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Review Article

Transferosome-Based Drug Delivery Systems: Formulation Approaches, Characterization And Recent Advances In Buccal And Transdermal Delivery

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ABSTRACT

Transferosomes are highly deformable lipid-based vesicular carriers developed to improve drug transport across biological barriers. Their defining feature is a phospholipid bilayer containing an edge activator, which reduces membrane rigidity and permits extensive deformation under an applied stress or hydration gradient. This review provides an expanded formulation-oriented analysis of transferosomes, with particular emphasis on their composition, mechanisms of formation and barrier interaction, preparation methods, critical formulation variables, characterization and pharmaceutical applications in transdermal and buccal delivery. Phospholipid type, edge-activator identity and concentration, drug properties, lipid-to-surfactant ratio, hydration conditions and processing energy can markedly influence vesicle size, polydispersity, surface charge, entrapment efficiency and deformability. The review also discusses the importance of complementary characterization, because small particle size alone does not establish functional transferosomal behavior. Applications in transdermal delivery are considered in relation to the stratum corneum, hydration gradients, vesicle deformation and drug deposition. Buccal delivery is discussed separately because mucosal residence, saliva, mucus turnover and epithelial permeability create a different set of formulation requirements. The incorporation of transferosomes into mucoadhesive gels and polymeric films is highlighted as a strategy for combining vesicular transport with prolonged residence and convenient dosing. Recent advances include quality-by-design approaches, hybrid and surface-modified vesicles and improved analytical characterization. Despite substantial experimental evidence, translation remains constrained by formulation instability, lipid oxidation, variability in

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deformability testing, scale-up, biological variability and regulatory uncertainty. Standardized critical quality attributes and clinically relevant comparative studies are therefore required to advance transferosome-based systems toward robust pharmaceutical products.

INTRODUCTION

Drug delivery systems are designed not only to transport an active pharmaceutical ingredient to the body but also to control the rate, site and duration of drug exposure. Conventional dosage forms can be limited by poor aqueous solubility, chemical or enzymatic degradation, extensive first-pass metabolism, short biological half-life, variable absorption and inadequate patient adherence. Non-invasive routes such as transdermal and buccal administration can offer useful alternatives for selected drugs.

However, both routes contain physiological barriers that must be addressed by formulation design.

The skin provides an attractive route for systemic and local therapy because it is accessible, relatively large and capable of supporting prolonged administration. The principal barrier is the stratum corneum, which has a highly organized lipid–protein architecture and strongly restricts penetration of many compounds. Conventional passive diffusion is therefore generally most suitable for molecules with favorable molecular size, lipophilicity and potency. Transferosomes were developed to overcome some of these limitations through an ultra-deformable vesicular architecture. Their phospholipid bilayer contains an edge activator, typically a surfactant or bile salt, that introduces controlled flexibility into the membrane.[1–4]

The proposed advantage of transferosomes is not simply that they are nanoparticles or vesicles. Their functional identity is associated with deformability. Edge activators alter lipid packing and permit the vesicle to change shape under stress.

Under suitable non-occlusive conditions, the hydration gradient between the formulation and skin can contribute to directed transport. Experimental evidence suggests that vesicle composition, deformability, hydration and interaction with skin lipids jointly influence delivery.[1–5]

The buccal mucosa presents a different biological environment. It is moist, continuously exposed to saliva and mechanical movement, and subject to mucus turnover. At the same time, buccal delivery can avoid gastrointestinal degradation and may reduce first-pass hepatic exposure for drugs that are absorbed directly through the mucosa. Transferosomes have therefore been investigated in buccal gels and other mucosal systems. A human pharmacokinetic study of loratadine-loaded transferosomal gel reported favorable bioavailability characteristics and reduced inter-individual variability compared with oral administration, supporting further interest in this route.[6]

The current literature is extensive but heterogeneous. Studies differ in phospholipid source, edge activator, drug concentration, preparation technique, measurement conditions and definitions of deformability. Recent critical reviews have consequently emphasized standardization, reproducibility, scale-up and the need to connect physicochemical attributes with biological performance.[7,8] This review addresses these issues by integrating formulation science, analytical characterization and applications in transdermal and buccal drug delivery.

2. CONCEPT, HISTORY AND TERMINOLOGY

Transferosomes are generally described as ultra-deformable lipid vesicles derived conceptually from conventional liposomes. The term is associated with vesicles containing at least one vesicle-forming phospholipid and an edge activator that makes the bilayer highly flexible.[7–9] The edge activator is usually a single-chain surfactant or related amphiphile. Examples include sodium cholate, sodium deoxycholate, Tween 20, Tween 80, Span 60 and Span 80.[8–10]

The development of transferosomes addressed a fundamental limitation of conventional liposomes: a relatively rigid bilayer may have difficulty passing through narrow intercellular pathways. In an ultradeformable vesicle, membrane components can redistribute during deformation.

The edge activator preferentially stabilizes curved regions and reduces the energetic cost of shape change.[8]

Terminology in this field requires care. Terms such as transfersome, transferosome, ultradeformable liposome and elastic vesicle are sometimes used interchangeably, while related systems such as ethosomes and transethosomes have different compositions and mechanisms. A transferosome should therefore be characterized by its composition and functional deformability rather than by size alone. Recent literature specifically identifies inconsistent terminology and non-harmonized deformability assays as barriers to comparison among studies.[7]

3. STRUCTURE AND COMPOSITION

A transferosome consists primarily of a phospholipid bilayer, an edge activator and an aqueous phase. Additional components may be introduced to modify membrane properties, improve stability, enhance drug loading or facilitate incorporation into a final dosage form.

3.1 Phospholipids

Phospholipids provide the structural bilayer. Soy phosphatidylcholine and egg phosphatidylcholine are commonly reported materials. The degree of saturation, fatty-acid chain length, purity and transition characteristics of the phospholipid can affect membrane packing and elasticity. A more ordered bilayer may provide greater structural rigidity, whereas excessive fluidity may increase leakage.

3.2 Edge activators

Edge activators are the defining functional excipients. Commonly reported materials include sodium cholate, sodium deoxycholate and non-ionic surfactants such as Tween and Span derivatives. Their concentration must be optimized because increasing edge activator content may improve deformability up to an optimum, while excessive surfactant can destabilize or solubilize the bilayer.[8–10]

3.3 Cholesterol

Cholesterol may be included to regulate membrane packing and reduce permeability or leakage. Its effect is concentration-dependent. Excessive cholesterol can increase membrane order and reduce flexibility, potentially opposing the intended ultradeformable behavior.

3.4 Alcohol and penetration modifiers

Some transferosomal formulations contain ethanol or another alcohol, especially when the preparation process or drug properties require a cosolvent. Ethanol can modify lipid organization and skin permeability. However, systems with

substantial ethanol may overlap conceptually with ethosomal or transethosomal platforms, so the composition should be reported clearly.[3],[8]

3.5 Hydration medium

Water or buffered aqueous media are commonly used for hydration. The pH and ionic strength can influence drug ionization, vesicle surface charge and colloidal behavior. For buccal systems, the formulation pH also becomes important for mucosal tolerability.

4. MECHANISM OF FORMATION AND DRUG ENCAPSULATION

When amphiphilic phospholipids are exposed to an aqueous environment, hydrophobic tails tend to minimize contact with water while hydrophilic head groups interact with the aqueous phase. This spontaneous organization produces bilayer structures that can close into vesicles. Edge activators insert into the phospholipid bilayer and modify membrane curvature and elasticity.

Hydrophilic drugs are primarily associated with the aqueous compartment, while lipophilic drugs can partition into the bilayer. Amphiphilic drugs may distribute between both regions. Entrapment efficiency therefore depends on drug solubility, partition coefficient, ionization state, lipid composition, vesicle concentration and preparation conditions.

A useful formulation principle is that drug loading and deformability may not change in parallel. Increasing lipid concentration may increase the amount of drug associated with vesicles but can also change viscosity and membrane organization. Likewise, increasing surfactant may improve elasticity while reducing entrapment if the bilayer becomes excessively disrupted. Optimization is therefore a multidimensional problem rather than a single-variable adjustment.

5. MECHANISM OF TRANSDERMAL TRANSPORT

The stratum corneum is commonly described as a 'brick-and-mortar' barrier, in which corneocytes are embedded within an organized lipid matrix. Transferosomes are proposed to overcome this barrier through a combination of deformability, hydration-driven movement, lipid interaction and drug release.

The hydration-gradient hypothesis is particularly important. Under non-occlusive application, the skin surface is relatively dry compared with the deeper hydrated tissue. This gradient can act as a driving force for vesicle movement. Highly deformable vesicles may squeeze through pathways smaller than their apparent diameter while maintaining vesicle integrity to some extent.[4],[8],[11]

However, intact vesicle penetration should not be assumed for every formulation. Depending on membrane composition and environmental conditions, vesicles may partially disintegrate, exchange lipids with the skin, release drug near the barrier or modify the organization of skin lipids. Current reviews emphasize that the relative contribution of these mechanisms remains formulation-dependent.[7],[11]

Consequently, claims of 'intact vesicle penetration' should be supported by appropriate experimental evidence rather than inferred from enhanced permeation alone. Permeation enhancement can arise from several mechanisms, and fluorescent labeling or particle tracking should be interpreted carefully because labels may dissociate from the vesicle.

6. PREPARATION METHODS

6.1 Thin-film hydration

Thin-film hydration remains one of the most frequently used laboratory approaches. Phospholipid and lipid-soluble components are dissolved in a volatile organic solvent system. The solvent is removed under reduced pressure or controlled evaporation to obtain a thin lipid film. The film is then hydrated with an aqueous phase containing the drug or other water-soluble components. Hydration is followed by agitation, sonication, extrusion or homogenization when smaller and more uniform vesicles are required.[4],[8]

6.2 Ethanol injection

In ethanol injection, lipid components are dissolved in ethanol and injected or added into an aqueous phase under controlled mixing. Rapid dilution changes the solvent environment and promotes vesicle formation. This method can be relatively simple but requires control of ethanol concentration, mixing rate and residual solvent.

6.3 Reverse-phase evaporation

A water-in-oil emulsion is prepared from aqueous and organic phases, followed by removal of the organic solvent. The method can provide useful entrapment of hydrophilic compounds but involves more complex solvent handling.

6.4 Sonication, extrusion and homogenization

These are generally size-reduction or post-formation processing approaches rather than independent vesicle-composition strategies. Sonication can reduce vesicle size but excessive energy may increase temperature or promote leakage. Extrusion through defined membranes can narrow the size distribution. High-pressure homogenization can be useful for scale-up but requires process optimization.

6.5 Mechanical stirring

Magnetic stirring or mechanical agitation may be used during hydration and dispersion. Stirring alone may produce larger or more heterogeneous vesicles than high-energy methods, depending on composition and conditions. The method can nevertheless be useful for preliminary formulation development when the objective is to investigate composition before applying a defined size-reduction step.

6.6 Freeze-drying

Lyophilization can improve storage stability by removing water, but vesicle fusion or leakage may occur during freezing and rehydration. Cryoprotectants such as sugars may be required and must be optimized.

7. FORMULATION VARIABLES AND QUALITY-BY-DESIGN

Transferosome development benefits from systematic identification of critical material attributes (CMAs) and critical process parameters (CPPs). Typical CMAs include phospholipid type and concentration, edge activator type and concentration, drug concentration, cholesterol concentration and aqueous-phase composition. CPPs may include hydration time, mixing speed, temperature, sonication time, extrusion cycles and solvent-removal conditions.

The phospholipid-to-edge-activator ratio is particularly influential. An insufficient amount of edge activator may produce a relatively rigid vesicle, whereas excessive surfactant can disrupt the bilayer. The optimal ratio is drug- and

composition-specific and should be established experimentally.

Design-of-experiments approaches can evaluate multiple variables simultaneously and identify interactions that would be missed by one-factor-at-a-time experimentation. Responses can include vesicle size, PDI, zeta potential, entrapment efficiency, deformability and drug release. For a final pharmaceutical dosage form, additional responses such as film thickness, folding endurance, mucoadhesion and ex-vivo permeation may be incorporated.

A useful QbD workflow is: define the quality target product profile; identify critical quality attributes; conduct risk assessment; select experimental factors; perform DoE; model responses; confirm the optimum; and establish a control strategy. This approach is especially valuable when several formulation components interact.

8. CHARACTERIZATION OF TRANSFEROSOMES

8.1 Vesicle size

Dynamic light scattering is widely used to measure hydrodynamic diameter. Results depend on sample concentration, dilution medium, viscosity, temperature and instrument algorithm. Measurements should therefore be reported with sufficient detail for reproducibility.

8.2 Polydispersity index

PDI describes the breadth of the particle-size distribution. Lower PDI generally indicates a more homogeneous dispersion, but there is no universal single cutoff that defines an acceptable transferosome for every route. The value should be interpreted with the measurement quality and formulation purpose.

8.3 Zeta potential

Zeta potential provides information about electrokinetic behavior and can help monitor changes during storage. Highly charged systems may show greater electrostatic repulsion, but steric stabilization and surfactant effects can also contribute to colloidal stability. A modest zeta potential does not automatically mean a formulation is unstable.

8.4 Entrapment efficiency

Entrapment efficiency is usually calculated as: EE (%) = [(Total drug − Free drug) / Total drug] × 100.
The separation technique must efficiently distinguish vesicle-associated drug from free drug without causing vesicle disruption.

8.5 Morphology

TEM, cryo-TEM, SEM and AFM can provide complementary information. Conventional drying for SEM can collapse or deform soft vesicles, so the resulting image should not automatically be interpreted as the native hydrated structure. Cryo-TEM is better suited for preserving hydrated morphology but may not be available in all laboratories.

8.6 Deformability

Deformability is a central functional attribute. One common approach measures vesicle passage through a membrane with a defined pore size under controlled pressure. Deformability indices are calculated from the amount or volume of dispersion passing through the membrane and the vesicle size before and after the test. Because

equations differ among studies, the exact method must be reported.

8.7 Drug release

In-vitro release can be evaluated using dialysis, diffusion cells or other validated systems. Membrane resistance, sink conditions and formulation dilution can substantially affect the observed release profile.

8.8 Ex-vivo permeation

Franz diffusion cells are commonly used for skin studies. Parameters include cumulative amount permeated per unit area, steady-state flux, permeability coefficient and lag time. Drug retained in the skin should also be quantified when local delivery is relevant.

8.9 Stability

Stability should include visual appearance, vesicle size, PDI, zeta potential, drug content, entrapment and leakage. Lipid oxidation should be considered when appropriate. The final dosage form, such as a film, requires separate stability evaluation because drying and storage can change the vesicular state.

9. TRANSDERMAL APPLICATIONS

Transferosomes have been investigated for delivery of analgesics, anti-inflammatory agents, corticosteroids, antihypertensives, antifungals, antioxidants, peptides and other therapeutic agents.[4],[5],[12–15] Their main attraction is the possibility of improving penetration of drugs that otherwise have inadequate passive skin permeability.

NSAIDs are a particularly relevant class because local transdermal delivery may provide high concentrations at the site of inflammation while reducing some gastrointestinal exposure associated with oral administration. Studies have investigated meloxicam, diclofenac, ketoprofen and other drugs using transferosomal gels and related systems. However, enhanced skin permeation should not automatically be equated with improved clinical efficacy; pharmacodynamic and safety outcomes require separate evaluation.

For macromolecules, transferosomes are attractive because deformability may provide an opportunity for non-invasive delivery of peptides and proteins. Nevertheless, the molecular size and stability of such agents make the formulation and biological evaluation more challenging. Claims of successful systemic delivery should be supported by validated bioanalytical and pharmacokinetic data.

10. BUCCAL DRUG DELIVERY

The buccal mucosa is a promising site for systemic and local drug delivery. It is relatively accessible, well vascularized and can provide an alternative to swallowing. Drugs absorbed through the buccal mucosa can potentially avoid gastrointestinal degradation and a portion of hepatic first-pass metabolism. Nevertheless, saliva dilution, swallowing, mucus turnover and mechanical movement reduce formulation residence time.

Transferosomes may address part of the permeability problem through flexible vesicular structures. The formulation must, however, remain at the mucosal site long enough for drug release and permeation. Therefore, mucoadhesive polymers are important components of many buccal transferosomal systems.

A notable example is loratadine-loaded transferosomal gel. In the reported study, optimized vesicles had a submicron size of approximately 380 nm and about 60%

loading/entrapment characteristics; incorporation into a mucoadhesive gel improved release, permeation and mucoadhesion compared with a transferosome-free gel. Human pharmacokinetic testing showed bioavailability comparable to the reference oral product, while inter-individual variability in Cmax and AUC was reduced.[6] This study demonstrates the value of combining vesicle engineering with a dosage-form strategy rather than evaluating transferosomes only as a dispersion.

11. TRANSFEROSOME-LOADED BUCCAL FILMS

Buccal films are thin polymeric dosage forms that can provide unit-dose administration, ease of handling and prolonged mucosal residence. A transferosome-loaded film combines the functions of two delivery technologies: the transferosome serves as the drug carrier and permeability-enhancing vesicle, while the polymeric film provides structural support and retention.

Hydroxypropyl methylcellulose grades, carbomers and other hydrophilic polymers can be used as film-forming materials. Plasticizers such as propylene glycol or glycerol may improve flexibility. The formulation pH should be compatible with buccal tissue, while excessive acidity or alkalinity should be avoided.

The manufacturing process is critical. Solvent casting can involve mixing the vesicular dispersion with a hydrated polymer solution followed by casting and controlled drying. Excessive temperature, prolonged drying or strong mechanical processing may change vesicle size, promote aggregation or alter drug leakage. Consequently, transferosome characteristics should ideally be measured both before incorporation and after reconstitution of the final film.

Recommended film evaluations include appearance, thickness, weight variation, folding endurance, tensile strength, surface pH, swelling index, moisture content, drug content uniformity, mucoadhesive strength, residence time, in-vitro release, ex-vivo permeation and stability. Where the scientific objective is to demonstrate a vesicular mechanism, particle size/PDI and other vesicle characteristics after film hydration should also be assessed.

12. COMPARISON WITH RELATED VESICULAR SYSTEMS

Transferosomes should be distinguished from related systems because formulation composition determines mechanism and performance. Conventional liposomes use phospholipid bilayers but are generally less deformable. Ethosomes contain relatively high concentrations of ethanol and depend strongly on alcohol-mediated changes in skin structure and lipid fluidity. Transethosomes combine deformable vesicles with ethanol. Niosomes are based mainly on non-ionic surfactants and can provide useful encapsulation and stability but have different membrane characteristics.

No single vesicular system is universally superior. Comparative studies should control drug dose, composition, administration conditions, tissue model and analytical methods. A formulation that gives smaller vesicles is not necessarily better if its deformability, drug loading or biological performance is inferior.

13. ADVANTAGES AND LIMITATIONS

Potential advantages include improved penetration, ability to carry hydrophilic and

lipophilic drugs, non-invasive administration, potential sustained release and adaptability to gels, films and patches. Transferosomes may be particularly useful when conventional passive diffusion is inadequate.

Limitations include susceptibility of phospholipids to oxidation and hydrolysis, leakage during storage, aggregation, sensitivity to formulation composition, potential surfactant irritation, complex scale-up and lack of standardized deformability testing. Biological barriers also vary substantially between experimental models and human tissues. Recent critical reviews identify inconsistent terminology, heterogeneous formulation strategies and limited clinical translation as major challenges.[7],[8]

14. RECENT ADVANCES AND FUTURE DIRECTIONS

Recent work has increasingly moved toward rational design rather than empirical formulation. Quality-by-design methods, factorial designs and response-surface approaches can help identify optimal combinations of phospholipid, edge activator and processing variables. Hybrid systems, surface modification, polymer coatings and lyophilization are being explored to improve stability and targeting.[7],[16]

For mucosal delivery, future systems may combine transferosomes with mucoadhesive polymers, stimuli-responsive materials or rapidly dissolving films. Surface modification could improve residence time, while controlled hydration could regulate release. Integration with microneedles or other physical enhancement technologies is also being explored for transdermal applications.

The most important future requirement is stronger translational evidence. Studies should report standardized critical quality attributes, use validated analytical methods and compare optimized transferosomes with appropriate controls. Ex-vivo permeation should be followed by pharmacokinetic or pharmacodynamic evaluation where systemic or therapeutic benefit is claimed. Long-term safety and irritation studies are also essential.

15. TABLES

Table 1. Major components of transferosomes and their functions

Component	Examples	Principal function	Important formulation consideration
Vesicle-forming phospholipid	Soy phosphatidylcholine, egg phosphatidylcholine	Forms bilayer and provides vesicle structure	Purity, saturation and concentration affect rigidity, loading and stability
Edge activator	Tween 20/80, Span 60/80, sodium cholate, sodium deoxycholate	Increases membrane flexibility and deformability	Type and concentration require optimization; excess can destabilize bilayer
Cholesterol	Cholesterol	Modulates membrane packing and leakage	Excess may reduce deformability
Alcohol/cosolvent	Ethanol	May aid solubilization and modify	Residual solvent and classification of the

		membrane/skin lipid organization	system should be considered
Hydration medium	Water, phosphate buffer	Hydrates lipid film and forms aqueous vesicle compartment	pH and ionic strength can affect drug ionization and colloidal properties
Film-forming polymer	HPMC, carbomer	Provides structural matrix for buccal film	Concentration affects flexibility, release and vesicle mobility
Plasticizer	Propylene glycol, glycerol	Improves film flexibility	Excess may increase tackiness and moisture uptake

Table 2. Common preparation approaches

Method	Basic principle	Advantages	Limitations
Thin-film hydration	Solubilize lipids, remove solvent, hydrate dry film	Widely used; simple laboratory workflow	Solvent removal; often requires subsequent size reduction
Ethanol injection	Inject lipid/ethanol phase into aqueous phase	Simple and rapid vesicle formation	Residual solvent; mixing strongly affects size
Reverse-phase evaporation	Form water-in-oil emulsion and remove organic solvent	Can support hydrophilic drug loading	More complex and solvent-intensive
Sonication	Apply ultrasonic energy to reduce vesicle size	Can produce smaller vesicles	Heating, possible leakage and aggregation if excessive
Extrusion	Force dispersion through membranes of defined pore size	Good control of size distribution	Membrane fouling and multiple passes may be required
Homogenization	High shear/pressure reduces particle size	Potentially scalable	Equipment and process optimization required
Lyophilization	Remove water after freezing	Can improve storage stability	Rehydration may cause fusion or leakage

Table 3. Critical characterization parameters

Parameter	Typical technique	Purpose	Interpretation
Vesicle size	Dynamic light scattering	Determine hydrodynamic diameter	Useful for batch consistency and dispersion behavior

PDI	Dynamic light scattering	Assess size-distribution breadth	Lower values generally indicate greater uniformity
Zeta potential	Electrophoretic light scattering	Assess electrokinetic surface behavior	Interpret with steric stabilization and other attributes
Entrapment efficiency	Separation + assay	Quantify drug associated with vesicles	Indicates loading efficiency but not biological performance
Morphology	TEM/cryo-TEM/AFM/SEM	Assess shape and aggregation	Method-dependent; dried images may not represent hydrated vesicles
Deformability	Membrane extrusion/filtration assay	Assess ability to deform under stress	Key functional attribute; method must be standardized
Drug release	Dialysis/diffusion cell	Determine release kinetics	Affected by membrane and sink conditions
Ex-vivo permeation	Franz diffusion cell	Measure tissue transport and deposition	Provides biological performance data
Stability	Periodic physicochemical testing	Monitor changes during storage	Should include size, PDI, drug content and leakage

Table 4. Transferosomes compared with related vesicular systems

System	Main structural feature	Key advantage	Main limitation/consideration
Conventional liposome	Phospholipid bilayer	Versatile encapsulation and biocompatibility	Lower deformability
Transferosome	Phospholipid + edge activator	High deformability and barrier transport potential	Stability and standardization challenges
Ethosome	Phospholipid + high ethanol	Enhanced skin penetration	Alcohol-related formulation and tolerability considerations
Transethosome	Deformable vesicle + ethanol	Combines flexibility and alcohol-mediated enhancement	More complex composition

Niosome	Non-ionic surfactant vesicle	Good chemical stability and versatile formulation	Different membrane properties and possible surfactant effects

Table 5. Representative literature on transferosome applications

Drug/active	Route/system	Key finding reported	Reference
Loratadine	Buccal transferosomal gel	Enhanced release/permeation; human pharmacokinetic evaluation	6
Meloxicam	Transdermal transferosomal systems	Enhanced skin permeation reported in comparative studies	4,5
NSAIDs and anti-inflammatory agents	Transdermal gels/vesicles	Frequently investigated because of local/systemic delivery potential	4,5,12
Peptides/proteins	Transdermal research systems	Transferosome deformability investigated for macromolecular delivery	4,5
Donepezil and other neurotherapeutics	Mucosal/transdermal experimental systems	Recent research combines deformable vesicles with barrier-targeting strategies	7

Table 6. Formulation variables and expected effects

Variable	Possible increase	Potential beneficial effect	Potential adverse effect
Phospholipid concentration	↑	Higher vesicle material and possible loading	Higher viscosity, larger vesicles or aggregation

Edge activator concentration	↑ to optimum	Greater deformability and permeability	Excess may disrupt bilayer and increase leakage
Cholesterol	↑	Greater membrane packing and stability	Reduced flexibility/permeation at excessive levels
Sonication energy/time	↑	Smaller, more uniform vesicles	Heating, degradation or drug leakage
Hydration time	↑ to optimum	Improved hydration and vesicle formation	Extended processing may increase degradation
Polymer concentration in film	↑	Improved film integrity and residence	Slower release, reduced vesicle mobility and thicker film

16. CONCLUSION

Transferosomes are highly deformable phospholipid-based vesicular systems with potential to enhance delivery across biological barriers. Their performance is governed by the interaction among phospholipid composition, edge activator, drug properties, hydration and processing conditions. Vesicle size, PDI, zeta potential and entrapment efficiency are important quality attributes, but deformability and biological performance are particularly important for establishing the functional identity of a transferosome.

Transdermal delivery remains the most established research application, while buccal delivery provides an attractive emerging opportunity. Incorporating transferosomes into mucoadhesive gels and polymeric films can combine vesicular transport with improved residence and convenient dosing. Nevertheless, instability, scale-up, heterogeneous analytical methods and limited clinical translation remain important barriers. Future research should emphasize QbD-based development, standardized deformability testing, mechanistic permeation studies, long-term stability and clinically relevant comparative evaluation.

Ethical Statement

Not applicable; this is a narrative review and reports no new experiments involving humans or animals.

Conflict of Interest

The authors declare no conflict of interest.

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