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Original Article

Transferosomes for the Treatment of Psoriasis: A Novel Transdermal Drug Delivery Approach

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ABSTRACT

Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by excessive keratinocyte proliferation, abnormal epidermal differentiation, and persistent inflammation. It presents as red, thickened plaques covered with silvery scales, often causing itching and discomfort. Conventional treatments, including topical corticosteroids, vitamin D analogues, and systemic medications, may be limited by poor skin penetration, adverse effects, frequent application, and reduced patient adherence. The stratum corneum acts as a major barrier to effective drug delivery. Transferosomes are flexible vesicular carriers composed of phospholipids and edge activators that can deform and penetrate narrow spaces within the skin barrier, enhancing drug permeation and targeted deposition. These properties make them promising systems for topical and transdermal delivery of anti-psoriatic drugs. Potential benefits include improved drug absorption, controlled release, enhanced therapeutic efficacy, reduced systemic exposure, and fewer adverse effects. This review examines the principles and mechanisms of transferosomal drug delivery, formulation techniques, and the influence of formulation components on vesicle performance. It also discusses characterization parameters, drug-loading strategies, advantages, and limitations in psoriasis management. Recent developments and potential clinical applications are explored, emphasizing skin permeation, therapeutic effectiveness, stability, safety, and formulation optimization. Overall, transferosomes represent a promising approach to psoriasis treatment, although further preclinical and clinical investigations are required to establish their long-term safety, stability, and therapeutic effectiveness in clinical practice.

Keywords: Psoriasis, Transferosomes, Vesicular Drug Delivery, Topical Drug Delivery, Anti-psoriatic Drugs, Skin Permeation, Transdermal Drug Delivery, Formulation Optimization, Phospholipids, Edge Activators

INTRODUCTION:

Psoriasis is a chronic inflammatory skin condition that affects approximately 2–3% of the global population. It is characterized by red, scaly plaques that develop due to abnormal immune activity and excessive proliferation of keratinocytes. Conventional topical treatments, such as corticosteroids, vitamin D analogues, calcineurin inhibitors, and retinoids, are commonly used to manage the condition. However, their therapeutic effectiveness may be limited by inadequate drug penetration into the skin, potential adverse effects, and poor patient compliance due to the need for frequent application. The stratum corneum, which forms the outermost layer of the epidermis, acts as the main protective barrier against the entry of foreign substances. This barrier significantly limits the penetration of many therapeutic agents, particularly those with high molecular weights or hydrophilic properties, making it difficult to deliver sufficient drug concentrations to the affected skin layers. Therefore, the development of advanced drug delivery systems capable of overcoming this barrier is essential for improving the effectiveness of topical psoriasis treatment.[1-4]

Transferosomes were introduced in the early 1990s as advanced vesicular carriers designed to overcome skin penetration barriers. Unlike conventional liposomes, they contain edge activators, such as surfactants or bile salts, that provide high membrane flexibility and deformability. This allows them to pass through narrow intercellular spaces in the stratum corneum, even when these spaces are smaller than the vesicles themselves. Their ability to respond to skin hydration gradients further promotes deeper penetration and improved drug deposition in the epidermis and dermis, making them promising carriers for psoriasis treatment.[2,4,6]

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Recent studies have shown that transferosomal formulations of anti-psoriatic agents, including methotrexate, cyclosporine A, betamethasone, and natural compounds such as 20-hydroxyecdysone, can improve skin permeation, provide sustained drug release, and enhance therapeutic efficacy compared with conventional formulations. This review examines transferosomes as a promising drug delivery approach for psoriasis management, focusing on their structure, formulation strategies, characterization, drug loading, and challenges in clinical translation.[4-8]

Psoriasis: Defination, Types & Mechanism:

1. Definition

Psoriass is a chronic inflammatory disorder involving the skin and sometimes joints, nails, and other organs. It results from interactions between genetic susceptibility, environmental triggers, innate immunity, and adaptive immunity.[9,10]

The most common form, **plaque psoriasis / psoriasis vulgaris**, accounts for roughly 85–90% of cases and presents as well-demarcated erythematous plaques with silvery-white scale.[10,11]



Figure 1: Skin Condition in Psoriasis

Table 1: Types of Psoriasis

Type	Main clinical features
Plaque psoriasis (psoriasis vulgaris)	Raised, red, scaly plaques; most common form. [10,12]
Guttate psoriasis	Small, drop-like scaly papules, often after streptococcal infection. [12]
Inverse psoriasis	Smooth, red inflammation in skin folds such as axillae, groin, and under the breasts.[12]
Pustular psoriasis	Sterile pustules on red skin; may be localized or generalized.[12,13]
Erythrodermic psoriasis	Widespread redness, scaling, pain, and itching; potentially severe/systemic. [12]
Psoriatic arthritis	Inflammatory joint disease associated with skin psoriasis. [9]

2. Mechanisms

1. Genetic predisposition

Psoriasis has a strong heritable component, particularly in early-onset disease. Risk variants affect skin-barrier function and immune regulation; HLA-C*06:02 is a well-known susceptibility allele.[10,14]

2. Environmental triggering

Triggers include skin trauma (**Koebner phenomenon**), infections, stress, smoking, obesity, and certain drugs. These events can initiate or worsen inflammatory signaling in genetically susceptible individuals. [10]

3. Innate immune activation

Keratinocytes and resident immune cells release antimicrobial peptides and inflammatory signals after injury or infection. Dendritic cells become activated and present antigens, promoting T-cell activation.[9]

4. Adaptive immune response

Activated dendritic cells drive differentiation of T cells, especially **Th17** and **Th1** cells. These cells infiltrate the skin and sustain chronic inflammation.[9]

5. Cytokine signaling: IL-23/IL-17 axis

The **TNF-α–IL-23–Th17–IL-17** pathway is central to plaque psoriasis. IL-23 supports Th17 cells, while IL-17, IL-22, and TNF-α stimulate keratinocytes and amplify inflammation.[13]

6. Keratinocyte hyperproliferation

Inflammatory cytokines cause keratinocytes to proliferate excessively and differentiate abnormally. This produces the thickened epidermis, parakeratosis, and scaling characteristic of psoriatic plaques.[12]

7. Angiogenesis and reduced apoptosis

New blood-vessel formation and reduced apoptosis of keratinocytes help maintain the inflamed, thickened plaque.[12]

Simple pathway

Trigger → activation of dendritic cells and keratinocytes → T-cell activation → IL-23/IL-17/TNF-α signaling → keratinocyte proliferation and inflammation → scaly plaque formation.[12]

Transferosomes : defination types mechanisms:

1. Definition

A transferosome is a vesicular nanocarrier with at least one aqueous core enclosed by a lipid bilayer, modified by an edge activator to become ultra-flexible. Under non-occlusive conditions, it can deform and squeeze through skin pores much smaller than its own diameter.[15,16]

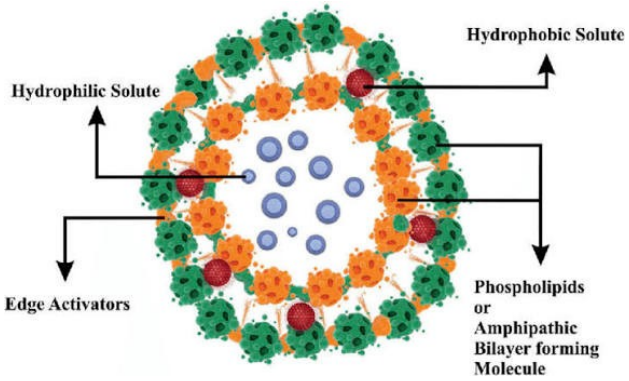


Figure 2: Struture of Transferosomes

Table 2: Composition of Transferosomes

Component	Role
Phospholipids	Form the vesicle bilayer and encapsulate the drug. [18]
Edge activator	Usually a surfactant such as sodium cholate, sodium deoxycholate, Span, Tween, or bile salts; reduces interfacial tension and increases membrane elasticity. [19]
Water/aqueous phase	Forms the internal compartment and supports vesicle structure. [18]
Drug	May be hydrophilic, lipophilic, or macromolecular, depending on the formulation.[10]

2. Types / related forms

Transferosomes are mainly classified by their composition and membrane-modifying agents:

- **Classical transferosomes:** Phospholipid + edge activator; the standard ultradeformable vesicle system.[15,18]
- **Bile-salt transferosomes:** Use bile salts such as sodium cholate or deoxycholate as edge activators.[19]
- **Nonionic surfactant transferosomes:** Use Spans or Tweens as edge activators to improve flexibility and stability[18]
- **Ethosomes:** Ethanol-containing elastic vesicles; more permeabilizing but structurally distinct from transferosomes.[18]
- **Transethosomes:** Hybrid vesicles combining ethanol and edge activators/surfactants.[18]
- **Transgelosomes / transferosomal gels:** Transferosome-loaded gel systems used to improve residence time and application convenience.[21]

3. Mechanism

1. Formation of elastic vesicles

The edge activator inserts into the phospholipid bilayer and destabilizes it locally. This lowers membrane rigidity and allows the vesicle to change shape without rupturing.[19,20]

2. Creation of an osmotic gradient

When applied to skin under **non-occlusive** conditions, water evaporates from the formulation surface. This creates a transepidermal hydration/osmotic gradient that drives transferosomes inward.[15]

3. Deformation and penetration

The vesicle follows the osmotic gradient and squeezes through narrow intercellular channels of the stratum corneum. It can pass through openings approximately one-tenth of its own diameter.[16]

4. Drug transport

Two mechanisms may operate:

- The intact vesicle crosses the stratum corneum while carrying the drug.
- The vesicle releases or exchanges drug during passage, improving deposition in deeper skin layers.[22]

5. Enhanced skin delivery

Their flexibility, lipid compatibility with skin, and ability to carry both hydrophilic and lipophilic drugs make them more effective than conventional liposomes for transdermal delivery.[17]

Advantages

- High deformability and skin-penetration ability. [15,16]
- Can deliver hydrophilic and lipophilic drugs, including peptides and proteins.[17]
- Improved drug entrapment and controlled release compared with some conventional systems.[18]
- Non-invasive alternative to injections for selected transdermal drugs.

Limitations

- Formulation stability can be affected by surfactant type and concentration.18]
- Edge activators may irritate skin at high concentrations.[20]
- Large-scale manufacturing and reproducibility remain translational challenges.

Drug Profile: Anti-Psoriatic Agents Suitable for Transferosomal Delivery

1. Small Molecule Drugs

Methotrexate (MTX): Methotrexate, an antifolate and antimetabolite drug commonly used to treat moderate-to-severe psoriasis, has limited skin permeability and may cause systemic toxicity when administered orally or parenterally. Transferosomal encapsulation has been reported to improve skin deposition by 3–5 times compared with conventional gels and provide sustained drug release for up to 24 hours, potentially reducing systemic absorption. Optimized methotrexate-loaded transferosomes also demonstrated a deformability index of 27.13, supporting their ability to penetrate narrow spaces within the stratum corneum.[1,7]

Cyclosporine A (CyA): Cyclosporine A (CyA) is a potent calcineurin inhibitor with immunosuppressive properties. Its high molecular weight (1202 Da) and lipophilicity limit its penetration through the skin. Ethosomal and transferosomal formulations can improve its skin delivery, with ethosomes often showing greater permeation due to ethanol-induced disruption of the stratum corneum. In contrast, transferosomes may promote localized drug deposition, making them a promising option for targeted psoriasis treatment with potentially reduced systemic exposure.[1]

Corticosteroids (Betamethasone, Clobetasol): Corticosteroids are potent anti-inflammatory agents widely used to treat psoriasis. Transferosomal delivery can enhance their skin penetration, including follicular delivery, and may help reduce local adverse effects such as skin atrophy. In preclinical psoriasis models, betamethasone dipropionate-loaded transferosomes showed improved tolerability and favorable safety outcomes, highlighting potential for topical psoriasis management.[4,8]

2. Natural Bioactive Compounds

20-Hydroxyecdysone (20-HE): 20-Hydroxyecdysone (20-HE) is a phytoecdysteroid with antioxidant, anti-inflammatory, and cytoprotective properties that may help reduce psoriatic lesions by modulating the IL-23/IL-17 inflammatory pathway. However, its poor skin permeability and limited physicochemical stability present challenges for effective delivery. Transferosomal formulations of 20-HE, alone or combined with resveratrol, have demonstrated high apparent encapsulation efficiency (~90%), actual encapsulation of 25–30%, particle sizes of 100–200 nm, and good stability over 30 days. These formulations also showed no observed cytotoxicity in human keratinocytes or zebrafish embryos, supporting their potential for further investigation in psoriasis treatment.[3]

Resveratrol: Resveratrol is a polyphenolic compound with antioxidant and anti-inflammatory properties that modulates NF-κB signaling and helps reduce excessive keratinocyte proliferation in psoriasis. However, its poor solubility and rapid degradation limit its therapeutic potential. Transferosomal encapsulation can improve its stability and enhance dermal delivery, making it a promising approach for psoriasis treatment.[3]

Berberine: Berberine is an isoquinoline alkaloid with anti-inflammatory and antiproliferative properties. Berberine-loaded transferosomes have shown improved skin penetration and enhanced therapeutic effects in preclinical psoriasis models, highlighting their potential for topical psoriasis treatment.[9]

3. Biologics and Peptides

Emerging research is investigating transferosomes for delivering biologic agents and peptides that target key inflammatory cytokines, including IL-17, IL-23, and TNF-α, involved in psoriasis. Although challenges related to drug stability and loading efficiency remain, transferosomes can accommodate both hydrophilic and lipophilic compounds, making them promising carriers for next-generation biologic therapies.[4,5]

Structural Basis and Formulation Design of Transferosomes

1. Defining Features

Transferosomes are phospholipid-based, ultra-deformable vesicles containing edge activators within their bilayer structure. Unlike conventional liposomes, they possess flexible membranes that allow them to change shape under stress while maintaining their structural integrity. This combination of flexibility and stability makes transferosomes promising carriers for transdermal drug delivery.[2,4]

2. Composition

Phospholipids: Phosphatidylcholine, commonly obtained from soy, egg, or hydrogenated sources, is the main component of transferosomes and forms their bilayer structure. It allows hydrophilic drugs to be incorporated into the aqueous core and lipophilic drugs into the lipid bilayer. The choice of phospholipid affects vesicle formation, membrane fluidity, drug permeability, and encapsulation efficiency. [2,4,17]

Edge Activators: Edge activators, such as Tween 80, Span 80, Tween 20, Span 20, and bile salts like sodium cholate and sodium deoxycholate, are incorporated into the phospholipid bilayer to increase membrane flexibility. Their concentration is important, as optimal levels improve vesicle deformability, whereas excessive amounts may destabilize vesicles and reduce drug entrapment efficiency.[2,4,17]

Cholesterol: Cholesterol is often incorporated into transferosomes (0–50 mol%) to regulate bilayer packing, control excessive permeability, and improve storage stability. However, higher concentrations may reduce membrane flexibility and vesicle deformability.[2,4]

Charge-Inducing Agents: Stearylamine and dicetyl phosphate are used to adjust the surface charge of transferosomes, producing positive and negative zeta potentials, respectively. This helps improve colloidal stability and influences interactions with the skin.[2,4]

Cryo/Lyoprotectants: Sucrose and trehalose are used as cryoprotectants to protect transferosomes during freeze-drying and improve their long-term stability.[2,4]

Table 3: Summarizes the Main Components and Their Functional Roles.[2,4,17]

Component Class	Representative Examples	Main Functional Role	Impact on Performance
Phospholipids	SPC, EPC, DMPC	Bilayer framework, drug compartments	Influences vesicle formation, fluidity, encapsulation
Edge Activators	Tween 80, Span 80, sodium cholate	Membrane flexibility, deformability	Enhances skin penetration; excess causes instability
Cholesterol	Cholesterol	Bilayer stabilization	Improves integrity; high levels reduce deformability
Charge Agents	Stearylamine, dicetyl phosphate	Surface charge modulation	Affects zeta potential, aggregation, skin interaction
Cryoprotectants	Sucrose, trehalose	Lyophilization protection	Enhances storage stability

3. Preparation Methods

Thin-Film Hydration: Phospholipids, edge activators, and the drug are dissolved in an organic solvent mixture, such as chloroform and methanol. The solvent is evaporated under reduced pressure to form a thin lipid film, which is then hydrated with an aqueous phase. Probe sonication or extrusion is subsequently performed to reduce vesicle size and obtain a uniform formulation.[3,4,17]

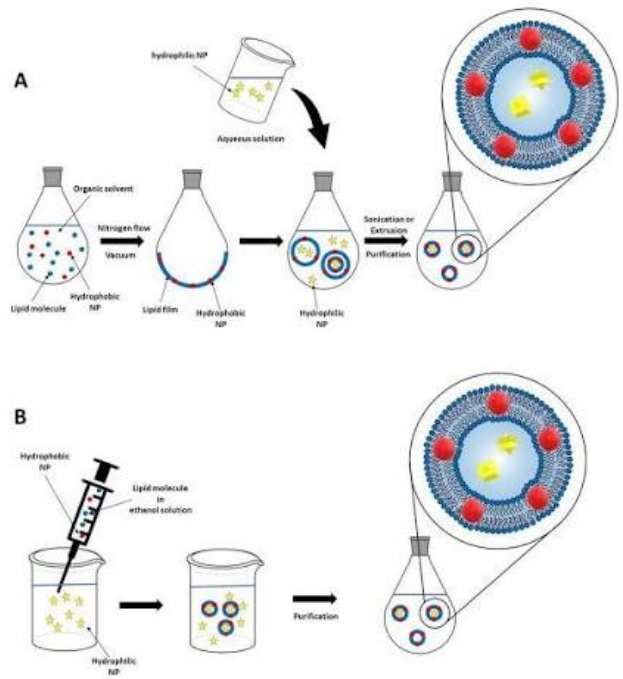


Figure 3: Thin-Film Hydration

Rotary Evaporation-Sonication: This method is similar to thin-film hydration, where rotary evaporation removes the organic solvent, followed by vortexing and sonication to produce uniform, nanosized transferosomal vesicles.[3,17]

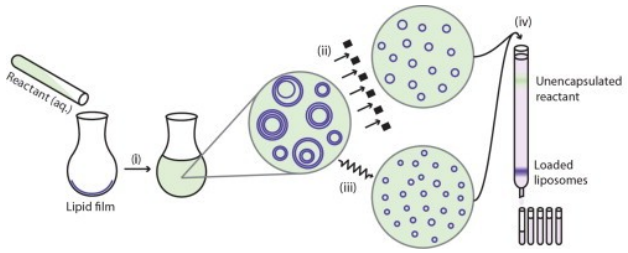


Figure 4: Rotary Evaporation-Sonication

Vortexing-Sonication: All formulation components are mixed in an aqueous buffer, followed by vortexing and sonication to form transferosomal vesicles. This method is suitable for heat-sensitive drugs due to its relatively mild processing conditions.[17]

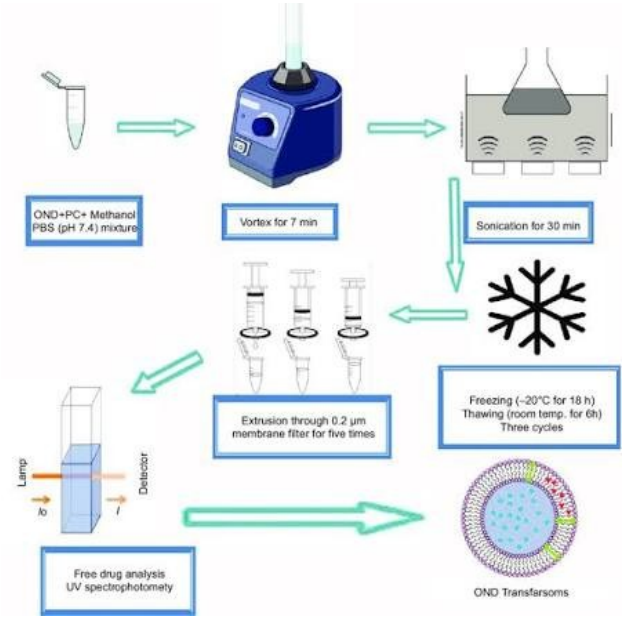


Figure 5: Vortexing-Sonication

Micellar Aggregation: The phospholipid and edge activator are mixed at a concentration above the critical micelle concentration, followed by dilution to form transferosomal vesicles.[4]

Optimization of phospholipid-to-edge-activator ratio, hydration temperature, sonication time, and aqueous phase composition is critical for achieving desired vesicle properties.[2,3,4]

Preparation methods

1. Thin-film hydration method[23]

This is the most widely used method for transferosomes.

Steps:

1. Dissolve phospholipid, edge activator, and drug in an organic solvent such as chloroform or methanol.
2. Evaporate the solvent under reduced pressure using a rotary evaporator to form a thin lipid film.
3. Vacuum-dry the film to remove residual solvent.
4. Hydrate the film with aqueous buffer or water above the lipid transition temperature, with gentle shaking or rotation.
5. Sonicate, extrude, or pass the suspension through a suitable membrane to reduce vesicle size.

Advantages: Good control over vesicle size, entrapment efficiency, and batch composition.

Limitations: Requires organic solvent removal, rotary evaporation, and careful control of hydration conditions.

2. Modified hand-shaking method[24]

A simplified version of thin-film hydration in which lipid, surfactant, and drug are dissolved, dried to a film, and hydrated by manual shaking or vortexing.

Advantages: Simple, inexpensive, and useful for preliminary screening.

Limitations: Poorer reproducibility and often larger, less uniform vesicles.

3. Reverse-phase evaporation method[23]

Phospholipid and drug are dissolved in an organic phase, mixed with an aqueous phase to form an emulsion, and the organic solvent is removed under reduced pressure. This produces vesicles with a relatively high aqueous-core volume.

Advantages: Suitable for hydrophilic drugs and can provide high encapsulation.

Limitations: Uses organic solvents; requires careful solvent removal and may produce heterogeneous vesicles.

4. Ethanol injection method[24]

Lipid, edge activator, and drug are dissolved in ethanol and rapidly injected into an aqueous medium under stirring. Ethanol diffuses out, allowing vesicles to self-assemble.

Advantages: Simple, rapid, and relatively easy to scale up.

Limitations: Residual ethanol must be removed; drug solubility in ethanol can limit use.

5. Supercritical fluid / supercritical anti-solvent method[24]

Lipids and drug are dissolved in supercritical carbon dioxide or an anti-solvent system, then rapidly depressurized or mixed with aqueous phase to form vesicles.

Advantages: Avoids or minimizes toxic organic solvents and can improve particle uniformity.

Limitations: Requires specialized equipment and higher cost.

Table 4: Key Formulation Variables

Variable	Effect on transferosomes
Phospholipid concentration	Affects vesicle size, drug loading, and membrane strength.[24,25]
Lipid-to-surfactant ratio	Controls elasticity; excessive surfactant may destabilize vesicles. [25]
Lipid-to-drug ratio	Influences entrapment efficiency and drug-release behavior.[25]
Hydration medium and temperature	Affects vesicle formation, lamellarity, and encapsulation.[24,25]
Sonication/extrusion conditions	Determines particle size and polydispersity.[24]

Evaluation Parameters

1. Vesicle size and size distribution

Measured by **dynamic light scattering (DLS)** or **photon correlation spectroscopy (PCS)**. Typical transferosome sizes are about 50–300 nm, though the optimum depends on the drug and intended route.[24]

2. Polydispersity index (PDI)

PDI indicates uniformity of the vesicle population. A lower PDI means a more homogeneous formulation; values around 0.1–0.3 are generally considered desirable.[24]

3. Zeta potential

Zeta potential measures surface charge and predicts colloidal stability. Values greater than about ±25–30 mV generally indicate good electrostatic stabilization. [24]

4. Entrapment efficiency

Entrapment efficiency (EE%) shows how much drug is retained inside the vesicles. It is commonly calculated after separating free drug by ultracentrifugation, dialysis, or filtration. Reported EE% often ranges from about 70–95%, depending on formulation composition.[24]

5. Vesicle morphology

Examined by **transmission electron microscopy (TEM)**, **scanning electron microscopy (SEM)**, or

cryo-TEM. This confirms vesicular structure, shape, lamellarity, and surface appearance.[26]

6. Deformability index

This is the most important transferosome-specific test. It measures the ability of vesicles to pass through a membrane or porous filter under pressure, reflecting their capacity to squeeze through skin pores.[24,26]

7. In vitro drug release

Performed using dialysis bags, Franz diffusion cells, or similar apparatus. It evaluates sustained or controlled release and is often expressed as cumulative percentage drug released over time.[24]

8. Ex vivo skin permeation

Conducted using Franz diffusion cells with excised human, porcine, rat, mouse, or other animal skin. Parameters include **flux**, **permeation coefficient**, **lag time**, and drug retained in skin layers.[23]

9. Drug content

Determines the actual amount of drug present in the final transferosomal formulation. It helps assess dose uniformity and preparation efficiency.[23]

10. Stability studies

Formulations are stored at different temperatures, commonly 4°C, 25°C, and sometimes 40°C, and monitored for size, PDI, zeta potential, drug content, leakage, and appearance over time.[24]

Practical evaluation checklist

- Vesicle size, PDI, and zeta potential by DLS/PCS.[24]
- Morphology by TEM/SEM.[26]
- Entrapment efficiency and drug content.[24]
- Deformability index.[24]
- In vitro release and ex vivo permeation.[23]
- Stability and drug-leakage studies.[24]

Characterization of Transferosomes:

1. Particle Size and Polydispersity Index (PDI)

Dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA) are used to measure vesicle size and size distribution. Transferosomes designed for transdermal delivery typically range from 100–300 nm, with a polydispersity index (PDI) below 0.3, indicating a relatively uniform vesicle population.[2,3]

2. Zeta Potential

Zeta potential measures the surface charge of transferosomes and helps assess their colloidal stability. Values above +30 mV or below −30 mV generally indicate better electrostatic stabilization against aggregation. Transferosomes commonly exhibit negative zeta potentials ranging from −25 to −50 mV, depending on the edge activator and charge-inducing agents used.[2,3]

3. Encapsulation Efficiency (EE%)

Encapsulation efficiency (EE%) is determined using HPLC or UV spectroscopy after separating free drug from vesicle-associated drug through size-exclusion chromatography (SEC) or dialysis. Apparent EE% may overestimate actual encapsulation because it includes surface-associated drug, whereas SEC-corrected measurements provide a more accurate estimate. Typical EE% values range from 25–90%, depending on the drug's lipophilicity and formulation composition.[2,3]

4. Deformability Assessment

Extrusion Method: Vesicles are passed through polycarbonate membranes with pores smaller than their diameter to evaluate deformability. The deformability index is calculated using the vesicle size after extrusion and the membrane pore size. Lower values generally indicate greater vesicle deformability and flexibility.[4,7]

Atomic Force Microscopy (AFM): Microscopy techniques are used to observe changes in transferosome shape and structure under mechanical stress, helping assess their deformability and flexibility.[4]

Fluorescence Recovery After Photobleaching (FRAP): Fluorescence recovery after photobleaching (FRAP) measures the lateral movement of lipids within the bilayer, providing an indication of membrane fluidity.[4]

5. Morphology

Transmission electron microscopy (TEM) and cryo-TEM are used to examine vesicle morphology, lamellarity, and structural integrity. Transferosomes generally appear as spherical vesicles with a single or multiple lipid bilayers.[2,4]

6. Stability Studies

Transferosome stability is evaluated over 1–6 months at different temperatures (4°C, 25°C, and 40°C) by monitoring changes in particle size, PDI, zeta potential, encapsulation efficiency, and drug content. Lyophilized formulations containing cryoprotectants generally provide better long-term stability.[2,3,4]

7. In Vitro Drug Release

In vitro drug release is evaluated using dialysis or Franz diffusion cell methods in simulated skin fluid at pH 5.5 and 32°C. Transferosomal formulations often provide sustained drug release over 12–48 hours, following kinetic models such as Higuchi or Korsmeyer–Peppas.[4,7]

8. Skin Permeation and Deposition

Franz diffusion cells using excised human or animal skin, such as rat or pig skin, are used to measure drug permeation (μg/cm²/h) and skin retention (μg/cm²). Transferosomes generally achieve 2–5 times greater skin deposition than conventional liposomes or gels.[1,4,7]

Mechanism of Transdermal Penetration

Transferosomes enhance skin penetration through several mechanisms:

- **Deformability-Driven Penetration:** Edge activators increase membrane flexibility, allowing transferosomes to pass through narrow intercellular pathways in the stratum corneum that may be smaller than the vesicles themselves.[2,4,6]
- **Osmotic Gradient Response:** Under non-occlusive conditions, water evaporation from the skin surface creates a hydration gradient that may drive transferosomes toward deeper, more hydrated skin layers.[2,4,6]
- **Stratum Corneum Lipid Fluidization:** Edge activators, particularly surfactants, can temporarily disturb the lipid arrangement in the stratum corneum, increasing its fluidity and permeability.[1,4]
- **Follicular Penetration:** Transferosomes can accumulate in hair follicles, which act as pathways for drug delivery and reservoirs that support sustained release.[4,8]
- **Vesicle Penetration and Drug Release:** It remains uncertain whether intact transferosomes cross the skin barrier or mainly act as drug reservoirs, releasing their payload near the skin surface. The released drug may then penetrate more effectively because of improved solubility or changes in barrier properties. Despite this uncertainty, studies indicate that transferosomes can enhance drug deposition in deeper skin layers.[2,4]

Advantages of Transferosomes in Psoriasis Therapy

- **Enhanced Skin Penetration:** Transferosomes can increase drug deposition in the viable epidermis and dermis by approximately 2–5 times compared with conventional formulations.[1,4,7]
- **Targeted Delivery:** Localized drug accumulation in the skin may reduce systemic exposure and associated adverse effects.[1,4]
- **Sustained Release:** Prolonged drug release over 12–48 hours can reduce application frequency and improve patient compliance.[4,5,7]
- **Versatile Drug Loading:** Transferosomes can encapsulate both hydrophilic drugs, such as methotrexate, and lipophilic drugs, including cyclosporine and corticosteroids.[4,5]
- **Biocompatibility:** Their use of phospholipids and suitable surfactants can support good biocompatibility.[3,4]
- **Improved Drug Stability:** Encapsulation may protect sensitive compounds, such as resveratrol and 20-hydroxyecdysone (20-HE), from degradation.[3]
- **Reduced Skin Irritation:** Optimized formulations may use lower surfactant concentrations than some conventional penetration-enhancing systems, potentially reducing skin irritation.[4,8]

Challenges and Limitations

- **Scalability:** Laboratory preparation methods, such as sonication and extrusion, can be difficult to scale up for industrial production. High-pressure homogenization and microfluidic techniques may help overcome these limitations.[2,4]
- **Storage Stability:** Transferosomes may undergo aggregation, fusion, hydrolysis, and drug leakage

durwn greater drug diffusion through rat skin than conventional patches or gels.[7,11]

- **Naturaling storage:** Lyophilization with suitable cryoprotectants can improve their stability.[2,3,4]
- **Standardization:** The absence of standardized deformability tests and characterization methods makes it difficult to compare results across studies.[2,4]
- **Regulatory Uncertainty:** The regulatory pathway for transferosome-based topical products remains challenging, and approval requirements for these nanocarriers need further clarification.[2,4]
- **Cost:** Specialized equipment and high-quality phospholipids can increase manufacturing costs compared with conventional creams and gels.[4]
- **Mechanistic Uncertainty:** The relative contributions of intact vesicle penetration and drug release followed by diffusion remain unclear, complicating formulation optimization.[2,4]

Recent Advances and Future Perspectives

- **Hybrid Systems:** Transferosomes combined with microneedles, iontophoresis, or hydrogels show synergistic enhancement of skin permeation. Methotrexate-loaded transferosomal microneedle patches demonstrated substantial increase in drug diffusion over rat skin compared to traditional patches or gels.[4,17]
- **Product Delivery:** Transferosomes loaded with phytochemicals such as 20-hydroxyecdysone (20-HE), resveratrol, berberine, and thymoquinone may support multi-target therapy through their anti-inflammatory, antioxidant, and antiproliferative properties.[1,3,8]
- **Quality by Design (QbD):** Statistical methods, including Box–Behnken and central composite designs, can help optimize formulation variables, such as phospholipid type and edge activator concentration, to achieve consistent particle size, encapsulation efficiency, and deformability.[2,4]
- **In Vivo Efficacy:** Preclinical studies using imiquimod-induced psoriasis models in mice have reported improvements in disease severity, epidermal thickening, and inflammatory markers, including IL-17A, IL-23, and IL-6, following transferosomal treatment.[3,8]
- **Personalized Medicine:** Future research may focus on developing transferosomal formulations tailored to different psoriasis subtypes, such as plaque, guttate, and pustular psoriasis, using patient-specific genetic and inflammatory profiles

CONCLUSION

Transferosomes are a promising transdermal drug delivery system for psoriasis, designed to overcome the stratum corneum barrier through highly deformable vesicles. Their ability to improve skin penetration, sustain drug release, and deliver a wide range of anti-psoriatic agents offers potential advantages over conventional topical formulations. However, challenges related to large-scale production, storage stability, and regulatory approval remain. Advances in hybrid delivery systems, natural product encapsulation, and Quality by Design (QbD) approaches may further improve their effectiveness and reproducibility. Further research into their penetration mechanisms, clinical efficacy, and cost-effective manufacturing is essential for their successful translation into clinical practice.

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