WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 21, 1005-1014. Review Article ISSN 2277–7105

TRANSFEROSOMES: AN APPROACH TO IMPROVE DRUG ACTIVITY

Shafiya Samreen[1], Venu Madhav Katla[1]* and Somnath De[2]

[1]MPharmacy Student, Department of Pharmaceutics, St. Pauls College of Pharmacy, R.R District, Telangana, India- 501510.

[1*]Professor, Department of Pharmaceutics, St. Pauls College of Pharmacy, R.R District, Telangana, India- 501510.

[2]Professor, Department of Pharmacology, St. Pauls College of Pharmacy, R.R District, Telangana, India- 501510.

Article Received on
19 October 2023,

Revised on 09 Nov. 2023,
Accepted on 30 Nov. 2023

DOI: 10.20959/wjpr202321-30437

***Corresponding Author**
Venu Madhav Katla
Professor, Department of Pharmaceutics, St. Pauls College of Pharmacy, R.R District, Telangana, India- 501510.

ABSTRACT

Achieving a Successful therapeutic intervention can be challenging in numerous cases, Factors like First-pass metabolism in the liver, the onset Undesirable side effects, reluctance towards, Invasive medical procedures and insufficient Adherence to medical recommendations by the patient. all contribute to the complexity of the process. Consequently, extensive research and development efforts have been dedicated to addressing challenges from previous decades. A particularly encouraging solution involves the adoption of transdermal drug delivery systems, given their minimally invasive nature and the advantage of bypassing first-pass metabolism. In the 1990s, a novel carrier system known as transferosomes was introduced. Comprising phospholipids and an edge activator—a membrane-softening agent—these transferosomes exhibit an ultra-deformable property. Upon entering skin pores, transferosomes demonstrate the ability to modify the flexibility of their cell membranes, enabling Facilitate their passage through the skin pores naturally. This is also said to be self-optimizing deformability. Effortlessly traversing even, the narrowest pores, refine these lipid aggregates with inherent self-optimization and remarkable deformability have been widely employed in extensive preclinical testing. Furthermore, their utilization extends to Phase I and Phase II clinical

studies, demonstrating effectiveness In the transcutaneous administration of peptides and proteins, as well as in sustaining the release of desired therapeutic agents.

KEYWORDS: Transferosomes, ultra-deformable vesicles, first phase metabolism.

1. INTRODUCTION

The formulation has the capacity to improve the solubility of hydrophobic drugs, thereby augmenting their efficacy. Transferosomes represent a vesicular carrier system uniquely crafted to feature an inner Water-based compartment encased by A double layer of lipids, incorporating A stimulating agent at the borders. This design results in ultra-deformable vehicles with both Inherent optimizing and self-regulating abilities.[1,2] They are elastic in nature, Deforming and compressing into intact vesicles without any loss as they pass through the narrow pores of the skin.[3-4]

Comprising a Phospholipid element and a lone-chain surfactant functioning as a periphery activator, the liposomal vesicular system is structured.[5] Edge activators serve as agents causing membrane destabilization, enhancing the flexibility of vesicle membranes. When blended in the appropriate proportion with suitable lipids, they create an optimal mixture, endowing the vesicles with deformable and ultra-flexible properties. This enhancement in flexibility ultimately results in an improved permeability capability. Hence, transferosomes address the significant limitations of Penetrating structures significantly smaller than their own diameter, altering liposomes. The incorporation of edge activators in the formulation has led to improved performance.[6-7] The inclusion of edge activators in the formulation of transferosomes leads to enhancements in skin permeation, the extent of which depends on the types and concentrations of these edge activators.[8-13]

Table 1: Difference between Liposome, Transferosomes and Ethosomes.

Characters	Liposomes	Transferosomes	Ethosomes
Formulations	Lipids and cholesterol	Phospholipids along with edge activators	Phospholipids in combination with ethanol.
Characteristics	Minuscule vesicle	Ultra-flexible vesicle	flexible vesicles
Flexibility	Stiff	Highly deformable due to vesicle surfactant	Phospholipids in combination with ethanol.
Permeation mechanism	Dispersion	Vesicle deformation for enhanced penetration.	Phospholipids in combination with ethanol.
Extent of skin penetration	Minimal penetration	Readily penetrable	Phospholipids in combination with ethanol.
Route of	Ingestible, injectable,	Cutaneous &	Phospholipids in

administration	surface-applied, and skin-penetrating**.**	transcutaneous	combination with ethanol.
Marked products	Ambisome, Liposomal daunorubicin	Transferosomes	Phospholipids in combination with ethanol.

2. ADVANTAGES[32-33]

1.They are highly efficient against Protecting the encapsulated drug against metabolic degradation.

2.Improves high deformability of the drug formulations.

3.They act as carriers.

4. They find Utilization in both systemic and local drug administration.

5.They have a high ability of biodegradable and biocompatible drug preparation.

6.They avoid the metabolic degradation of drug molecules.

7.They provide easy scale up simple procedures.

8.They have improvised site specific releases of drug property.

9.They can not only be used for systemic but also Delivery to the skin's surface of drugs.

10. They function as reservoirs, gradually releasing their contents over time.

3. DISADVANTAGES[32-33]

1.These are expensive drug formulations.

2. Purity of natural phospholipid difficult to achieve.

3. Their chemical instability stems from a tendency toward oxidative degradation.

4.Commercialization on a large scale is difficult due to oxidative degradation of the product.

4. APPLICATIONS

- Delivery of antioxidants[30]
- Delivery of anti-cancer.[15]
- Delivery of corticosteroids.[31]
- Delivery of anti-inflammatory.[32]
- It shows potential for the regulated release of the administered drug and enhancing the stability of delicate drugs by incorporating phospholipids.[29-33]
- Actinic keratosis.
- Insulin administration
- Administering proteins and peptides.
- Administering interferon.

- NSAID Are associated with several gastrointestinal Adverse reactions. These challenges can be addressed through Delivery through the skin utilizing ultra-deformable methods vesicle.
- Non-invasive treatment of local aim through topical route tetracaine.

5. COMPOSITION OF TRANSFERSOMES

Transferosomes are generally composed of.

Amphipathic agent (65-85%): The most commonly used hydrophilic, are soy phosphatidylcholine, egg phosphatidyl, that form mixtures Comprising lipids that are forming Assembling vesicle components to form a lipid bilayer.[14, 15]

Surface/edge activators (10-25%): Commonly utilized edge activators include surfactants such as Sodium cholate, sodium deoxycholate, Tween agents, and Span compounds. which are bilayer softening compounds which improve flexibility and permeability of the preparation.[16-19]

Solvent (3-10%): Solvent such as alcohol or hydrating medium Either water or a phosphate solution-buffered saline solution. (PH 6.5-7).[20,21]

6. MECHANISM OF ACTION[24-25]

Transferosomes conquer the difficult problem of Penetration of the skin occurs by compressing through the intracellular pathways within the lipid bilayer. The perfect mechanism of action of delivering an active agent is not yet widely recognized by Two proposed modes of operation have been suggested.

Among which is follow.

1. Transferosomes function as carriers for drugs, maintaining their integrity upon penetration of the skin membrane. Which may be through sweat glands, associated glands.
2. Transferosomes function as enhancers of penetration without disturbing the intricately organized structure of intracellular lipid bilayer of the transmembrane of the skin. which may be associated with glands, horny layer or sweat gland.

Table 2: Ingredients used in Transferosomes.

Ingredient	Examples	Function
Lipid containing phosphorous.	Soy-derived phosphatidylcholine, egg phosphatidylcholine, and disteryl. Phosphatidylcholine	Generation of vesicles Component

Surface-active agent.	Sodium cholate, sodium deoxycholate compounds, Polysorbate 80, Sorbitan monooleate.	For offering adaptability
Alcohol	Ethanol, Methanol	In the capacity of a solvent
Colouring substance.	Rhodamine-123, Rhodamine-DHPE, Fluorescein-DHPE, and Nil Red 6 Carboxyl fluorescence.	Examining samples Utilizing Confocal Scanning Laser Microscopy (CSLM).
Agent for stabilizing pH.	Buffer solution with Phosphate-buffered saline with a pH of 6.5, 7% v/v ethanol, and tris buffer with a pH of 6.5.	In the capacity of Moisturizing solution

7. PREPARATION OF TRANSFEROSOMES[22-23]

There are several approaches for the reparation of transferosome. The most employed technique for the preparation of transferosome is as follows.

1. Thin layer hydration method / The rotary evaporation technique

Phospholipids and an edge activator are dissolved in an organic solvent mixture, typically consisting of chloroform and methanol in a suitable ratio, within a round-bottom flask. The lipophilic drug can be included in this stage. The organic solvent is eliminated through evaporation Under pressure reduction, employing a rotary vacuum evaporation system. Subsequently, the deposited thin film is hydrated utilizing appropriate buffer 9 (PH7.4) at corresponding temperature. The resulting vehicle is expanded at room temperature and subjected to sonication in both to obtain a small vesicle.

2. The Handshake Technique

This technique is Performed in a round-bottom flask that is set up under room temperature conditions. In this approach, an organic solvent, a lipophilic drug, and the edge activator constitute the components. introduced into the flask. The mixture is allowed to dissolve thoroughly until all excipients completely form a transparent and clear solution. Subsequently, the organic solvent is eliminated through evaporation. Simultaneously, the flask with a round bottom is partially submerged in a high-temperature water bath. typically, around 40 degrees Celsius or above. A slender lipid layer is generated along the interior surface area of round-bottom flask and left overnight to ensure The organic solvent is entirely evaporated, and the resulting film is hydrated using a buffer solution while gently agitation beyond the transition temperature of a phase. In this stage, the water-soluble medication is incorporated.

8. EVALUATION PARAMETERS[28-29]

1. Distribution of Vesicle Sizes and Zeta Potential

The dynamic light scattering apparatus (DLS) was utilized to Determine vesicle dimensions, size distribution, and zeta potential using the Malvern Zetasizer.

2. Vesicle Morphology

Dynamic light scattering (DLS) or proton correlation spectroscopy can be utilized for determining vesicle diameter. Transferosome vesicles can be visualized through techniques such as TEM (transmission electron microscopy) and Methods such as phase-contrast microscopy, among others, can be employed to evaluate the stability of the prepared vesicles by examining their size and structure The average size is measured using dynamic light scattering (DLS), while structural alterations are observed through transmission electron microscopy (TEM).

3. Entrapment Efficiency

The entrapment efficiency is expressed as a percentage of the total entrapment was determined by the used mini column centrifugation method. The formula for expressing entrapment efficiency is as follows.

Entrapment Efficiency is calculated as [{Amount Entrapment}/{Total Amount Added}] x 100.

4. Drug Content

Analysing drug content can be accomplished using instrumental analytical techniques, including a customized high-performance liquid chromatography (HPLC) method with computerized analysis designed for the analytical process. specifications of the pharmacopeial drug.

5. Turbidity Measurement

The nephelometer is utilized for quantifying the turbidity of the drug substance. in an aqueous solution.

6. Penetration Ability

The permeability of transferosomes can be evaluated using well-established fluorescence microscopy methods.

7. Degree of Deformability/Permeability Measurement

Deformability is a key study to be considered in an evaluation. This is performed Against pure water as a reference standard. The Formulation of transferosomes, is passes Transferosomes traversing a significant n0 known pore size through Various microporous filters with pore diameters ranging between 80 nanometers to 400 nanometres. are employed, Particle dimensions, subject to the characteristics of the transferosome suspension Particle dimensions and size distribution are recorded by using DLS.

8. Occlusion effect

The occlusion effect of the skin is deemed significant In terms of permeation of drugs tropical reparation. Occlusion effect the hydration forces that hinders the Water evaporation from the skin.

9. Charge density and surface charge

Surface charge and charge density assessment can be conducted using a Zeta sizer.

10. Physical Stability

The drug formulation was stored and sealed in glass ampoules. They are stored at the condition of 20+ -4c for months. Then the sample from each ampoule were analyzed for drug leakage determination. The calculation of the percentage of drug loss involved using the initial drug entrapment as the reference point at 100%.

9. CONCLUSION

There ultra deformable system holds great potential In the administration of a vast array of medications substance, Which include large molecule like peptide hormone And to transport drugs through biological permeability barriers, such as the skin. Transferosome can be passed through a tiny pore efficiently.

Transferosomes possess enormous advantages over either transdermal drug delivery system. By avoiding Permeation, The passage of the drug through the stratum corneum. which is the limitation it provides not only safety but also efficacy The reformulation. And The dispensing of the drug. can also be regulated based on specific requirements.

10. REFERENCES

1. 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. doi: 10.1080/20022727.2017.1325708. [PMC free.
2. Walve JR, Bakliwal SR, Rane BR, Pawar SP. Transferosomes: a surrogated carrier for transdermal drug delivery system.
3. Sivan Narayana P, Rani AP, Saikishore V, Venu Babu C, Sri Rekha V. Transferosomes: Ultra deformable vesicular carrier systems in transdermal drug delivery system. Research Journal of Pharmaceutical Dosage Forms and Technology, 2012 Sep 1; 4(5): 1.
4. Sachan R, Parashar T, Soniya SV, Singh G, Tyagi S, Patel C, Gupta A. Drug carrier transferosomes': A novel tool for transdermal drug delivery system. International Journal of Research and Development in Pharmacy and Life Sciences, 2013 Feb; 2(2): 309-16.
5. Bhasin B., Londhe V.Y. An overview of transfersomal drug delivery. Int. J. Pharm. Sci. Res, 2018; 9: 2175–2184. doi: 10.13040/IJPSR.0975-8232.9(6).2175-84.
6. Lei W, Yu C, Lin H, Zhou X. Development of tacrolimus-loaded transferosomes for deeper skin penetration enhancement and therapeutic effect improvement in vivo. Asian journal of pharmaceutical sciences, 2013 Dec 1; 8(6): 336-45.
7. Pandey A, Mittal A, Chauhan N, Alam S. Role of surfactants as penetration enhancer in transdermal drug delivery system. J Mol Pharm Org Process Res, 2014; 2(113): 2-7.
8. Duangjit S, Opanasopit P, Rojanarata T, Ngawhirunpat T. Characterization, and in vitro skin permeation of meloxicam-loaded liposomes versus transferosomes. Journal of drug delivery, 2011; 2011.
9. Aggarwal N, Goindi S. Preparation and evaluation of antifungal efficacy of griseofulvin loaded deformable membrane vesicles in optimized guinea pig model of Micros Porum Canis—Dermatophytosis. International journal of pharmaceutics, 2012 Nov 1; 437(1-2): 277-87.
10. Chen J, Lu WL, Gu W, Lu SS, Chen ZP, Cai BC. Skin permeation behavior of elastic liposomes: role of formulation ingredients. Expert opinion on drug delivery, 2013 Jun 1; 10(6): 845-56.
11. Duangjit S, Opanasopit P, Rojanarata T, Ngawhirunpat T. Effect of edge activator on characteristic and in vitro skin permeation of meloxicam loaded in elastic liposomes. Advanced Materials Research, 2011 Apr 20; 194: 537-40.
12. Jacob L, Anoop KR. A review on surfactants as edge activators in ultra deformable vesicles for enhanced skin delivery. Int J Pharm Bio Sci, 2013; 4(3): 337-44.

13. Kim B., Cho H.-E., Moon S.H., Ahn H.-J., Bae S., Cho H.-D., An S. Transdermal delivery system in cosmetics. Biomed. Dermatol, 2020; 4: 1–12. doi: 10.1186/s41702-019-0053-z.
14. Jiang T, Wang T, Li T, Ma Y, Shen S, He B, Mo R. Enhanced transdermal drug delivery by transfersome-embedded oligopeptide hydrogel for topical chemotherapy of melanoma. ACS nano, 2018 Sep 5; 12(10): 9693-701.
15. Iskandarsyah, Rahmi A.D., Pangesti D.M. Comparison of the characteristics of transfersomes and protransfersomes containing azelaic acid. J. Young-Pharm, 2018; 10: S11–S15. doi: 10.5530/jyp.2018.2s.3.
16. Jain AK, Kumar F. Transfersomes: Ultradeformable vesicles for transdermal drug delivery. Asian J. Biomater. Res, 2017; 3: 1-3.
17. Rajan R, Jose S, Mukund VB, Vasudevan DT. Transferosomes-A vesicular transdermal delivery system for enhanced drug permeation. Journal of advanced pharmaceutical Technology & Research, 2011 Jul 1; 2(3): 138-43.
18. Kotla NG, Chandrasekar B, Rooney P, Sivaraman G, Larrañaga A, Krishna KV, Pandit A, Rochev Y. Biomimetic lipid-based nanosystems for enhanced dermal delivery of drugs and bioactive agents. ACS Biomaterials Science & Engineering, 2017 Jul 10; 3(7): 1262-72.
19. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, Bentley MV, Simões S. Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes. International journal of nanomedicine, 2015 Sep 18: 5837-51.
20. Pawar AY. Transfersome: A novel technique which improves transdermal permeability. Asian Journal of Pharmaceutics (AJP), 2016 Dec 21; 10(04).
21. Garg V, Singh H, Bimbrawh S, Kumar Singh S, Gulati M, Vaidya Y, Kaur P. Ethosomes and transfersomes: Principles, perspectives and practices. Current drug delivery, 2017 Aug 1; 14(5): 613-33.
22. Modi CD, Bharadia PD. Transfersomes: new dominants for transdermal drug delivery. Am J Pharm Tech Res, 2012; 2(3): 71-91.
23. Kadu S.D.P. Transfersomes—A boon for transdermal delivery. *Indo Am. J. Pharm. Sci*, 2017; 4: 2908–2919. doi: 10.5281/ZENODO.892229.
24. Maurya SD, Agarwal S, Tilak VK, Dhakar RC, Singh A, Maurya G. Enhanced transdermal delivery of indinavir Sulfate via transferosomes. Int J Compr Pharm, 2010; 1: 1–7.

25. Sheo DM, Shwetha A, Ram CD, Ghanshyam M, Girish K, Sunil KP. Transferosomes - A novel vesicular carrier for enhanced Transdermal delivery of stavudine: Development, characterization and performance evaluation. J Sci Speculations Resea, 2010; 130–6.
26. Kumar R., Singh M., Bala R., Seth N., RanaA.c., "Transfersomes : A Novel Approach For Trans Dermal Drug Delivery" International Research Journal Of Pharmacy, 2012; 3(1).
27. Patel SN, Patel N, Patel K.R., Patel N.M. "A Vesicular Transdermal Delivery System For enhance Drug Permeation-Ethosomes and Transferosomes" International Pharmaceutical Sciencia, 2012; 2(2).
28. Celtic Pharma Acquires Stake In Idea AG "21.7% Shareholding Purchased in Europe‟s leading targeted therapeutics Company IDEA prepares to Expand its late stage Clinical development programmes," Hamiltion, Bermuda And Munich, Germany: September 28, 2005.
29. Priyanka R., Shipra D., "Transferosomes: A Novel Carrier For Transdermal DrugDelivery System" International Journal Of pharmacy & Technology, April-2012; 4(1): 1854-1865.
30. Avadhani KS, Manikkath J, Tiwari M, Chandrasekhar M, Godavarthi A, Vidya SM, Hariharapura RC, Kalthur G, Udupa N, Mutalik S. Skin delivery of epigallocatechin-3-gallate (EGCG) and hyaluronic acid loaded nano-transfersomes for antioxidant and anti-aging effects in UV radiation induced skin damage. Drug delivery, 2017 Jan 1; 24(1): 61-74.
31. Cevc G., Blume G. Biological activity and characteristics of triamcinolone-acetonide formulated with the self-regulating drug carriers, Transfersomes® *Biochim. et Biophys. Acta (BBA) Biomembr,* 2003; 1614: 156–164. doi: 10.1016/S0005-2736(03)00172-X.
32. El Zaafarany G.M., Awad G.A.S., Holayel S.M., Mortada N. Role of edge activators and surface charge in developing ultradeformable vesicles with enhanced skin delivery. *Int. J. Pharm,* 2010; 397: 164–172. doi: 10.1016/j.ijpharm.2010.06.034.
33. Verma D.D., Verma S., Blume G., Fahr A. "Particle Size of liposomes influences dermal Delivery of substances into skin" International Journal of Pharmaceutical, 2003; 258: 141-151.