allowing glycerosomes to successfully cross intercellular lipid channels. This leads to increased medication deposition in deeper skin layers, which is especially useful for treating chronic and deep-seated fungal infections[85].

Glycerosomes also boost treatment effectiveness by allowing antifungal medicines to be delivered specifically and consistently to the site of infection[119]. Enhanced drug localization lowers the necessary dose and frequency of administration, enhancing patient compliance and treatment effects. At the same time, localized distribution reduces systemic drug exposure, which lowers the likelihood of systemic side effects.Another significant benefit is the high drug entrapment effectiveness of glycerosomal systems[97]. The adaptable vesicular structure may hold a variety of antifungal medicines, including lipophilic and amphiphilic compounds. Furthermore, the phospholipid bilayer shields the encapsulated medication from environmental and enzymatic degradation, increasing formulation stability and shelf life[86].

Glycerosomes are made up of biocompatible and skin-friendly ingredients, including phospholipids and glycerol, which closely mimic natural skin components. This yields great tolerance, little discomfort, and appropriateness for repeated or long-term topical use. Furthermore, glycerosomes may be readily included into traditional topical dose forms such as gels, creams, and ointments, increasing formulation diversity and patient convenience.

Limitations

Despite their benefits, glycerosomes confront certain formulation and translational problems. One of the most significant limitations is their physical and chemical stability during long-term storage. Vesicle aggregation, drug leakage, and changes in particle size distribution might occur over time, especially under adverse storage circumstances, demanding careful formulation composition and storage parameter optimization[87].

Scalability and manufacturing complexity provide further obstacles. Although laboratory-scale preparation procedures are well known, applying these techniques to industrial-scale production while preserving batch-to-batch uniformity can be challenging. Specialized equipment and process control may be necessary, thereby increasing manufacturing costs. Another issue is the scarcity of clinical data[88]. The majority of data for the effectiveness and safety of glycerosomes in antifungal treatment comes from *in vitro* and preclinical *in vivo* investigations. The scarcity of well-designed clinical studies prevents conclusive conclusions about their therapeutic advantages over conventional topical formulations[96]. Furthermore, high glycerol concentrations, while good for penetration augmentation, might cause skin pain or irritation in sensitive people if not adequately calibrated. As a result, a careful balance between penetration augmentation and skin tolerance is required[91,96].

Applications in antifungal therapy

Terbinafine hydrochloride delivery

Terbinafine hydrochloride, a broad-spectrum antifungal drug, has been used in several studies[104]. A biocompatible platform made up of glycerin, phospholipids, and cholesterol has been proposed for treating mycoses via the cutaneous route[89]. Optimized glycerosomal formulations of terbinafine outperformed traditional preparations in terms of deformability, antifungal efficacy, surface morphology,

and *in vitro*/*ex vivo* diffusion[89]. Notably, histopathological investigations verified the feasibility of glycerosomal carrier systems for transdermal administration of terbinafine hydrochloride, with higher penetration than commercial formulations[90].

Ophthalmic applications with Natamycin

Additionally, glycerosomes have been effectively created for the transport of antifungal medications into the eyes[120]. In comparison to pure liposomes, natamycin-loaded glycerosomes that were created utilizing the thin film hydration approach and refined by factorial design showed much greater entrapment efficiency (80.84%), *in vitro* penetration (93.42%), and superior stability[91]. With a zeta potential of -27.6 and a particle size of 394.5 nm, the modified glycerosomal formulation showed improved properties for ocular administration[91].

Antimicrobial potential with natural extracts

Glycerosomes containing antibacterial compounds produced from plants have also been investigated[121]. Glycerosomes had improved antibacterial and antifungal activity when prepared with extracts of Zingiber officinale and Allium sativum[92]. When compared to other preparations, these formulations showed enhanced efficacy against gram-negative bacteria, indicating glycerosomes as viable options for the safe and efficient treatment of microbial illnesses[95].

Position among vesicular systems

In topical drug delivery studies, glycerosomes are widely acknowledged as one of the most promising vesicular carriers[122-124]. Glycerosomes have been a particularly intriguing topic of interest for researchers among the several vesicular delivery systems studied for fungal skin infections, such as liposomes, ethosomes, niosomes, bilosomes, cubosomes, and ufasomes[93,125]. They are positioned as cutting-edge substitutes for traditional antifungal formulations due to their improved penetration, drug protection properties, and compatibility with topical therapies[94,130].

Translational challenges and clinical perspectives

Despite encouraging preclinical outcomes, several challenges remain before glycerosomal formulations can achieve clinical translation[152-156]. Large-scale manufacturing requires robust process control to ensure batch-to-batch reproducibility and long-term physicochemical stability. Regulatory approval also demands comprehensive safety, toxicity, and stability evaluations according to international guidelines[111-113]. Furthermore, limited clinical evidence currently restricts direct comparison with commercially available topical antifungal therapies[126-129]. Future studies should focus on pilot-scale production, regulatory harmonization, and well-designed clinical trials to facilitate industrial implementation[100-103].

Conclusions

Glycerosomes are a potential advanced vesicular drug delivery method for topical antifungal treatment[157]. They outperform standard formulations by using glycerol's penetration-enhancing characteristics and the vesicular design of lipid-based carriers. Optimizing formulation characteristics and conducting extensive therapeutic evaluations might propel glycerosomal systems into clinical use and better fungal infection treatment.

Glycerosomes have emerged as a potential improvement in liposome-based vesicular drug delivery systems for topical antifungal treatment, providing a reasonable answer to the long-standing constraints of traditional topical formulations[157]. The integration of glycerol into phospholipid bilayers results in different structural and physicochemical properties, such as better vesicle deformability, skin hydration, and medication retention within epidermal layers. These characteristics, taken together, result in increased antifungal activity, prolonged drug release, and reduced dose frequency, all of which are essential for effectively managing superficial and deep-seated fungal infections. The examined formulation techniques and mechanistic insights demonstrate glycerosomes as a versatile and adaptable platform capable of accommodating a diverse variety of antifungal drugs with varying physicochemical characteristics.

Despite these positive findings, future research should focus on overcoming translational and regulatory barriers to clinical use. Systematic optimization of formulation variables using quality-by-design methodologies, along with improved characterization techniques, is required to assure batch-to-batch repeatability and long-term stability. To demonstrate glycerosomes' therapeutic superiority, clinical investigations comparing them to proven vesicular systems such as transfersomes and ethosomes are required. Furthermore, incorporating glycerosomes into patient-friendly dose forms including gels, lotions, and sprays may improve patient compliance and real-world applicability. Advances in scalable manufacturing methods and regulatory harmonization will be critical in moving glycerosomal systems from laboratory research to clinical and commercial success. Overall, glycerosomes are a strong and future-ready vesicular technology with the potential to revolutionise topical antifungal medication delivery.

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Conflict of interest

The authors declare no conflict of interest.

Author's contribution statement

All authors contributed to the conception, literature review, manuscript preparation, revision, and approval of the final manuscript.

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