EJPMR, 2026, 13(5), 345-355 **Research Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

REVOLUTIONIZING ANTIPSYCHOTIC DRUG DELIVERY: THE ROLE OF TRANSFEROSOMES IN MODERN PHARMACEUTICS

[1]Shah Divyaben Rajendrakumar, *[2]Keyur S. Patel

[1]Research Scholar, Gujarat Technological University, Ahmedabad, Gujarat, India.
[*2]Professor, K.B. Raval College of Pharmacy, Shertha, Gandhinagar, Gujarat, India.

***Corresponding Author: Keyur S. Patel**

Professor, K.B. Raval College of Pharmacy, Shertha, Gandhinagar, Gujarat, India.

DOI: https://doi.org/10.5281/zenodo.20022290

How to cite this Article: [1]Shah Divyaben Rajendrakumar, *[2]Keyur S. Patel. (2026). Revolutionizing Antipsychotic Drug Delivery: The Role Of Transferosomes In Modern Pharmaceutics. European Journal of Pharmaceutical and Medical Research, 13(5), 345–355.

Article Received on 05/04/2026 **Article Revised on 25/04/2026** **Article Published on 04/05/2026**

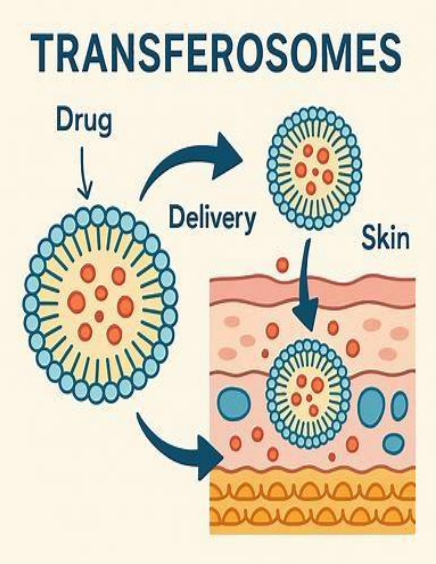
ABSTRACT

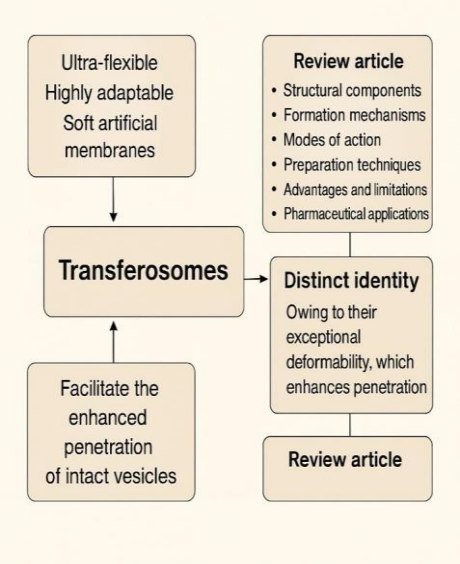
Transdermal drug delivery systems (TDDS) have gained significant attention as non-invasive platforms that enhance patient compliance and enable controlled drug release. However, their clinical utility is limited by the barrier function of the stratum corneum, which restricts the permeation of drugs, particularly those with high molecular weight and poor lipophilicity. Consequently, only a limited number of therapeutic agents are suitable for conventional transdermal administration. To overcome these limitations, transferosomes have emerged as a novel and promising vesicular carrier system. Transferosomes are ultra-deformable lipid-based vesicles composed of phospholipids and edge activators (surfactants) that impart elasticity and membrane flexibility. Their unique structural characteristics enable encapsulation of both hydrophilic and lipophilic drugs and facilitate penetration across the skin via intercellular and transcellular pathways under the influence of the transepidermal hydration gradient. By bypassing hepatic first-pass metabolism, transferosomes improve systemic bioavailability and enhance drug permeation efficiency. This review highlights the structural features, mechanism of action, preparation methods, advantages, limitations, and therapeutic applications of transferosomal drug delivery systems.

KEYWORDS: Stratum Corneum; Transferosomes; Transdermal Delivery System; Transdermal Patch; Techniques of Transferosomes.

Graphical Abstract (without Author Details)

Oral antipsychotic therapy is frequently limited by extensive hepatic first-pass metabolism, fluctuating plasma drug concentrations, and poor patient adherence, ultimately compromising therapeutic efficacy in chronic psychiatric disorders. Although transdermal delivery offers a non-invasive alternative, its application is restricted by the barrier properties of the stratum corneum. Transferosomes, ultra-deformable lipid vesicular systems composed of phospholipids and edge activators (e.g., sodium cholate, Tween 80), have emerged as a promising carrier platform to enhance transdermal permeation. Their high elasticity enables passage through intercellular lipid domains under the influence of the transepidermal hydration gradient. This review critically discusses formulation strategies, preparation techniques, and physicochemical characterization parameters of transferosomal systems, with particular emphasis on atypical antipsychotics such as risperidone and olanzapine. Transferosomal delivery bypasses hepatic first-pass metabolism, improves systemic bioavailability, and provides sustained drug release, thereby minimizing peak-related adverse effects including extrapyramidal symptoms. Consequently, transferosomes represent a rational and technologically advanced approach to improve therapeutic outcomes and patient compliance in long-term psychiatric management.





1. INTRODUCTION[1-3]

Psychiatric disorders such as schizophrenia and bipolar disorder require long-term pharmacotherapy to prevent relapse and maintain symptom control. Psychosis, in particular, is a chronic and disabling neuropsychiatric condition associated with significant social and functional impairment. Although typical and atypical antipsychotics have substantially improved clinical outcomes, their long-term use is often limited by poor patient adherence and dose-related adverse effects.

Oral antipsychotics such as risperidone and olanzapine undergo significant hepatic first-pass metabolism, resulting in variable systemic bioavailability (40–70%) and pronounced peak–trough plasma fluctuations. These fluctuations are associated with extrapyramidal symptoms, sedation, and metabolic disturbances, contributing to treatment discontinuation rates exceeding 40% in chronic schizophrenia management. While long-acting injectable formulations improve adherence, they are invasive and may reduce patient acceptability.

Transdermal drug delivery systems (TDDS) provide a non-invasive alternative capable of bypassing first-pass metabolism and maintaining sustained plasma drug concentrations. However, the barrier properties of the stratum corneum significantly restrict the permeation of most antipsychotics due to their molecular weight and physicochemical characteristics. To overcome this limitation, ultra-deformable vesicular carriers such as transferosomes have been developed. Transferosomes consist of phospholipid bilayers incorporating edge activators that impart elasticity, enabling the vesicles to traverse narrow intercellular pathways within the skin.

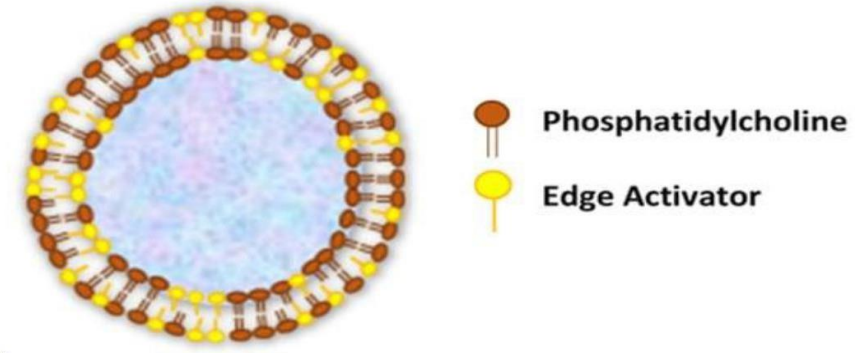


Figure 1.1: Structure of *Transferosomes.*

1.1 Transferosomes in Antipsychotic Drug Delivery

Atypical antipsychotics such as risperidone and olanzapine are widely prescribed for the management of schizophrenia and bipolar disorder; however, their clinical effectiveness is frequently compromised by pharmacokinetic variability and poor adherence. Both drugs undergo extensive hepatic first-pass metabolism, resulting in fluctuating plasma concentrations and dose-dependent adverse effects. Transdermal transferosomal delivery has emerged as a promising strategy to overcome these limitations by enhancing permeation across the stratum corneum while enabling sustained systemic drug exposure. Transferosomes, owing to their ultra-deformable lipid bilayer structure, can traverse intercellular lipid domains under the influence of the transepidermal hydration gradient. The presence of edge activators increases membrane flexibility, allowing vesicles to

penetrate intact skin without structural disruption. Several preclinical investigations have demonstrated improved permeation and enhanced drug retention for antipsychotic-loaded transferosomes compared with conventional formulations.[22,26]

Table 1: Transferosomal delivery studies of antipsychotics

Drug	Vesicle Size (nm)	Entrapment Efficiency (%)	Flux Enhancement	Experimental Model
Risperidone	120–180	65–85	2–4 fold	Rat skin (ex vivo)
Olanzapine	100–200	70–90	3–5 fold	Excised animal skin / ex vivo

Studies indicate that vesicle size below 200 nm with moderate surfactant concentration provides optimal deformability and entrapment efficiency, resulting in significantly higher transdermal flux compared with conventional gels or liposomal systems.[35,36]

1.2 Potential Reduction of Extra pyramidal Symptoms

EPS are strongly correlated with excessive D_2 receptor blockade resulting from high peak plasma levels. Conventional oral dosing often produces rapid systemic exposure, increasing the risk of motor side effects. Transferosomal transdermal systems provide controlled drug input, potentially maintaining receptor occupancy within the optimal therapeutic range (approximately 60–80%) without exceeding thresholds associated with EPS.Although clinical data remain limited, preclinical pharmacokinetic studies suggest that transferosome-mediated delivery achieves smoother plasma concentration–time profiles compared to oral administration Such modulation may reduce peak-related dopaminergic blockade and improve long-term tolerability.[22, 37]

1.3 Advantages over Long-Acting Depot Injections4

Long-acting injectable antipsychotics improve adherence but are associated with several limitations:

- Pain at injection site
- Requirement for clinical supervision
- Risk of post-injection syndrome
- Limited dose flexibility

Transferosomal transdermal systems offer a non-invasive alternative that maintains sustained plasma concentrations while allowing dose adjustment through patch modification. Additionally, transdermal systems eliminate the need for repeated intramuscular administration and may enhance patient acceptance, particularly in chronic psychiatric populations where treatment adherence is critical.[28,41]

1.4 Mechanism of Transferosomes

The image shows a particle deforming to penetrate the outermost layer of the epidermis through the intercellular gap and then reforming after penetration of the stratum corneum. The top part shows a spherical particle approaching the outermost layer of the epidermis. The middle part shows the particle deforming to pass through the intercellular gap. The bottom part shows the particle reforming its spherical shape after penetrating the stratum corneum.[4]

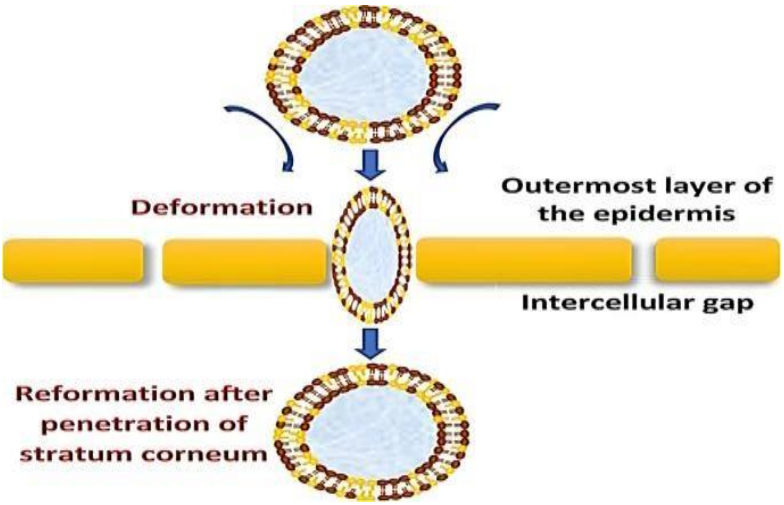


Figure 1.2: Mechanism of Transferosomes.

2. MATERIALS AND METHODS FOR TRANSFEROSOMES

2.1. Materials

Table 2: Factors Influencing Transferosomal Formulation and Performance.

Factor	Effect on Transferosomal Formulation
Phospholipid: Edge Activator Ratio	The ratio of phospholipid to edge activator (e.g., lecithin:surfactant) plays a critical role in determining vesicle size, entrapment efficiency, deformability, and permeation. Excess surfactant may increase bilayer fluidity and membrane permeability, leading to drug leakage and reduced entrapment efficiency. Conversely, insufficient surfactant may result in larger, less deformable vesicles with reduced transdermal flux [5,6].
Hydration Medium	The choice of hydration medium (distilled water or phosphate buffer, pH 6.5–7.0) influences vesicle formation, drug ionization, and stability. Maintaining an optimal pH ensures the drug remains predominantly in its unionized form, thereby improving entrapment efficiency and enhancingskin permeation [7].
Solvents	Organic solvents such as ethanol or methanol are selected based on solubility compatibility of lipids and drug. Complete dissolution of formulation components is essential for uniform thin-film formation and vesicle stability. Ethanol may also function as a penetration enhancer; however, excessive ethanol can increase bilayer permeability and reduce entrapment efficiency due to drug leakage [7].
Edge Activators	The type and concentration of edge activator significantly influence vesicle deformability, size distribution, and drug release behavior. Appropriate surfactant selection enhances elasticity and penetration capacity, whereas excessive concentrations may destabilize the bilayer and promote drug leakage. Surfactant structure and hydrophilic–lipophilic balance (HLB) value are critical determinants of transferosomal performance [8].

3. METHODS OF PREPARATION[12-20]

3.1 Rotary Film Evaporation Method

The thin-film hydration method, originally described by Bangham, is one of the most widely employed techniques for the preparation of vesicular systems. In this method, phospholipids and surfactants (edge activators) are dissolved in an organic solvent such as chloroform, methanol, or a mixture of both. The organic phase is then transferred into a round-bottom flask and subjected to rotary evaporation under reduced pressure at a controlled temperature. This process removes the solvent and results in the formation of a thin, uniform lipid film on the inner wall of the flask. The dried lipid film is subsequently hydrated with an aqueous phase, which may contain the drug, under continuous agitation. Upon hydration, the lipids swell and spontaneously organize into multilamellar vesicles due to the formation of bilayer structures. To obtain vesicles of uniform and reduced size, further processing techniques such as extrusion or sonication are employed. Extrusion involves passing the vesicular dispersion through polycarbonate membranes of defined pore size, whereas sonication utilizes high-frequency ultrasonic energy to reduce vesicle size and achieve a more homogeneous dispersion.[18]

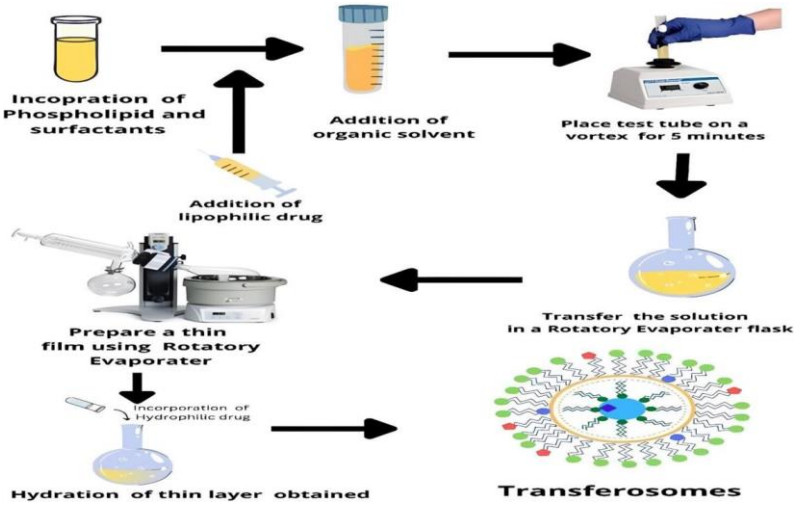


Figure 3.1: Rotary Evaporation Method.

3.2 Modified hand shaking Process

The modified hand-shaking method follows principles similar to the conventional rotary evaporation–sonication technique but utilizes a simplified procedure. Lipids such as phospholipids and surfactants (edge activators) are dissolved in an appropriate organic solvent (e.g., chloroform or methanol) to obtain a clear solution, while the drug is separately dissolved in an aqueous phase

based on its solubility. The organic lipid solution is added drop wise to the aqueous drug solution under continuous manual agitation, resulting in the formation of a milky vesicular suspension. The dispersion is then sonicated using a probe or bath sonicator to reduce vesicle size and obtain a homogeneous and stable transferosomal formulation.[19]

3.3. Vortexing-sonication method

In this method, phospholipids, surfactants (edge activators), and the drug are directly dispersed in a suitable aqueous medium, typically phosphate buffer. The mixture is subjected to vortex mixing until a homogeneous, milky transferosomal suspension is formed. Vortexing facilitates uniform dispersion of lipid components within the aqueous phase and promotes initial vesicle formation. The resulting suspension is then subjected to sonication using either a probe sonicator or a bath sonicator to reduce vesicle size and improve uniformity. Sonication applies ultrasonic energy that breaks down larger vesicles into smaller, more homogeneous nano-sized transferosomes, thereby enhancing stability and improving drug encapsulation efficiency.

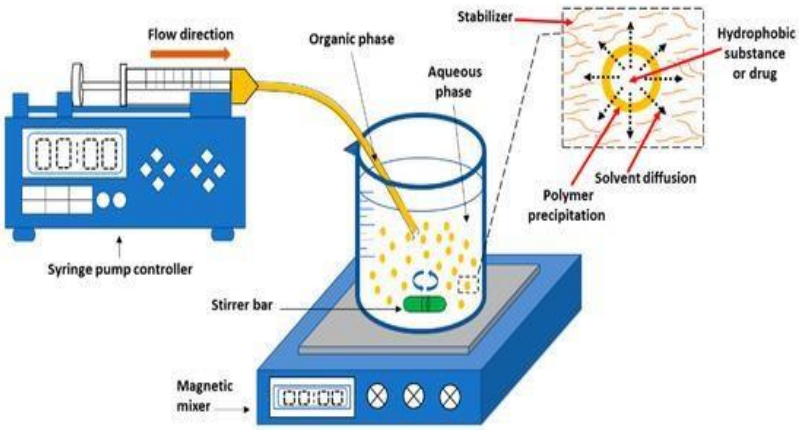


Figure 3.3 Vortexing Sonication Method.

3.4. Suspension homogenization method

Transferosomes are prepared by dissolving phospholipids and surfactants (edge activators) in an organic solvent such as chloroform or ethanol. The lipid solution is then mixed with an aqueous buffer under continuous stirring to form a coarse vesicular suspension. The suspension is subsequently homogenized using high-pressure homogenization or micro-fluidization to reduce vesicle size and obtain uniformly distributed, stable transferosomal vesicles.

3.5 Centrifugation process

Phospholipids, edge activators, and the lipophilic drug are dissolved in a suitable organic solvent. The solvent is removed under reduced pressure using a rotary evaporator or vacuum system, resulting in the formation of a thin lipid film on the inner wall of the flask. The dried lipid film is hydrated with an appropriate buffer solution to form a vesicular suspension. The suspension is then subjected to ultracentrifugation using a density gradient system. During centrifugation, transferosomes migrate to the upper layer of the gradient, from where they are collected and washed with fresh buffer to remove un-entrapped drug and residual impurities.

3.6 Reverse -phase evaporation Method

Phospholipids and an edge activator are dissolved in a round-bottom flask containing an organic solvent mixture such as diethyl ether and chloroform. A lipophilic drug may be incorporated at this stage. The solvent is partially evaporated using a rotary evaporator to obtain a concentrated lipid phase. The lipid phase is then re-dissolved in a volatile organic solvent (e.g., isopropyl ether or diethyl ether), and the aqueous phase is added to form a biphasic system. Hydrophilic drugs can be introduced during this step. The mixture is sonicated using a bath sonicator to produce uniform water-in-oil (w/o) emulsion. Subsequent slow evaporation of the organic solvent under reduced pressure results in the formation of a viscous gel, which ultimately converts into a transferosomal vesicular suspension.

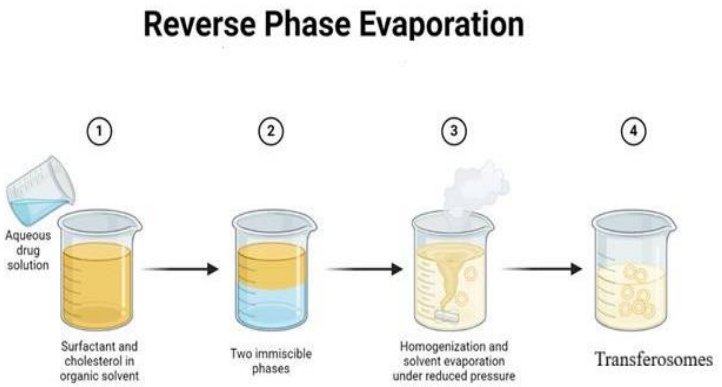


Figure 3.5: Reverse Phase Evaporation.

3.7 High-pressure homogenization Technique

Phospholipids, edge activators, and the drug are uniformly dispersed in phosphate-buffered saline or distilled water containing a small amount of alcohol. The dispersion is subjected to simultaneous stirring and ultrasonic treatment to promote vesicle formation. Intermittent sonication further reduces initial vesicle size and improves uniformity. The resulting suspension is then processed using a high-pressure homogenizer, where intense shear forces reduce lipid bilayer structures into smaller, uniformly distributed transferosomal vesicles.

3.8 Ethanol injection method

The organic phase is prepared by dissolving phospholipids, edge activators, and the lipophilic drug in ethanol under magnetic stirring until a clear solution is obtained. The aqueous phase, containing phosphate buffer and water-soluble components (including hydrophilic drug, if applicable), is prepared separately. Both phases are heated to 45–50 °C. The ethanolic lipid solution is then injected drop wise into the aqueous phase under continuous stirring, leading to spontaneous vesicle formation. Stirring is continued to allow complete evaporation of ethanol, followed by sonication to reduce particle size and obtain uniform transferosomal dispersion.

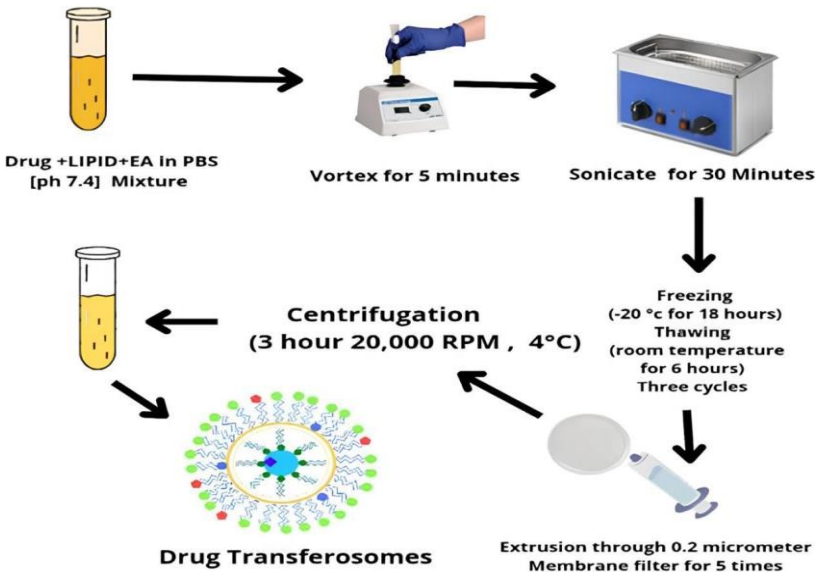


Figure 3.7: Ethanol Injection Method.

4. EVALUATION OF THE TRANSFEROSOME[21-29]

Characterization of transferosomes is a crucial step in evaluating their physicochemical properties, stability, and therapeutic performance. The following are some of the commonly employed methods used for the characterization of transferosomal formulations:

4.1 Vesicle Size, Size Distribution, and Zeta Potential

Vesicle size, polydispersity index (PDI), and zeta potential are critical parameters for evaluating the stability and uniformity of transferosomal formulations. These parameters are commonly determined using Dynamic Light Scattering (DLS) with instruments such as a Malvern Zetasizer. Vesicle size influences drug permeation and distribution, while PDI indicates homogeneity of the dispersion. Zeta potential provides information about surface charge and electrostatic stability, helping predict long-term stability of the vesicular system.

4.2 Vesicle Morphology

Morphological evaluation provides insight into the structural characteristics of transferosomes. Techniques such as Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) are widely used to examine vesicle shape, surface characteristics, and lamellarity. These techniques confirm the spherical structure and integrity of the vesicles, while DLS can further support size measurements.

4.3 Entrapment Efficiency

Entrapment efficiency (EE%) reflects the capacity of transferosomes to incorporate and retain the drug within their lipid bilayers. Unentrapped drug is separated using ultracentrifugation, centrifugation, or dialysis techniques. The entrapment efficiency is calculated using the formula:

$$EE\ (\%) = [(\text{Total Drug} - \text{Free Drug}) / \text{Total Drug}] \times 100$$

High entrapment efficiency indicates effective formulation design and improved therapeutic performance.

4.4 Drug Content

Drug content analysis ensures uniform distribution of the drug within the vesicular system. Transferosomes are disrupted using suitable solvents, and the released drug is quantified using validated analytical methods such as High-Performance Liquid Chromatography (HPLC) or UV–Visible spectroscopy. This parameter confirms dosage accuracy and formulation reproducibility.

4.5 Turbidity Measurement

Turbidity measurement provides indirect information about vesicle formation and dispersion stability. It is determined using a nephelometer, which measures light scattering by suspended particles. Changes in turbidity may indicate aggregation or instability in the formulation.

4.6 Surface Charge and Charge Density

Surface charge and charge density are evaluated using zeta potential analysis. These parameters influence vesicle interaction with biological membranes and overall colloidal stability. A sufficiently high absolute zeta potential value generally indicates good physical stability of the dispersion.

4.7 Penetration Ability

The penetration ability of transferosomes is assessed to determine their effectiveness in crossing the stratum corneum barrier. Common evaluation techniques include Franz diffusion cells, confocal laser scanning microscopy (CLSM), and tape-stripping methods. These studies provide qualitative and quantitative data on drug permeation and skin distribution.

4.8 Occlusion Effect

The occlusion effect is evaluated to determine the formulation's ability to enhance skin hydration. Increased hydration may improve drug permeation across the skin barrier. This parameter is particularly relevant for topical and transdermal delivery systems.

4.9 In Vitro Drug Release

In vitro drug release studies are conducted to evaluate the release kinetics of the drug from transferosomes. The formulation is maintained at approximately 32 °C to simulate skin surface temperature. Samples are withdrawn at predetermined time intervals, and the released drug is analyzed after separation from vesicles. The release profile helps in understanding controlled and sustained delivery behavior.

4.10 In Vitro Skin Permeation Study

In vitro skin permeation studies are performed using a Franz diffusion cell apparatus consisting of donor and receptor compartments. Excised abdominal or animal skin is mounted between the compartments with the stratum corneum facing the donor side. The receptor compartment contains phosphate buffer (pH 7.4) maintained at 37 °C with continuous magnetic stirring. A specified quantity of formulation is applied to the donor compartment. At predetermined intervals, samples are withdrawn and replaced with fresh buffer to maintain sink conditions. Drug concentration in collected samples is determined using HPLC or spectroscopic methods.

5. COMPARATIVE ANALYSIS WITH OTHER VESICULAR SYSTEMS

Vesicular nanocarriers such as liposomes, ethosomes, and transferosomes have been extensively investigated for transdermal drug delivery. Although all three systems are lipid-based carriers designed to enhance dermal permeation, they differ substantially in composition, deformability, penetration mechanism, and clinical applicability.

5.1 Transferosomes vs Liposomes

Conventional liposomes are composed primarily of phospholipid bilayers enclosing an aqueous core. While they are capable of encapsulating both hydrophilic and lipophilic drugs, their relatively rigid bilayer structure limits deep skin penetration. Liposomes generally accumulate within the upper layers of the stratum corneum and are less effective in delivering drugs systemically through intact skin.[26,45] In contrast, transferosomes incorporate edge activators (e.g., sodium cholate, Tween 80, Span 80) that destabilize the lipid bilayer and impart high elasticity. This ultra-deformable nature enables transferosomes to pass through narrow intercellular pores that are significantly smaller than their own diameter without structural rupture. The penetration process is driven by the transepidermal hydration gradient, allowing deeper dermal and systemic drug delivery.[26,28]

Moreover, transferosomes exhibit superior deformability index and enhanced transdermal flux compared with conventional liposomes, particularly for drugs with

limited intrinsic permeability.[35,36]

5.2 Transferosomes vs Ethosomes

Ethosomes are lipid vesicles containing high concentrations of ethanol (20–45%), which acts as both a penetration enhancer and a bilayer fluidizer. Ethanol disrupts the ordered lipid structure of the stratum corneum, thereby facilitating enhanced drug permeation.[21]

While ethosomes demonstrate improved skin penetration compared with liposomes, their mechanism primarily relies on ethanol-induced lipid fluidization rather than vesicle deformability. High ethanol concentrations may compromise vesicle stability and increase the risk of skin irritation upon prolonged application.

Transferosomes, by comparison, rely on mechanical deformability rather than chemical disruption of the skin barrier. Their elastic membrane structure enables penetration through intact intercellular pathways without excessive lipid extraction. This may reduce irritation potential while maintaining efficient drug transport.[22,26]

Additionally, transferosomes generally exhibit higher entrapment efficiency for certain lipophilic drugs due to optimized phospholipid–surfactant interactions.[35]

5.3 Comparative Advantages of Transferosomes

Transferosomes offer several distinct advantages over conventional vesicular systems:

- Enhanced deformability allowing penetration through intact skin
- Improved transdermal flux and systemic bioavailability
- Ability to encapsulate both hydrophilic and lipophilic drugs
- Reduced peak–trough plasma fluctuations
- Potential to minimize dose-related adverse effects

These properties make transferosomes particularly attractive for chronic therapies such as antipsychotic treatment, where sustained plasma levels and improved adherence are essential.

5.4 Limitations of Transferosomes

Despite their advantages, transferosomes are not without limitations:

- High surfactant concentration may lead to membrane instability and drug leakage
- Risk of skin irritation depending on edge activator type
- Susceptibility to phospholipid oxidation and hydrolysis
- Challenges in large-scale manufacturing and reproducibility
- Limited clinical validation compared to liposomal products

Furthermore, optimization of phospholipid-to-surfactant ratio remains critical to balance deformability and stability.[5,9]

Table 3: Comparison of Liposomes, Ethosomes, and Transferosomes.

Parameter	Liposomes	Ethosomes	Transferosomes
Composition	Phospholipids + Cholesterol	Phospholipids + High Ethanol	Phospholipids + Edge Activators
Deformability	Low	Moderate	High (Ultra-deformable)
Penetration Mechanism	Passive diffusion	Ethanol-induced lipid fluidization	Hydration gradient- driven elastic penetration
Skin Penetration Depth	Superficial	Moderate to deep	Deep/systemic
Entrapment Efficiency	Moderate	Moderate	High (optimized systems)
Irritation Risk	Low	Moderate (ethanol- related)	Depends on surfactanttype
Stability	Good	Ethanol-dependent	Surfactant-dependent
Clinical Translation	Established	Emerging	Limited but promising

6. LIMITATIONS AND TRANSLATIONAL CHALLENGES

Despite promising preclinical findings, several limitations restrict the clinical translation of transferosomal systems.

One of the primary concerns is surfactant-related toxicity. Edge activators such as sodium cholate, Tween 80, and Span derivatives enhance vesicle deformability but may disrupt skin lipid integrity at higher concentrations, potentially causing irritation or long-term barrier impairment.[5,26] Therefore, optimization of surfactant type and concentration is essential to balance elasticity and safety.

Scale-up reproducibility represents another major challenge. Parameters such as vesicle size, polydispersity index, and deformability are highly sensitive to preparation techniques, solvent removal rate, and homogenization pressure. Maintaining batch-to-batch consistency during industrial-scale production remains technically demanding.[23,37]

Additionally, regulatory uncertainty limits commercialization. There are currently no universally standardized guidelines specifically addressing ultra-deformable vesicular systems, which complicates quality control, stability assessment, and bioequivalence

evaluation.[28]

Most importantly, the lack of well-designed clinical trials significantly restricts translational advancement. Although numerous in vitro and ex vivo studies demonstrate enhanced permeation, robust pharmacokinetic and long-term safety data in human subjects remain limited.[22,26]

Addressing this formulation, manufacturing, regulatory, and clinical gaps will be crucial for the successful integration of transferosomal antipsychotic therapy into routine clinical practice.

7. FUTURE PERSPECTIVES

Future advancements in transferosomal antipsychotic delivery are likely to focus on technological integration and translational refinement. One promising direction is the combination of transferosomes with microneedle-assisted delivery systems, which may further enhance skin permeation by creating transient microchannels while preserving controlled vesicular transport. Such hybrid systems could improve dose precision and reduce variability associated with passive transdermal diffusion.

The application of artificial intelligence (AI) and machine learning algorithms in formulation optimization represents another emerging approach. Predictive modeling of vesicle size, deformability index, and entrapment efficiency based on formulation variables may significantly reduce experimental workload and improve reproducibility during scale-up.
Additionally, combination therapy strategies, incorporating dual antipsychotics or adjunctive agents within a single vesicular platform, may offer synergistic therapeutic benefits while minimizing dose-dependent adverse effects.

Finally, the development of long-acting transdermal antipsychotic systems capable of maintaining stable plasma concentrations over extended periods (days to weeks) could provide a non-invasive alternative to depot injections, thereby enhancing patient adherence and long-term treatment outcomes.

Continued multidisciplinary research integrating nanotechnology, clinical pharmacology, and regulatory science will be essential to translate these innovations into clinically viable products.

8. CONCLUSION

Transferosomal systems represent a promising advancement in transdermal delivery of antipsychotic agents by addressing key limitations associated with conventional oral and injectable therapies. Their ultra-deformable structure enables enhanced permeation across the stratum corneum, improved systemic bioavailability, and the potential to maintain stable plasma drug concentrations, thereby reducing peak-related adverse effects and improving patient adherence. However, despite encouraging preclinical evidence, several barriers remain, including surfactant-related safety concerns, formulation stability issues, manufacturing reproducibility, and limited clinical validation. Regulatory standardization and large-scale pharmacokinetic and long-term safety studies are essential to establish therapeutic equivalence or superiority over existing formulations. Future research should prioritize scalable production strategies, integration with advanced delivery technologies, and well-designed clinical trials to facilitate successful translation of transferosomal antipsychotic systems into routine clinical practice.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

ACKNOWLEDGEMENT

The author gratefully acknowledges the guidance and support provided by Dr. Keyur S. Patel, whose expertise in pharmaceutical formulation and drug delivery systems significantly enriched the development of this review. The author also extends sincere thanks to Dr. Pranav and Dr. Dhawal for their valuable encouragement and contributions to this review paper.

Appreciation is further expressed to fellow researchers and peers for their insightful discussions and constructive feedback during the conceptualization and preparation of this manuscript. This work was carried out as part of the academic requirements for the completion of the Ph.D. degree, and the author acknowledges the institutional support and academic framework that facilitated this scholarly endeavor.

9. REFERENCES

1. Muthangi S, Pallerla P, Nimmagadda S. Transdermal delivery of drugs using transferosomes: a comprehensive review. J Adv Sci Res., 2023; 14(6): 30–35.
2. Singh A, Fatima Z, Srivastava D. A comprehensive review on polyphenol-based nanovesicular systems for topical delivery. Curr Drug Deliv., 2025; 22(2): 123–139.
3. Wani SN, Singh S, Sharma N, et al. Transferosome-based intranasal drug delivery systems for the management of schizophrenia: a futuristic approach. Bio Nano Sci., 2024; 14: 3811–3829.
4. Rajendran A, Elumalai V, Balasubramaniyam S, et al. Transferosome formulations as innovative carriers for transdermal drug delivery: composition, properties, and therapeutic applications. Biomed Mater Devices. 2025.
5. Bnyan R, Khan I, Ehtezazi T, Saleem I, Gordon S, O'Neill F, et al. Surfactant effects on lipid-based vesicle properties. J Pharm Sci., 2018; 107(5): 1237–1246.
6. Dudhipala N, Mohammed RP, Youssef AA, Banala

N. Effect of lipid and edge activator concentration on development of aceclofenac-loaded transfersomes gel for transdermal application: in vitro and ex vivo skin permeation. Drug Dev Ind Pharm., 2020; 46(8): 1334–1344.
7. Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev., 2004; 56: 603–618.
8. Banerjee S, Roy P, Gupta M. Size-dependent efficiency of transferosomes in drug penetration: a recent study. Nanomedicine, 2023; 19: 401–410.
9. Pandey A, Gupta P, Singh VK. Optimizing the blend of edge activators and phospholipids for enhanced transferosome flexibility and drug delivery. J Control Release, 2022; 350: 121–129.
10. Opatha SAT, Titapiwatanakun V, Chutoprapat R. Transfersomes: a promising nanoencapsulation technique for transdermal drug delivery. Int J Pharm., 2020; 587: 119643.
11. Rai S, Pandey V, Rai G. Transfersomes as versatile and flexible nano-vesicular carriers in skin cancer therapy: the state of the art. Nano Rev Exp., 2017; 8: 1325708.
12. Cevc G, Schätzlein AG, Blume G. Transdermal drug carriers: basic properties, optimization and transfer efficiency in the case of epicutaneously applied peptides. J Control Release, 1995; 36: 3–16.
13. Cevc G, Gebauer D, Stieber J, Schätzlein A, Blume G. Ultraflexible vesicles transport therapeutic amounts of insulin across intact mammalian skin. Biochim Biophys Acta, 1998; 1368: 201–215.
14. Shakthi A, et al. Transferosomes: a promising nanoencapsulation technique for transdermal drug delivery. Pharmaceutics, 2020; 12(9): 855.
15. Prajapati ST, Patel CG, Patel CN. Transfersomes: a vesicular carrier system for transdermal drug delivery. Asian J Biochem Pharm Res., 2011; 1(2): 507–524.
16. Modi CD. Transfersomes: new dominants for transdermal drug delivery. J Pharm Tech Res., 2012; 2(3): 115–116.
17. Solanki D, et al. Transferosomes: a review. World J Pharm Pharm Sci., 2001; 5(10): 435–449.
18. Priyanka R, Shipra D. Transferosomes: a novel carrier for transdermal delivery system. Int J Pharm Technol., 2009; 4(1): 1854–1865.
19. Sharma T, Garg A, Aman, et al. Recent advances in transdermal delivery of drugs through lipid vesicles. Colloids Surf B Biointerfaces, 2020; 187: 110716.
20. Kaur G, Mehta SK. Advances in transdermal drug delivery using transferosomes for anti-inflammatory and analgesic formulations. Int J Pharm., 2022; 624: 121827.
21. Khatri M, Hiranandani L, Pillay V. Ethosome and ethosomal carriers: a novel paradigm in transdermal drug delivery. Eur J Pharm Biopharm., 2021; 159: 19–34.
22. Tiwari S, Verma P, Gupta G. Transferosomes: a breakthrough approach in transdermal drug delivery. J Drug Deliv Sci Technol., 2023; 84: 104523.
23. Trofimov A, Zhang Y, Zhu X. Fabrication techniques for lipid-based vesicles including transferosomes for drug delivery. J Control Release, 2022; 343: 10–27.
24. Kumar A, Pathak K. Formulation optimization of transferosomal drug delivery system using zeta potential and size-based studies. Eur J Pharm Sci., 2021; 161: 105804.
25. Mahajan HS, Deshmukh SR, Deshmukh TA. Techniques for characterization and in vitro evaluation of transferosomes for topical applications. J Drug Deliv Sci Technol., 2020; 59: 101918.
26. Zhao J, Liu S, Ma W. Transferosomes in transdermal drug delivery: mechanisms, development and applications. Colloids Surf B Biointerfaces, 2023; 219: 112873.
27. Rao PN, Santhosh SM, Kothakota A. Advances in analytical characterization techniques for lipid-based nanocarriers. J Mol Liq., 2022; 364: 120227.
28. Benson HAE. Transfersomes for dermal and transdermal drug delivery. RSC Adv., 2020; 10: 1–18.
29. Wahi N, Kaur G, Narang JK. Transferosomes—a lipid-based vesicular carrier with versatile applications. Int J Pharm Sci Rev Res., 2023; 81: 78–84.
30. Patel V, Pandey AK. Transferosomes for transdermal immunization: a novel approach to vaccine delivery. J Control Release, 2022; 349: 141–150.
31. Garg M, Sharma R. Optimization of transferosome size for effective skin penetration. Int J Pharm., 2022; 616: 121617.
32. Gupta P, Jain R, Kumar S. Impact of transferosome size on drug delivery efficiency. Colloids Surf B Biointerfaces, 2023; 219: 112875.
33. Kumar A, Sharma S, Singh R. Transferosome-mediated transdermal drug delivery: overcoming the barrier of skin permeability. J Drug Deliv Sci Technol., 2022; 77: 103851.
34. Gupta M, Khatri V, Jain P. Comparative analysis of transferosomes and liposomes for enhanced transdermal drug delivery. Colloids Surf B Biointerfaces, 2023; 220: 113005.
35. Lee K, Tanaka H, Suzuki Y. Novel applications of transferosomes in biologic delivery: insulin case study. Drug Deliv Sci Technol., 2023; 83: 115678.
36. Sharma P, Verma R, Jain S. Role of transferosomes in overcoming transdermal drug delivery challenges. Int J Pharm., 2022; 625: 122051.
37. Singh R, Singh A. Transferosomes: a promising drug delivery system for enhanced transdermal drug permeation. Colloids Surf B Biointerfaces, 2023; 223: 113144.
38. Sharma V, Gupta P, Bhatt S. Role of transferosomes in improving bioavailability. J Drug Deliv Sci Technol., 2023; 82: 104376.
39. Johnson L, Carter J, Wilson R. Transferosomes in inflammatory drug delivery:

mechanisms and advancements. Adv Drug Deliv Rev., 2023; 195: 114123.
40. Ahmad K, Khan R, Ahmad M. Versatile potential of transferosomes in delivering diverse therapeutic agents. Eur J Pharm Biopharm., 2023; 179: 46–58.
41. Sharma A, Singh P. Liposome-based drug delivery systems: formulation and therapeutic potential. J Drug Deliv Sci Technol., 2023; 85: 104391.
42. Jaiswal R, Pal M, Bose A. Multi-drug encapsulation in transferosomes. J Multi Drug Sci., 2023; 7: 89–95.
43. Patel M, Chauhan V. Advances in liposomal drug delivery systems. Colloids Surf B Biointerfaces, 2023; 225: 113245.
44. Kumar S, Mahajan R. Advanced liposomal formulation techniques for drug delivery. J Drug Deliv Sci Technol., 2023; 84: 104383.
45. Gupta V, Singh A. Recent advances in liposome technology for biotechnology applications. Int J Pharm., 2023; 627: 122345.
46. Patel M, Kaur S. Vortexing sonication: a method for liposome formulation and drug delivery applications. J Drug Deliv Sci Technol., 2023; 84: 104372.