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Transferosome Technology in Advanced Drug Delivery and Translational Research

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ABSTRACT:
Vesicular drug delivery system has been considered as a feasible system to counteract the shortcomings of the traditional dosage forms especially low bioavailability, low penetration to tissues and systemic side effects. Out of these systems, the transferosomes-ultra deformable lipid vesicles, which are composed of phospholipids and edge activators have attracted a lot of interest because of their superior elasticity and capability to cross biological barriers, and in particular, the stratum corneum. Their peculiar deformability makes them effective to transport both lipophilic and hydrophilic drugs through small intercellular channels, leading to increased drug penetration, targeted delivery and higher therapeutic effect. Transferosomes have a therapeutic potential in a variety of applications, such as dermal and transdermal delivery, delivery to macromolecules and vaccines, oncology and localized therapy and so on, which are discussed in a systematic fashion. The latest technological developments in surface modification, hybrid vesicular systems and combination with new technologies like microneedles, 3D printing and artificial intelligence-aided formulation optimization are also mentioned. Although they have shown good results at the preclinical phase, there are several issues like stability and scalability, reproducibility, regulatory uncertainty and absence of uniform evaluation guidelines that limit the clinical translation of transferosomes. In general, the article highlights the promise of transferosomes as the next generation vesicular carriers but still mentions that special efforts are needed to commercialize and implement transferosomes in therapeutical practices.

KEYWORDS: Transdermal drug delivery, Transferosomes, Vesicular drug delivery, Nanocarriers, Controlled drug release.

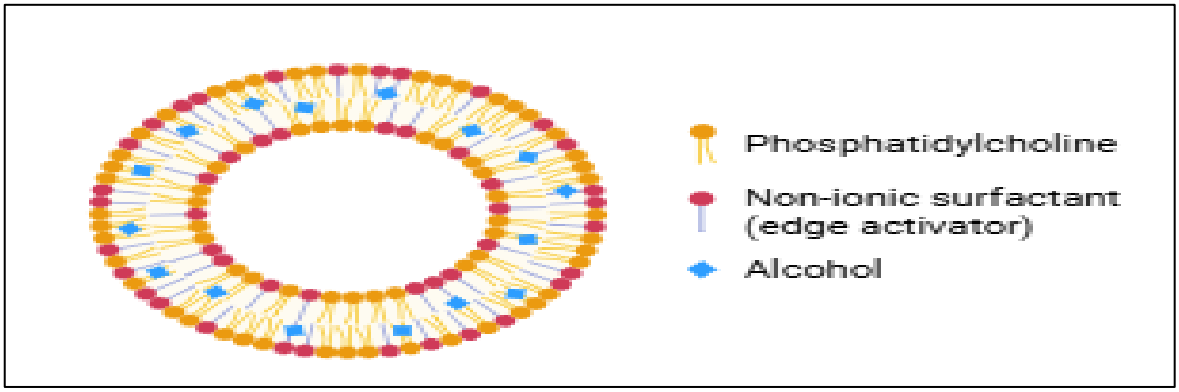

FIG 1: STRUCTURE OF TRANSFEROSOME

I. INTRODUCTION

Transferosomes, also known as ultra-deformable vesicles, are applied to skin and contain an aqueous layer and a lipid bilayer system enriched with phospholipid and an edge activator. The lipophilicity determines whether the active ingredient is contained encapsulated in the core or embedded in the bilayer. When applied topically, transferosomes have a greater ability to spread deeper parts of the skin than liposomes. [1]

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The construction of a transferosome is given in Fig 1. These are a sophisticated collective that is incredibly resilient to stress. This allows transferosomes to function as a medicine carrier for

non-invasive targeted medicine administration and therapeutic compound prolonged release after effectively passing through a variety of transportation barriers. [2,3]

Because transferosomes may deliver more active chemicals to the membrane's deeper layers, they are considered promising drug delivery vehicles for transdermal therapy. Transferosomes reach the SC either intracellularly or transcellularly by generating an "osmotic gradient". [4,5] This is beneficial for delivering several medications and phytochemical simultaneously delivers the agent into the systemic circulation.[6]

Overview and Rationale of Vesicular Drug Delivery Systems

Out of the many transdermal drug delivery systems (TDDS), vesicular systems have over the years proved to be a key and effective system of drug delivery in a sustained manner. They facilitate systemic availability, especially of ill-soluble drugs and may also lower the cost of treatment. The vesicular nanocarriers, which include liposomes, niosomes and transferosomes have been associated with certain benefits that have been enumerated as the ability to entrap both hydrophilic and lipophilic drugs, elimination of dose-related side effects, protracted therapeutic effect, and protracted systemic circulation. One of the roles of these systems is to regulate drug degradation and loss and a sufficient amount of drugs to the target site. Nevertheless, in spite of the improvement in the traditional and vesicular drug delivery systems,

there are still certain challenges including low bioavailability, minimal penetration through the biological barriers, systemic side effects, and low patient compliance. The use of traditional vesicular carriers, such as liposomes and niosomes, cannot be applied to transdermal and targeted delivery because of their rigid bilayer structure and poor skin penetration. In a bid to beat these shortcomings, ultradeformable vesicles like transferosomes have come as a viable solution. Transferosomes are made up of phospholipids and edge activators, which results in their high flexibility and deformability allowing them to diffuse through small intercellular spaces of the stratum corneum and other biological barriers facilitating increased tissue penetration and better therapeutic outcomes. [7,8]

II. COMPOSITION OF TRANSFEROSOMES

Although Transferosomes (TFS) has an enhanced stability profile, this deformable nanosystem is mostly made up of many components. Some are used in the synthesis of TFS but others are crucial for maintaining its structural integrity such as phospholipid and edge activator (described in detail below) [9]

Surface active agents act as edge activators

Surface active agents, sometimes referred to as edge activators, give TFS deformability and allow penetration through stratum corneum pores much smaller then their own size. [10] Monomers with both a edge activators are composed of both hydrophilic and hydrophobic region examples of commonly used Tween 80, Tween 20, Span 60 and Span 80 Sodium edge activators cholate and Sodium deoxycholate were frequently utilized. The main factors used to choose an edge activator are its value of the hydrophilic/lipophilic balance (HLB), elasticity and entrapment efficiency. Tween 80 provides vesicles with more flexibility than span 80, according to reports in the literature. [11] Tween 80, Span 20 edge activator were used to make TFS in a different investigation. However, the findings demonstrated that Tween 80 offered greater flexibility than sodium cholate and Span 80. [12]

Solvents

The type, attention and selection of detergent used in the medication of transferosomes have a significant impact on their expression and characteristics. multitudinous studies indicate that the stability, size and release profile of liposomes and transferosomes can be affected by the solvent selection. [13] likewise, it has been proved that polar organic solvents

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analogous as glycerol, formamide or ethylene glycol can produce nanoscale vesicles, indicating the effectiveness of soap systems in producing lipid-predicated structures with unusual characteristics. For factual use in drug delivery systems, these factors bear a thorough understanding of how solvents affect transferosomes, as well as the significance of solvent selection for transdermal system advancements. [14,15]

Buffering agent

Softening agents must be incorporated into the expression of transferosomes, which are lipid-grounded vesicles employed in drug delivery. Monosodium phosphate, saline sodium citrate, tromethamine, 2- (N-morpholino) ethane sulfonic acid (MES), 2-(4-(2-hydroxyethyl)-1-piperazinyl) ethane sulfonic acid (HEPES) and other substances have been shown to disrupt lipid bilayers and impact the hydration of interfaces. Additionally, it may be simpler to remove buffering agents from the interface when utilizing them in conjunction with salt. To optimize transferosome features for usage in drug delivery systems, buffering agent and lipid membrane behaviour must be taken into account. [16]

Phospholipid

A key constituent in forming the lipid bilayer of Transferosomes: In water-based solvents, phospholipids self-assemble into lipid bilayer forming vesicles because they are amphipathic (containing both hydrophilic and hydrophobic sections. [17] Phospholipids, which are mainly composed of phosphatidylcholine, are found in both hydrogenated and unhydrogenated forms. [18] Table:1 provides a list of diverse ingredients utilized in preparation of Transferosomes. While water soluble drugs are entangled within the vesicular core oriented towards the head section, hydrophobic drugs are caught within the tail region of the phospholipid bilayer structure. [19]

TABLE 1: DIVERSE INGREDIENTS UTILIZED IN PREPARATION OF TRANSFEROSOMES

COMPONENT CATEGORY	MATERIALS USED	PURPOSE
Phospholipids	Soya phosphatidylcholine Egg phosphatidylcholine Dipalmitoyl phosphatidylcholine Distearoyl phosphatidylcholine	Vesicle formation substances
Edge Activators	Sodium cholate Sodium deoxycholate Tween 80, Span 80	Promoting bilayer deformability
Alcohol	Ethanol, Methanol Isopropyl alcohol	Solvent agent
Neutralizing Agent	Saline phosphate buffer (pH 6.4)	Used as hydration medium
Dye	Rhodamine 123, Rhodamine DHPE	For confocal scanning laser microscopy

III. DESIGN PRINCIPLE AND FORMULATION STRATEGIES

Contact with the skin barrier

Stratum corneum, the outermost skin layer, function as a major barrier limiting the penetration of various molecules. It is composed of dead keratinized corneocytes organized with lamellar lipid matrix forming a characteristic brick and mortar structure. Penetration of transferosomes through this barrier may occur via a numerous number of mechanisms: hydration and lipid fluidization. When transferosomes are placed on the skin, the SC lipids are disrupted and liquid as a result of the interaction of surfactants in the vesicle. This brief destabilization of the SC barrier will decrease resistance to transferosomes penetration [20]. As an illustration, phosphatidylcholine sodium cholate transferosomes will raise lipid fluidity in the SC resulting into over fivefold greater penetration of diclofenac than using

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traditional liposomes. Additionally, penetration induced by deformability (squeezing process) refers to the situation where transferosomes are highly elastic to permit deformability to compress and, as a result of the trans-epidermal hydration gradient enables vesicles to deform and pass through microscopic intercellular pathways between corneocytes. For instance, due to the squeezing process and the osmotic and moisture gradient effect, transferosomes loaded with ketotifen fumarate had three times as much medicine in the epidermis and dermis as liposomes. The vesicles are drawn into a more hydrated area by the natural osmotic gradient across the skin. [21] Transferosomes are highly hydrophilic and flexible and thus are able to penetrate deeper skin layers. It is a self-driving process, that does not use external energy advertising. Take the case of insulin-loaded transferosomes, which were capable of permeating intact rat skin and exhibit the capability of resulting in a reduction in blood glucose levels, thereby confirming transdermal delivery via osmotic gradient driven mechanisms. Vesicle fusion and lipid exchange is another mechanism in this instance where upon transferosomes have reached the viable epidermis, the transferosomes either fuse with the cells or lipids exchange, hence the release of the drug delivery directly into epidermal cells or through intercellular lipid channels. To illustrate this point, the curcumin-loaded transferosomes were able to fuse easily with intracellular membranes of the keratinocytes and the drug was accumulated in more by the skin than was the case with the fusibility of a liposomal preparation. [22]

Squeezing through skin pores

Transferosomal penetration via the skin is primarily governed by natural hydration (osmotic) gradient across the stratum corneum. Upon application of a lipid-based transferosomal formulation to non-occluded skin, loss of water from the skin surface creates a transdermal water gradient that drives vesicle movement toward deeper, more hydrated skin layers.[23] Owing to their ultra-deformable phospholipid bilayer enriched with edge activators, transferosomes exhibit exceptional elasticity, enabling them to retain their aqueous content and deform without rupture while squeezing through intercellular pores significantly smaller than their own diameter.[24] Although this process differs from classical forward osmosis, it involves a hydration-driven transport mechanism in which intact vesicles migrate through the stratum corneum via trans epidermal pathways. During this process, transferosomes transiently deform to traverse narrow constrictions and subsequently rehydrate upon reaching the viable epidermis, allowing efficient delivery of encapsulated drugs.[25,26]This unique interaction with the skin enables transferosomes to penetrate more effectively than conventional liposomes and facilitates the transdermal transport of a wide range of therapeutic agents, including small molecules, hydrophilic drugs, peptides, proteins and nucleic acids.[27] The penetration pathway of transferosomes is explained in Fig.2

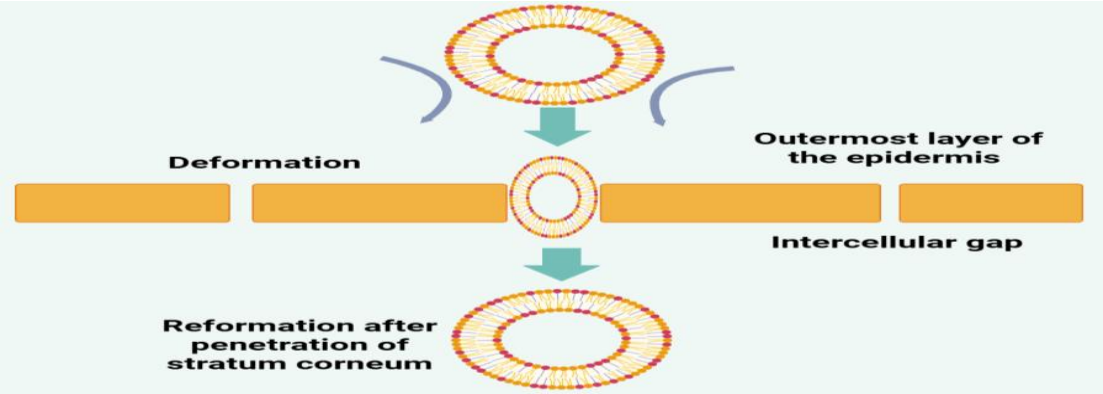

FIG 2: PENETRATION PATHWAY OF TRANSFEROSOMES

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IV. STRATEGIES OF FORMULATION OF TRANSFEROSOMES

Different methods have been invented in the preparation of transferosomes with the main difference being on the mode of forming lipid film and the creation of vesicles. The techniques that are commonly used are Thin film Hydration method, reverse phase evaporation, ethanol injection and vortex sonication, which are further explained.

Thin film Hydration

Under this technique the phospholipids, edge activator and the drug are dissolved in a volatile organic solvent. Diluted under low pressure places the solvent into a thin lipid film and then the water phase is added to form multilamellar vesicles. Sonication or extrusion is used to further reduce the size of resulting vesicles to get homogenous transferosomes.

Reverse Phase Evaporation Method

The entire mixture of phospholipids, surfactant, and drug are dissolved in an organic solvent and then an aqueous phase is introduced creating a water-in-oil emulsion. When the organic solvent is removed under reduced pressure, the system enters into vesicles. This dispersion is further subjected to processing to get homogeneous transferosomes of smaller particle size.[28]

Ethanol Injection Method

In this method, the lipids and the drug can be dissolved in ethanol and injected into a preheated aqueous phase with constant stirring. The Spontaneous vesicle formation has been observed as it is diffused in the aqueous medium in the presence of ethanol. Any remaining solvent is extracted off and the vesicles are further refined in terms of size.

Vortex Sonication Method

This technique requires the dissolution of components of formulations and hydration by the use of an aqueous phase to create vesicles. The vortex mixing and sonication of the dispersion are used to promote the formation of vesicles and downsizing of the particles to produce homogeneous transferosomal systems.[29]

V. QUALITY BY DESIGN AND OPTIMIZATION METHODS

Design of Experiments (DoE) and Quality by Design (QbD) in Transferosome Development

Quality by Design (QbD) is a contemporary, science- and risk-based systematic method that guarantees product quality by comprehending the variables of formulation, and process during the initial stages of the product development through the manufacturing process. It emphasizes the need to specify the desired product performance and managing sources of variability instead of depending on the testing of the end product alone.[30]

Critical Process Parameters (CPPs), Critical Material Attributes (CMAs) and Critical Quality Attributes (CQAs)

CQAs are the product features of transferosomal product that should be regulated to deliver efficacy, safety and performance (e.g., vesicle size, deformability index, entrapment efficiency, drug release profile, stability). CMAs are the properties of input material including the type/concentration of lipids, the type of edge activator, physical and chemical properties of drugs that greatly affect CQAs. CPPs are process variables, i.e. hydration time, sonication energy, temperature and mixing speed that influence CQAs during the manufacturing process.[31]

Design Space Establishment

Design space is the area in the CMAs and CPPs which is in the multidimensional space and CQAs fall within acceptable preset limits. The definition of this space based on systematic experimental designs enables manufacturers to work and flex within limits without having to be re-regulated whenever a small change is made in the space. They are built up in mathematical models that establish the effect of CMAs and CPPs on the CQAs by DoE (factorial, Box-Behnken, response surface methodology) to enable optimization and prediction of product performance. [32]

Risk Assessment Tools

Early risk assessment can be used to provide priority to the factors of influence and concentrate the energy of experiments effectively. Examples are: Ishikawa

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(fishbone) diagrams in order to visualize cause/outcome relationships, Failure Mode and Effect Analysis (FMEA) in order to scale severity and probability of risks, Risk matrices to classify high/medium/low risk variables that affect CQAs.

VI. CHARACTERIZATION AND EVALUATION OF TRANSFEROSOMES

Vesicular size distribution, surface charge (zeta potential) and morphology

Determining vesicular size is essential for transferosome production, lot-to-lot comparison, scale-up procedures. Changes in vesicle size during storage have an influence on formulation physical stability. Transferosomes of larger sizes are drawn associated via van der waals contacts, while vesicles slighter than 40 nm are more probable to progress via membrane fusion mechanisms due to their elevated curvature. Vesicle size is measured using methods such as Dynamic Light Scattering (DLS) and Photon Correlation Spectroscopy (PCS). Electrophoretic mobility can be used to determine zeta potential, which affects stability. Phase contrast microscopy and TEM are utilized to identify transferosome nanovesicles.[33]

In vitro drug release

This characterization obtained for diffusion rate. It takes time to achieve consistent accompaniment dispersion, permeation flow and enlightenment in samples that are introverted at various intervals. The quantity of drug freed is then approximated circumlocutory from the degree of drug implication at zero times the initial quantity (100% implicated and 0% freed). Several analytical techniques such as UV, HPLC and HPTLC are used for apprehension.[34]

Stability Studies

The transferosomes stability the released drug quantity is subsequently measured circumlocutory from the quantity of medication implicated at zero times the starting amount (100% implicated and 0% liberated). Several analytical techniques, including UV, HPLC, and HPTLC are used for apprehension. The % age drug loss is computed by considering the original 100% entrapment. [35,36]

Entrapment Efficiency

It is the quantity of medication trapped in the formulation. Using a variety of methods, including mini-column centrifugation, the unentrapped medication is separated from the vesicles to calculate the EE. The %EE can be found in this procedure using either direct or indirect approaches. The direct system would involve draining the supernatant after ultracentrifugation and also employing an applicable detergent that can lyse the deposition to rupture the laid vesicles. The pollutants can also be excluded by lacing and filtering the attendant result with a hype sludge (0.22 – 0.45 µm). Depending on the logical fashion used for the active pharmaceutical component (API), the medicine volume can be caught on using spectrophotometry or (HPLC) that has been modified. [37,38]

Degree of deformability

Degree of deformability this parameter is vital since it influences the transferosomal expression's penetration. Pure water is used as the standard in this disquisition. Several microporous pollutants with known severance compasses ranging from 50 to 400 nm are utilized to filter the medication. DLS measures are used to record the extent distribution and flyspeck size following each pass.[39]

$$D=J(rv/rp)$$

where J is the quantity of suspension extruded every five minutes, D is the degree of deformability, rv is vesicle size, rp is the barrier's pore size. [40,41]

In-vivo studies

The medication molecule affects in-vivo research carried out in an appropriate animal model. Before any animal research can start, the institutional animal ethics committee is required to give its approval. Research comparing the optimized transferosomal formulation with the commercial to further understand, regular formulations and a placebo could be planned. Depending on the kind of medication and the treatment plan, treatment will be administered for a specific amount of time. 24 hours after the final medication dose, the animals will be killed. Skin

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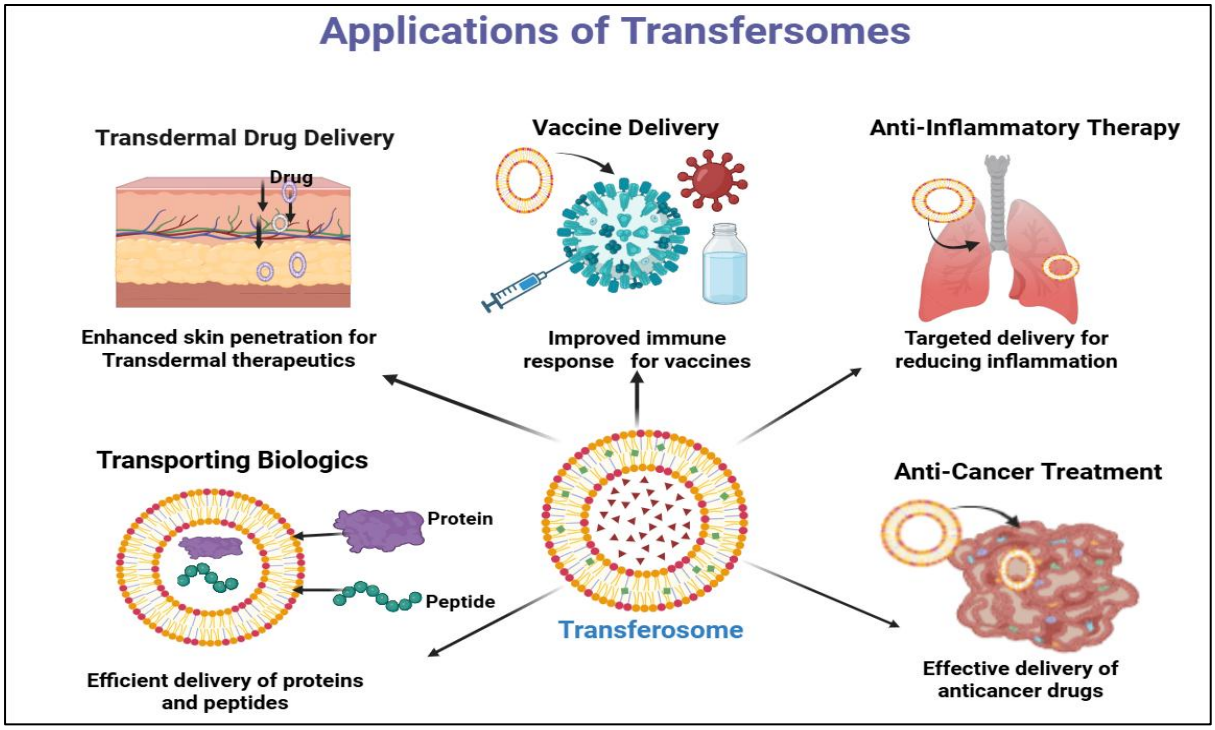
fragments will be removed and treated further before being examined under an electron microscope. To comprehend the drug's action, several additional features will be investigated.[42,43]

VII. APPLICATION OF TRANSFEROSOMES [44-48]

The transferosomes are currently in use in sophisticated drug delivery because of their high deformability and skin penetration. These are mainly applied in transdermal drug delivery to enhance bioavailability of water and lipid-soluble drugs. Also, they display promise in vaccine delivery, in improving immunogenic response, and in anti-inflammatory therapy, in increasing drug penetration and efficacy. The biologics such as proteins and peptides can also be delivered using transferosomes, providing an alternative non-invasive alternative to injections. Moreover, they allow targeted drug delivery and promise to be useful in anticancer therapy, especially in the local treatment.



APPLICATIONS OF TRANSFEROSOMES IN DRUG DELIVERY INCLUDING TRANSDERMAL DRUG DELIVERY, VACCINE DELIVERY, ANTI-INFLAMMATORY THERAPY, DELIVERY OF BIOLOGICS AND TARGETED ANTICANCER THERAPY

VIII. ADVANCED AND HYBRID TRANSFEROSOMAL SYSTEMS

Stimuli-Responsive Transferosomal Systems

Although literature more explicitly describing stimuli-responsive transferosomes is more recent, the idea of incorporating stimuli-responsive capabilities into deformable vesicles such as transferosomes is considered a direction in the future to advanced transferosomal systems: Transferosomes have been considered as belonging to the general category of stimuli-responsive nanocarrier where vesicles may be modified with physicochemical changes in response to pH, temperature, enzymes, redox or external signals in order to perform controlled release - a concept that targeted and on-demand delivery is addressed According to recent reviews, future studies show stimuli responsive transferosomal systems as well as integration of the microneedle and specific

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delivery to circumvent skin barriers and reach the local target release.[49,50]

Surface-Modified & Ligand-Targeted Transferosomal Systems

The most common approaches to nanocarrier studies are surface modification and ligand functionalization, which are aimed at ensuring targeted delivery. Although in most cases, the target is liposomes or nanoparticles, similar principles are being used to modify transferosomes: Ligand targeting (e.g. folate, antibodies, peptides) has a long history in vesicular nanocarriers to achieve specificity and the same design principles can be applied to transferosomal modification to target receptors over-expressed in disease tissues. Hyaluronan-modified transferosomes have been established in order to enhance targeting and delivery efficiency when incorporated into hydrogels. [51,52]

Transferosomes Loaded Gels, Films & Microneedle Combinations

Transferosomes Loaded Gels & Films: Transferosomal gels or polymeric films are used with hybrids to increase retention, comfort of application and controlled release: Transferosomal gels are extensively discussed to be the advanced vesicular system of topical/transdermal delivery because of the enhanced skin permeation and retention of drugs. Transferosomes/transethosomal gels are compounds of phytochemicals with gels and ethosomal properties that promote penetration of phytochemicals into the dermis. Bigel hybrid systems combine transferosomes and bigel matrices in order to combine ultra-deformable vesicle penetration and controlled gel release. [53]

Transferosome-Loaded Microneedle Systems: Microneedles (MNs) penetrate the stratum corneum by physical force to facilitate deeper delivery of ultra-deformable vesicles: Transferosome-loaded microneedle array patches are optimized systematically to facilitate enhanced topical delivery of methotrexate with sustained release and reduced systemic exposure, an advanced hybrid platform. [54]

Nano Hybrid Systems (Transferosome + Nanoparticles / Other Carriers)

Hybrid systems that combine transferosomes with other nanoscale materials are aimed at incorporating multiple functionalities e.g. controlled release, targeting, imaging -although specifically called transferosome-nanoparticle hybrids are still more of a conceptual idea than an area of deep exploration in open literature: Strategies of vesicle hybridization with other nanoparticle systems (e.g. magnetic, polymeric) to enable stimuli-responsive release and theranostic functionality Surface modification and entrapment within a hydrogel matrix or polysaccharide.[55,56]

IX. LIMITATIONS AND CHALLENGES

Limitations

Transferosomes face certain limitations that restrict their widespread use. The high cost of formulation, mainly due to the requirement of pure natural phospholipids, makes them expensive for large-scale applications. [57,58] They are also chemically unstable and prone to oxidative degradation, although this can be minimized by removing dissolved gases and avoiding inert gases in the medium. Additionally, the cost of lipid excipients significantly affects overall production expenses, even though phosphatidylcholine is commonly used as a relatively economical option. [59,60]

Challenges

Stability problems

One significant restriction on the use of transferosomes is their stability. Transferosomes made of phospholipids have stability issues because they might fuse and agglomerate over time, leaking the therapeutic medication and reducing its pharmacologic activity. It has also been demonstrated that phospholipids, especially unsaturated phospholipids, oxidatively deteriorate, which may contribute to vesicles unreliability. The product's shelf life, regulatory approval and commercialization for therapeutic use will all be restricted by stability issues. To address these problems, a number of strategies could be investigated for stabilizing transferosomes, such as lyophilization with

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cryoprotectants (such as sucrose or trehalose), adding antioxidants, or creating a polymer–lipid hybrid system (which should lessen both oxidative degradation and fusion-related instability). In the end, there should be a way to strike a balance between long-term stability and obtaining the required bilayer deformability can be maintained by appropriate selection of lipid composition and controlled storage conditions. [61]

Formulation complexity

To ensure drug delivery and vesicle flexibility, transferosomal formulations must be optimized in terms of surfactant (edge activator) type and concentration. Vesicle instability, early drug release, and skin irritation can result from higher surfactant concentrations. [62] Many factors, including vesicle size, elasticity, deformation and entrapment efficiency, must be optimized in formulations. Formulation parameters can be systematically optimized by using Quality by Design (QbD) and Designing for Experiments (DoE). Hybrid polymer-lipid surfactants and gentler, biocompatible surfactants can stabilize formulations and reduce the possibility of formulation irritation. [63,64]

Variability in skin barrier

The effectiveness of transdermal distribution via transferosomes depends on the patient's age, skin condition, and level of hydration. [65,66] Young, hydrated skin allows for higher vesicle penetration, but older or damaged skin may reduce effective absorption. Modifying the viscosity of the formulation, utilizing occlusive dressing or combining transferosomes with microneedles and iontophoresis are examples of tailored strategies that address variations in skin features. Topical formulations continue to be helpful in a variety of patient populations, according to ex vivo studies conducted on human skin models. [67]

Safety and tolerability concerns

Although edge activators (such as sodium cholate & Tween 80) are essential for the vesicle bilayer flexibility, they can irritate or trigger allergic reactions that show up as swelling, erythema, pruritus and in rare cases respiratory distress.[68,69] Edge activators have the potential to impair cellular health and the integrity of cell membranes at high doses.[70-72] By choosing biocompatible surfactants, titrating edge activators to the lowest effective dose and conducting preclinical safety studies, these concerns can be minimized. Encapsulating surfactants or creating a prodrug can help reduce local irritation even further. A prodrug or an encapsulating strategy can be used to provide vesicle function while reducing irritating effects.

Limitations in encapsulation efficiency

Transferosomes work well for hydrophobic and amphipathic medicines, but their limited affinity for the lipid phase makes it more challenging to transfer bigger hydrophilic macromolecules like proteins and peptides, which frequently results in low and unpredictable drug loading.[73,74] Ionic complexation, covalent conjugation to lipid anchors, the utilization of polymer stabilized core systems in conjugation with reverse phase evaporation are some methods that can improve encapsulation efficiency. While preserving vesicle deformability and structural integrity, the suggested encapsulation techniques also increase therapeutic reliability.

X. CLINICAL TRANSLATION AND COMMERCIALIZATION STATUS

Transferosomes have provided strong preclinical efficacy in increasing transdermal delivery of small molecules, peptides and proteins by surmounting the stratum corneum using their ultra-deformable architecture. The studies involving animal models and ex vivo human skin samples all demonstrate increased permeation, increased bioavailability, decreased dosing frequency and reduced systemic toxicity than more traditional topical formulations. Although these encouraging results were achieved, there has been a sluggish advancement in clinical translation with few formulations going beyond preclinical human trials mostly because of the complexity of formulations, stability and regulatory unpredictability. However, there is clinical evidence-of-concept Diractin had been approved regulatory wise as a ketoprofen transferosomal gel, which is used to manage musculoskeletal pain, and this supports the commercial viability of transferosome-

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Volume 11, Issue 3, May-June2026, pp:2176-2192 www.ijprajournal.com ISSN:2456-4494

based products. Other transferosomes surrogacies have been moving through preclinical development stages, such as Transfersulin 02 02 (insulin transferosomes) and corticosteroid-containing transferosomal formulations, but without going fully commercialized, indicating the continuing trans-laboratory to trans-market chasm. [75]

Manufacturing Scalability Challenges

The transferosomes cannot yet be mass produced due to the sensitivity of the process and the batch to batch variability of vesicle size and elasticity besides the issues of aggregation and leakage of the drug. Conventional ways of preparation (thin-film hydration, sonication, extrusion) are hard to make industrialized keeping in mind the essential product features. Furthermore, the price of phospholipids of drug grade is extremely high and quality control is very tough and hence the production cost is very expensive and this limits business viability**.** [76]

Intellectual Property Landscape

Transferosomes intellectual property (IP) is operational and disjointed with patents on vesicle composition, edge activator selection, surface modification, and manufacturing process. Early foundational patents belonged to industrial developers, but newer applications are on hybrid systems (e.g. transferosomes with microneedles or hydrogels). Freedom-to-operate is also a major factor to consider with commercialization particularly as newer formulations are based on the current vesicular technologies. [77]

VARIABLE	TRANSFEROSOMES	LIPOSOMES	ETHOSOMES	NIOSOMES
Composition	Phospholipids + edge activators	Phospholipid bilayer ± cholesterol	Phospholipids + high ethanol	Non-ionic surfactants + cholesterol
Deformability	Very high (ultradeformable)	Low (rigid)	Moderate	Moderate
Skin penetration	Excellent; penetrates intact skin	Limited	Good (ethanol-enhanced)	Moderate
Drug loading	Hydrophilic & lipophilic drugs	Hydrophilic and lipophilic drugs	Preferably lipophilic drugs	Hydrophilic & lipophilic drugs
Stability	Moderate	High	Lower (ethanol volatility)	High
Skin irritation	Low–moderate (edge activator dependent)	Low	Possible irritation	Low

TABLE 2: COMPARISON OF TRANSFEROSOMES WITH OTHER VESICULAR AND NANOCARRIER SYSTEMS

XI. EXISTING TRENDS AND FUTURE PROJECTIONS

Artificial Intelligence-based and Person-Centric Progress in Transferosomal Drug Delivery

Formulation design and individualized transdermal therapy with the help of AI are transforming transferosomal drug delivery by allowing more sophisticated, patient-specific methods. Artificial intelligence (AI) is enabling the data-driven and predictive formulation design, optimizing key formulation variables, and decreasing the workload of experimental processes using machine learning models and in silico screening and digital twin models. Such inventions can result in next generation transferosomal systems of autonomous, AI-managed formulation labs. At the same time, the area of personalized transdermal therapy is redefining the delivery of drugs, whereby the formulations are based on the skin characteristics, genetic makeup and the disease state in an individual. Combining nanovesicles, microneedles, biosensors, and AI-

based analytics enables the ability to control the drug dosage and monitor the drug delivery in real time. A combination of all these changes brings out a future of highly efficient, customized and patient-centric transferosomal therapies. [78,79]

Smart and stimuli-responsive vesicles

It is a significant progress in the vesicular drug delivery because it allows a high level of control over the drug release in response to internal and external stimuli. Due to their ultra-deformability and dynamic membrane behaviour, transferosomes are especially easily adapted to work in smart vesicular platforms. Such systems have spatiotemporal regulation, multimodality and directed therapy, which makes them potentially promising vectors of advanced therapy of chronic diseases, cancer, wound healing and inflammatory diseases. [80]

Regulatory harmonization strategy

To ensure faster global clinical translation of advanced nanovesicular and transdermal drug delivery systems, it is necessary. Regional barriers can be brought down by using unified standards of characterization, risk-based assessment, QbD frameworks and adaptive regulatory pathways and enhances the efficiency of approvals. These well-balanced approaches will invest the effective commercialization of transferosomes, intelligent vesicles, AI-driven formulations and wearable drug delivery systems throughout the world.[81]

XII. CONCLUSION

The novel use of transferosomes in vesicular drug delivery is an important development due to their distinctive ultra-deformable architecture and the possibility to deliver therapeutic agents through adverse biological environments. The latter, along with their capacity to entrap hydrophilic and lipophilic molecules and their capacity to enter cells with ease and deposit drugs in specific locations, makes transferosomes multi-purpose vehicles in the delivery of therapeutic, dermal and transdermal therapeutic agents. The increasing preclinical data indicates that they are better than the traditional vesicular systems including liposomes, ethosomes and niosomes with regard to deformability and delivery capabilities. The design principles, formulation strategies, mechanistic insights and various therapeutic uses of transferosomes have been critically reviewed in this review and novel innovative applications that have increased their functional applications highlighted. The translational capabilities of transferosomal systems have also been enhanced by recent developments in surface engineering, hybrid vesicular systems and connection to new technologies of microneedle delivery, 3D printing and artificial intelligence. In spite of these positive trends, the clinical and commercial application of transferosomes is still limited to the effects of physicochemical stability, mass scale production, batch to batch reproducible, uncertainty in regulation and lack of standardized tests. These limitations will be overcome by strong formulation optimization, scalable manufacturing, harmonization of regulations and properly designed clinical trials to be essential in making their therapeutic implementation successful. In general, transferosomes have significant potential as a new generation of vesicles carriers. Their potential should be unlocked by further interdisciplinary research and closer translational studies and they should be moved out of the experimental platforms and into clinically viable drug delivery systems.

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