

BEYOND THE BARRIER: A COMPREHENSIVE REVIEW OF TRANSFEROSOMES AS  
THE NEXT GENERATION OF ULTRA-DEFORMABLE CARRIERSRakesh R<sup>1\*</sup>, Deekshitha<sup>2</sup><sup>1</sup>PG Scholar, Srinivas College of Pharmacy, Mangalore, Karnataka, India.<sup>2</sup>Associate Professor, Department of Industrial Pharmacy, Srinivas College of Pharmacy, Mangalore, Karnataka, India.**\*Corresponding Author: Rakesh R**

PG Scholar, Srinivas College of Pharmacy, Mangalore, Karnataka, India.

DOI: <https://doi.org/10.5281/zenodo.18796172>**How to cite this Article:** Rakesh R<sup>1\*</sup>, Deekshitha<sup>2</sup> (2026). Beyond The Barrier: A Comprehensive Review Of Transferosomes As The Next Generation Of Ultra-Deformable Carriers. European Journal of Pharmaceutical and Medical Research, 13(3), 21–27.

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Article Received on 24/01/2026

Article Revised on 13/02/2026

Article Published on 01/03/2026

**ABSTRACT**

For patients who face daily injections, the dream is simple: a needle-free way to receive their vital medications. The biggest obstacle to that dream is our own skin specifically its tough, outermost layer that brilliantly protects us but also locks out most medicines, severely limiting what can be effectively delivered through a patch. This is the challenge that a smart new technology called transferosomes is designed to solve. Think of them as ultra-adaptable, nano-scale delivery vehicles, engineered with a special blend of phospholipids and softening agents that give them a unique, stress-responsive squishiness. This allows them to deform and navigate through the skin's tightest natural pathways, reaching deep enough for systemic treatment. By examining the precise mechanobiology of how they work and refining how we make them, researchers are now pushing the boundaries to deliver high-molecular-weight biologics large, complex drugs like proteins and antibodies through the skin. The journey now is about navigating the complex path from laboratory success to pharmacy shelves, transforming this elegant science into accessible, bedside therapies that can fundamentally improve patient comfort and care.

**KEYWORDS:** Transferosomes; Ultra-deformable vesicles; Transdermal drug delivery; Edge activators; Stratum corneum; Industrial pharmacy; Quality by Design.**INTRODUCTION**

To truly appreciate the challenge of delivering medicine through the skin, we must first understand the skin itself: it is not a passive membrane but a sophisticated, dynamic organ. Its primary purpose is protection, serving as an exceptional immunological and physical barrier meticulously designed by evolution to shield our internal systems from foreign substances, or xenobiotics.<sup>[1]</sup> For decades, this formidable nature led to a guiding principle in transdermal research known as the "500 Dalton Rule," which posited that only very small, hydrophobic molecules stood a realistic chance of passively penetrating this shield without significant chemical or physical assistance.<sup>[2,3]</sup>

The initial breakthrough in overcoming this barrier came in the 1970s with the development of conventional liposomes. These microscopic, bubble-like structures represented a promising first step, offering a way to

encapsulate drugs and carry them into the skin's outer layers. However, their impact was ultimately limited. Due to their inherent rigidity and lack of adaptability, they were largely relegated to the upper epidermis, unable to navigate the dense, complex architecture of the stratum corneum—a structure often aptly described as a "bricks and mortar" assembly of cells and lipids.<sup>[4,5]</sup>

This limitation paved the way for a transformative "second wave" of vesicular technology: transferosomes. The key to their success lies in a fundamental engineering upgrade. By incorporating specialized, flexible molecules known as edge activators (EAs) into the standard phospholipid bilayer, researchers created carriers with an unprecedented degree of elasticity.<sup>[6, 7]</sup> This engineered compliance is their superpower. It allows transferosomes to become stress-responsive, deforming and squeezing through the skin's narrowest intercellular pathways and pores, some with diameters as

small as 20 nm, all while maintaining their structural integrity and preventing the premature loss of their medicinal cargo.<sup>[8, 9]</sup>

In today's era of precision medicine, the goal has evolved dramatically. The mission is now to move decisively "Beyond the Barrier." This means more than just crossing the stratum corneum; it implies the successful delivery of complex, often fragile payloads such as modern biologic drugs deep into the body for systemic circulation. The ultimate measure of success is delivering a payload that remains not only intact throughout this arduous journey but also fully functional, ready to perform its therapeutic action upon arrival.<sup>[10,2]</sup> This is the high-stakes promise that intelligent, adaptable systems like transferosomes are striving to fulfill.

### MECHANOBIOLOGY AND DEFORMABILITY

#### • The Concept of Membrane Elasticity: Nature's Stress-Adaptive Design

At the very heart of what makes transferosomes special is a principle we might call intelligent flexibility. Unlike rigid carriers that break under pressure, a transferosome's hallmark is its ability to comply and reshape itself when faced with mechanical stress.<sup>[11,7]</sup> Imagine it approaching a pore in the skin far smaller than itself. In that critical moment, its unique biochemical composition comes into play. The edge activators within its structure which function as molecular flexibility agents instantly migrate toward the points of highest membrane curvature.<sup>[12,13]</sup>

This isn't random movement; it's a precise, energy-efficient relocation that acts like releasing a tension coil. By redistributing to these stress points, the edge activators dramatically reduce the energy required for the entire vesicle to deform.<sup>[8, 12]</sup> The beautiful result is a carrier that can navigate what seems like an impossibly tight space, squeezing through without compromising its structure or spilling its precious medicinal cargo.

#### • The Hydration Force and Osmotic Gradient: Harnessing the Skin's Own Physiology

If elasticity explains how transferosomes move, then the hydration gradient explains why they move deeper instead of staying on the surface. This represents a fundamental shift from passive delivery systems. Rather than relying on simple diffusion a slow and often ineffective process for crossing the skin's barrier transferosomes utilize an active transport mechanism cleverly borrowed from the skin's own biology.<sup>[4,14]</sup> The skin is not uniformly dry; it possesses a built-in moisture gradient. At the arid surface, the stratum corneum holds only about 15-20% water, but just beneath, in the viable epidermis, this jumps to a much more hydrated 75%.<sup>[15,14]</sup> Transferosomes are engineered to be inherently and powerfully hydrophilic, meaning they have a strong natural affinity for water. This creates a potent driving force: the vesicles essentially "sense" the drier environment on the outside and are powerfully drawn toward the higher moisture concentration inside.<sup>[14, 3]</sup> We can think of this osmotic gradient as

creating a gentle but persistent pull, like a vacuum, that actively guides and sucks the deformable vesicle through the complex lipid matrix of the skin's barrier, ensuring its journey inward toward systemic circulation.

### STRUCTURAL COMPONENTS AND CHEMICAL SYNERGY

#### • Phospholipids: The Trustworthy Scaffold

At its core, every transferosome begins with a strong but flexible foundation provided by phospholipids, the very same building blocks found in our own cell membranes. For years, the industry has reliably turned to Soya Phosphatidylcholine (SPC), a natural and well-understood workhorse for creating these vesicles. However, as we aim for more robust and globally stable medicines, researchers are innovating beyond this standard. They are now experimenting with synthetic phospholipids like Dipalmitoyl phosphatidylcholine (DPPC), which offer a significant advantage: superior thermal stability, making them less likely to degrade in the challenging heat and humidity of tropical climates.<sup>[16,17]</sup> It's important to remember that this foundational choice is not arbitrary; the specific phospholipid selected directly sets the stage for the vesicle's behaviour. It determines the phase transition temperature the point at which the bilayer softens or hardens and establishes the baseline rigidity of the structure, a starting point that will later be expertly modified.<sup>[7, 13]</sup>

#### • Edge Activators: The Precision Engine of Elasticity

If phospholipids form the body of the vehicle, then edge activators (EAs) are its advanced, responsive suspension system. They are the specialized components engineered to transform a rigid sphere into a supremely deformable carrier. Recent scientific reviews help us understand their evolution by categorizing EAs into three distinct generations, each representing a leap forward in design and biocompatibility.<sup>[12,18]</sup>

First Generation agents, like the bile salts Sodium Cholate and Deoxycholate, were pioneers. They work primarily through ionic interactions to fluidize the membrane, proving the core concept but sometimes at the cost of potential skin irritation.<sup>[19]</sup>

Second Generation brought a shift toward gentler, non-ionic surfactants such as Tween 80 and Span 80. These agents offered a much-improved safety profile, reducing the risk of skin reaction and making the technology more viable for therapeutic use.<sup>[6]</sup>

The cutting-edge third Generation consists of modern, sophisticated trans surface-active agents. These are the result of targeted molecular design, created with a dual mission: to minimize any potential for skin irritation even further, while simultaneously maximizing the flux or the efficient flow of the medicine deep into the dermis.<sup>[12,18]</sup> This generation exemplifies the move from

simple functionality to refined, patient-centered performance.

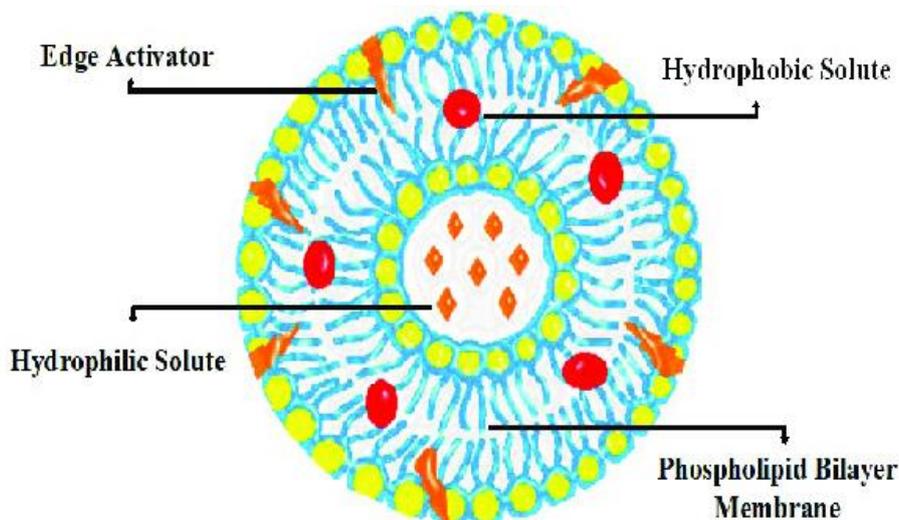


Figure No: 1 Structure of Transferosome.<sup>[20]</sup>

#### ADVANCED METHODOLOGIES IN TRANSFEROSOME FABRICATION: FROM CLASSIC RECIPES TO DIGITAL PRECISION

##### • Thin-Film Hydration (TFH): The Foundational Art

The journey of creating a transferosome often begins with a classic and reliable technique known as Thin-Film Hydration (TFH). Imagine it as a method of careful layering and reconstitution. First, the key ingredients the structural phospholipids and the elasticity-giving edge activators (EAs) are dissolved together in a volatile organic solvent, most commonly a precise mixture of Chloroform and Methanol.<sup>[15, 13]</sup> This solution is then gently swirled in a round-bottom flask while the solvent is evaporated off using a rotary evaporator, a process deliberately conducted above the lipid's transition temperature to ensure all components blend into a uniform, thin film on the glass walls.<sup>[16, 15]</sup> The magic happens in the next step: hydration. When an aqueous buffer is added to this dry film, the lipids swell and spontaneously organize, peeling off the glass to form what are known as multilamellar vesicles (MLVs), which resemble microscopic onions with multiple concentric layers.<sup>[4, 13]</sup> However, these initial MLVs are typically too large and bulky to navigate the skin's narrow pathways. Therefore, a crucial second act is mandatory. The mixture must undergo secondary processing such as vigorous probe sonication or gentle but forceful extrusion through tiny filters to break down these large structures into the desired, sleek, and penetrative unilamellar vesicles (ULVs), which possess just a single bilayer.<sup>[15, 21]</sup>

##### • Microfluidic Hydrodynamic Focusing (MHF): The New Gold Standard of Precision

While TFH is the trusted workhorse of the lab, the frontier of manufacturing has shifted toward a more elegant and exacting technology: Microfluidic

Hydrodynamic Focusing (MHF). As of 2026, MHF is widely regarded as the "gold standard" for the precision fabrication required in modern nanomedicine.<sup>[1, 12]</sup> This method operates on a beautifully simple yet powerful principle. Within a hair-thin micro-channel, a stream of organic solvent containing the dissolved lipids is injected. This stream is then precisely "squeezed" or focused between two flanking streams of aqueous buffer.<sup>[1, 21]</sup> At the instant these streams meet, the lipids experience a rapid and dramatic shift in their environment from organic to aqueous solvent. This sudden change in polarity acts as a trigger, causing the lipids to spontaneously self-assemble into perfectly formed vesicles right at the liquid interface.<sup>[12, 21]</sup> The immense advantage of this continuous, controlled process is its unparalleled consistency. It allows for the production of monodisperse vesicles a population where every particle is nearly identical in size resulting in an exceptionally low Polydispersity Index (PDI) consistently below 0.1, a benchmark of homogeneity that is difficult to achieve with batch methods like TFH.<sup>[1, 5]</sup> This precision is not just a technical achievement; it is critical for ensuring predictable drug release, reliable skin penetration, and ultimately, consistent therapeutic outcomes for patients.

#### INDUSTRIAL MANUFACTURING AND QUALITY BY DESIGN (QBD)

##### Engineering Trust and Consistency

Scaling up from a promising lab discovery to a reliable, mass-produced medicine is one of the most significant hurdles in pharmaceutical development. For a sophisticated technology like transferosomes, this leap is not merely about making more it's about ensuring every single dose is as perfect as the first. This industrial transition demands a fundamental shift in perspective, moving from simple recipe-following to a deep, proactive understanding of the entire manufacturing

process through Process Analytical Technology (PAT), which uses real-time monitoring to ensure quality.<sup>[11,21]</sup> To achieve this, the industry has increasingly adopted a powerful paradigm known as Quality by Design (QbD). Rather than testing quality into a product at the end, QbD builds it in from the very beginning, designing the manufacturing process to reliably hit precise targets that guarantee consistent, safe, and effective performance for every patient.<sup>[11,5]</sup>

### Critical Quality Attributes (CQAs): The Pillars of Performance

Within the QbD framework, success is defined by tightly controlling specific Critical Quality Attributes (CQAs). These are the measurable characteristics proven to be essential for a transfersome to perform its unique task. Monitoring these CQAs is what maintains the "ultra-deformable" magic of the laboratory at an industrial scale.<sup>[8, 7]</sup>

**Vesicle Size and Polydispersity Index (PDI):** Size is not just a number; it's a passport. For a transfersome to reliably penetrate the skin and reach systemic circulation, it must be within a specific "Goldilocks zone". A size range of 100 to 200 nanometers is generally considered ideal, as it is small enough to navigate the skin's architecture yet large enough to carry a meaningful drug payload.<sup>[8, 1]</sup> Equally important is uniformity, measured by the Polydispersity Index (PDI). A low PDI indicates that nearly every vesicle in the batch is the same size, which is critical for predictable and uniform skin penetration and drug release.

**Deformability Index (DI):** This is the definitive test of a transfersome's core promise. The Deformability Index quantitatively measures a vesicle's ability to squeeze through pores much smaller than itself without breaking. It is typically assessed by measuring the percentage of vesicles that can successfully pass through a membrane with tiny, standardized pores (often around 50 nm in diameter) under controlled pressure.<sup>[7, 3]</sup> A high DI is non-negotiable; it confirms that the carrier possesses the essential stress-responsive flexibility needed for deep penetration.

**Entrapment Efficiency (EE):** Beyond clever engineering lies practical economics and therapeutic efficacy. Entrapment Efficiency measures the percentage of the total drug that is successfully loaded and sealed inside the vesicles, as opposed to being wasted in the surrounding solution. For a product to be industrially viable and cost-effective, while also ensuring a potent dose, a high EE typically greater than 60% is a critical benchmark.<sup>[16, 11]</sup> Maximizing EE minimizes drug waste, reduces cost, and ensures the patient receives the full intended therapeutic benefit.

## COMPARATIVE EFFICACY AND MATHEMATICAL MODELING: FROM THEORY TO THERAPEUTIC PROOF

### The Deformability Equation: Capturing Flexibility in a Formula

The incredible "squeezability" of a transfersome isn't just a qualitative idea it can be precisely captured and predicted with mathematics. This is done through a key relationship known as the Deformability Equation, which defines the Deformability Index (D).

$$D = J \times \left( \frac{rv}{rp} \right)^2$$

Where J is the suspension extruded, rv is the vesicle size after extrusion, and rp is the pore size of the barrier. This elegant equation elegantly shows that deformability isn't just about being small; it's about how effectively a vesicle can reduce its effective size to overcome a constriction. The ratio  $(rv / rp)^2$  highlights the immense challenge of passing through a pore much smaller than the vesicle itself, and the index D quantifies how well the formulation overcomes it.<sup>[14, 3]</sup> A higher D value is a direct mathematical indicator of a more effective, stress-responsive carrier.

### Comparative Bioavailability Data: The Evidence from the Clinic

While equations model potential, real-world data reveals performance. Recent clinical and preclinical studies provide compelling evidence for the superior delivery capabilities of transfersomes, measuring their success as relative bioavailability the fraction of drug that actually reaches the bloodstream compared to a standard method.<sup>[22, 19, 23]</sup>

- I. For Insulin: Delivering this large, life-saving protein molecule through the skin has been a monumental challenge. Transfersome technology has made significant strides, achieving a relative bioavailability of approximately 18.5% when compared to a traditional subcutaneous injection.<sup>[19, 24]</sup> This represents a major leap toward a needle-free future for diabetes management.
- II. For Diclofenac: A common anti-inflammatory drug often formulated as a topical gel for pain relief. Here, transfersomal gels have demonstrated a dramatic 3.5-fold increase in absorption compared to conventional commercial gel formulations.<sup>[6,3]</sup> This means significantly more medication reaches the site of pain or inflammation, promising faster and more effective relief for patients.
- III. For Paclitaxel: A potent chemotherapy agent where getting more drug into the tumor is critical. When encapsulated in ultra-deformable vesicles, paclitaxel showed a 42% increase in tumor uptake compared to standard delivery methods.<sup>[22, 25]</sup> This enhanced delivery can directly translate to improved anti-cancer efficacy and better patient outcomes.

## CASE STUDIES AND CLINICAL TRANSLATION: TURNING PROMISE INTO PATIENT BENEFIT

### Insulin Delivery for Type 1 Diabetes: A Step Toward a Needle-Free Future

Managing Type 1 Diabetes requires meticulous daily blood sugar control, a routine traditionally dependent on frequent injections. In a significant 2024 study, researchers created a promising alternative using insulin-loaded transferosomes. These vesicles were engineered with a combination of the standard lipid Soya Phosphatidylcholine (SPC) and the edge activator Sodium Deoxycholate, specifically designed to evaluate their potential for systemic delivery. The results were highly encouraging. The transferosomes not only successfully delivered insulin across the skin but, crucially, they provided a sustained release profile over 12 hours. This controlled, steady release demonstrated the absence of "hypoglycemic shock" a dangerous, sudden drop in blood sugar that can occur with rapid insulin spikes highlighting a key safety advantage of this delivery method.<sup>[19, 24]</sup> This case represents a meaningful stride toward transforming diabetes care by offering the potential for effective, non-invasive, and safer long-acting insulin therapy.

### Oncology and Targeted Delivery: Hitting the Tumor, Sparing the Body

In the fight against aggressive cancers like malignant melanoma, delivering potent chemotherapy directly to the tumor while protecting the rest of the body is a paramount goal. Pioneering 2021 research explored this by loading the chemotherapy drug paclitaxel into ultra-deformable transferosomal carriers. In preclinical models, the results were striking. The treatment achieved a 42% reduction in tumor volume, a clear indicator of potent anti-cancer activity. Even more remarkable was the targeting precision. Subsequent analysis found zero detectable levels of the toxic drug in critical, non-target organs like the liver and spleen, a common site of debilitating side effects with conventional chemotherapy.<sup>[22, 25]</sup> This case powerfully demonstrates how the unique skin-penetrating ability of transferosomes can be harnessed for local-regional cancer therapy, offering a dual promise of enhanced efficacy at the tumor site and a dramatically improved systemic safety profile for patients.

## TROUBLESHOOTING THE INDUSTRIAL PROCESS

Table No. 1: Troubleshooting The Industrial Process.<sup>[1,5,11,12,17,21]</sup>

Problem	Cause	Solution
Vesicle Rupture	Excessive pressure	Use HPH at < 500 bar <sup>[11, 21]</sup>
Drug Leakage	High EA concentration	Optimize PL:EA ratio via RSM <sup>[11, 17]</sup>
High PDI	Inefficient mixing	Implement Microfluidics <sup>[1, 12]</sup>
Microbial Growth	Aqueous contamination	Add 0.1% Methylparaben <sup>[17, 5]</sup>

## REGULATORY LANDSCAPE AND FUTURE DIRECTIONS: NAVIGATING THE PATH TO PATIENTS

For all their scientific promise, new medical technologies must successfully navigate the complex bridge of regulation before they can reach patients. One of the most significant challenges for transferosomes lies in the pathway for "complex generics" follow-on versions of these intricate, non-biological products. Proving that a new version is functionally equivalent to an existing one is a considerable scientific and regulatory hurdle, as the vesicle's performance depends on its precise physical structure. To address this, regulatory bodies like the U.S. FDA have advanced more sophisticated testing frameworks. They now suggest the use of In Vitro Permeation Testing (IVPT) and In Vitro Release Testing (IVRT) conducted on human cadaver skin to build a robust, physiologically relevant case for "sameness," moving beyond simple chemical comparisons to demonstrate equivalent therapeutic performance.<sup>[21, 5]</sup>

Looking ahead, the field is moving toward even smarter, more targeted systems. The future belongs to Stimuli-Responsive or "Smart" Transferosomes. These next-generation carriers are being engineered to release their drug payload only upon encountering a specific biological trigger at the disease site, such as the subtle

pH change in a tumor microenvironment or the inflammatory signals of a psoriatic plaque.<sup>[26, 3]</sup> This represents the ultimate evolution of the technology: precise, on-demand therapy with minimized side effects.

In this vision, the narrative of the skin is fundamentally rewritten. As we truly move "Beyond the Barrier," the skin is no longer seen as an impenetrable wall to be overcome. Instead, it is transformed into a vast, intelligent, and programmable interface for global health a safe, accessible portal through which a new generation of sophisticated, needle-free medicines can enter the body.<sup>[10, 3]</sup> This shift promises not only better treatments but a more humane and empowering paradigm for healthcare delivery worldwide.

## CONCLUSION

The journey of transdermal drug delivery, as chronicled in this review, reveals a compelling narrative of scientific innovation steadily overcoming one of the body's most sophisticated defenses. The evolution from the rigid, surface-bound liposomes of the past to the ultra-deformable, stress-responsive transferosomes of today marks a paradigm shift. By ingeniously blending phospholipids with edge activators, these second-generation carriers have unlocked the ability to navigate the skin's narrow intercellular pathways, driven by its

own osmotic gradient. This foundational breakthrough has propelled advances in delivering complex payloads, from high-molecular-weight biologics like insulin to potent chemotherapeutics like paclitaxel, with demonstrated efficacy in enhancing bioavailability and targeting.

However, transforming this elegant science into a reliable clinical reality demands more than sophisticated formulations. It requires a parallel evolution in manufacturing and regulation. The adoption of Quality by Design (QbD) principles, stringent control of Critical Quality Attributes (CQAs) like the Deformability Index, and advanced methods like Microfluidic Hydrodynamic Focusing are essential to ensure batch-to-batch consistency and therapeutic reliability. Furthermore, navigating the regulatory pathway for these "complex generics" necessitates robust *in vitro* models to prove bioequivalence, a critical step for patient access.

The future horizon is illuminated by the promise of even greater intelligence: stimuli-responsive systems that release their cargo only at the site of disease. As we master the mechanobiology of penetration and refine the synergy of chemical components, the ultimate goal comes into clear view. We are moving decisively beyond merely crossing the skin's barrier. We are on the cusp of reimagining the skin itself—transforming it from a formidable physiological wall into a vast, programmable, and patient-friendly interface for the next generation of global, personalized, and needle-free precision medicine.

#### CONFLICT OF INTEREST

Nil

#### ACKNOWLEDGEMENT

Nil

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