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TRANSETHOSOMES: A PROMISING VESICULAR SYSTEM FOR OSTEOARTHRITIS DRUG DELIVERY

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ABSTRACT

Osteoarthritis (OA) is a long-term degenerative joint condition that progressively impairs movement and reduces quality of life, especially among older and obese individuals. Existing treatments, such as oral nonsteroidal anti-inflammatory drugs, mainly provide symptomatic relief but are often associated with systemic side effects and insufficient drug concentration at the site of action. This has created a need for more targeted and safer delivery approaches. In recent years, transethosomes have gained attention as a promising transdermal drug delivery system. These vesicular carriers, composed of phospholipids, ethanol, and surfactants, are designed to be highly flexible and capable of penetrating the skin barrier effectively. Their structure allows improved drug loading, enhanced permeation, and sustained release, making them suitable for delivering a wide range of therapeutic agents directly to affected tissues. However, certain challenges, including formulation instability, drug leakage, and the potential for skin irritation due to ethanol content, still need careful consideration. Emerging strategies such as dry transethosomal systems and incorporation into hydrogels are showing encouraging progress in addressing these limitations. Overall, transethosomes offer a practical and evolving solution for localized osteoarthritis treatment, with the potential to improve therapeutic outcomes and patient adherence as research advances.

KEYWORDS: *Osteoarthritis, Transethosomal, Skin permeation, phospholipids.*

INTRODUCTION

Osteoarthritis (OA) is a chronic, progressive joint disorder that significantly impairs mobility and quality of life worldwide.[1,2] It is characterized by cartilage degradation, subchondral bone remodeling, synovial inflammation, and progressive joint dysfunction. The condition imposes a substantial physical and economic burden globally, affecting an estimated half a billion individuals, with prevalence rising notably among aging and obese populations.[3] This growing disease burden underscores the urgent need for more effective and targeted therapeutic strategies. In recent years, there has been increasing interest in localized and transdermal drug delivery systems as a means to overcome these limitations. Such approaches aim to enhance drug concentration at the affected joint while minimizing systemic exposure and associated side effects. Among these, vesicular carrier systems have emerged as promising platforms due to their ability to improve drug permeability, stability, and controlled release. Conventional treatments, such as oral nonsteroidal anti-inflammatory drugs, typically offer only symptomatic relief and may cause systemic side effects upon long-term use. The heterogeneity of OA, coupled with the existence of unique joint transition zones, poses additional challenges for targeted and sustained drug delivery.[4,5]

VESICULAR SYSTEMS AND THE EVOLUTION OF TRANSETHOSOMES

In recent years, there has been a rapid transition from classic liposomes to sophisticated vesicular carriers such as ethosomes, transferosomes, and transethosomes, with the goal of boosting skin permeability and payload efficiency.[4,6,7]

Ethosomes leverage high ethanol content for enhanced membrane fluidity, while transferosomes add surfactants as edge activators to improve flexibility and transdermal passage.[2,8,9] However, these systems often fell short on

deep tissue targeting and drug leakage stability, prompting the development of transethosome hybrids.[10] Ethosomes use high ethanol concentration to increase membrane fluidity, whereas transferosomes use surfactants as edge activators to improve flexibility and transdermal transit.

TRANSETHOSOMES: STRUCTURE

Transethosomes comprise phospholipids, ethanol, and surface-active agents in a lamellar vesicle structure. Ethanol and surfactants (such as Span 80, Tween 80) synergize to disrupt stratum corneum lipids and provide vesicle deformability, enabling efficient skin and joint penetration. The resulting vesicles can encapsulate both hydrophilic and lipophilic drugs with high entrapment efficiency, minimize drug loss, and offer sustained release profiles.[11]

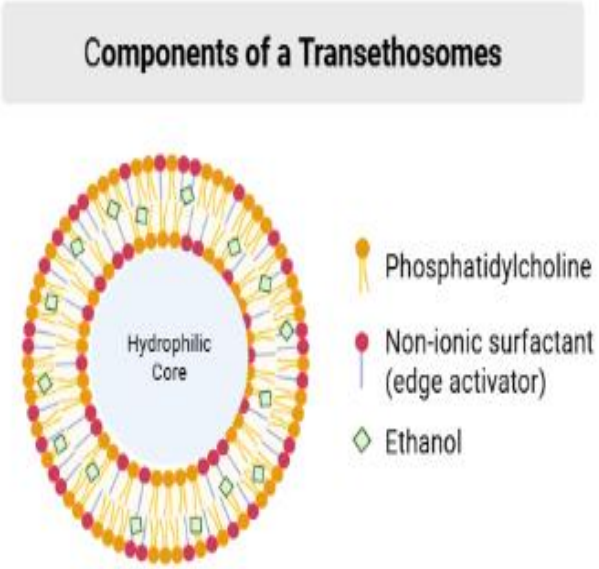

Fig1: Structure of Transethosomes.

MECHANISM OF PENETRATION

Phase I (Ethanol Effect): Ethanol interacts with the polar head groups of stratum corneum lipids, lowering their melting point and enhancing the fluidity of the skin barrier.

Phase II (Deformability): The edge activator (e.g., Span 80, Tween 80) accumulates at the vesicle's maximum curvature. When the vesicle comes across a narrow pore, the surfactant changes to accommodate the stress, allowing the vesicle to lengthen and pass through intact without rupturing.[12,13]

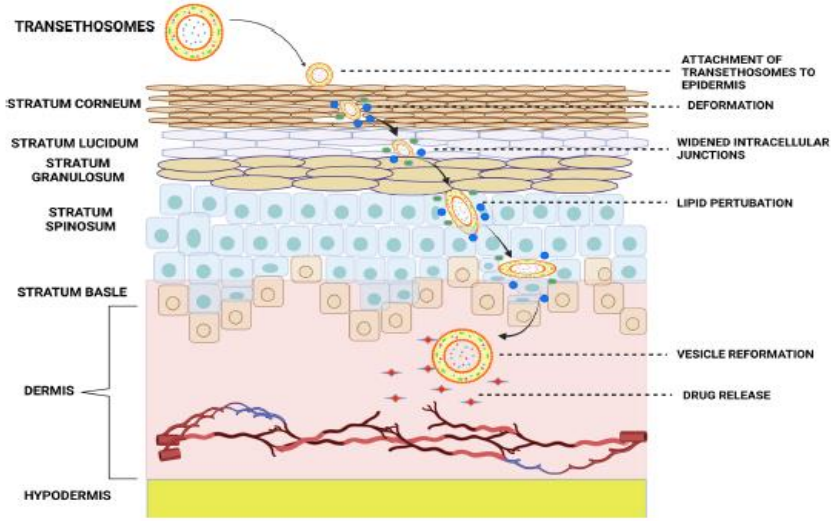

Fig2: Mechanism of Transethosomes-mediated skin penetration.[14]

METHOD OF PREPARATION[15]

- **Cold Method**: The Cold Method remains the industrial standard for heat-sensitive biologics and peptides. By operating strictly at room temperature (25°C), it prevents the thermal degradation of the payload, though it requires precise control over stirring speed to ensure uniform vesicle sizing.
- **Hot Method**: When utilizing lipids with a high phase transition temperature (e.g., Hydrogenated Phosphatidylcholine), the Hot Method is mandatory. Thermal energy (40°C) is required to disrupt the crystalline lattice of the lipid, although this introduces a risk of ethanol evaporation that must be mitigated by using sealed vessels.
- **Thin Film Hydration**: For highly lipophilic drugs (log P > 2), the Thin Film Hydration technique is superior. By first creating a dry lipid film, this method ensures the drug is embedded deep within the bilayer, typically yielding entrapment efficiencies >85% compared to liquid-phase methods.
- **Reverse Phase**: The Reverse Phase Evaporation technique is specialized for large hydrophilic molecules. The unique "inverted micelle" intermediate allows for a larger aqueous core-to-lipid ratio, accommodating bulky payloads that would otherwise leak from standard vesicles.

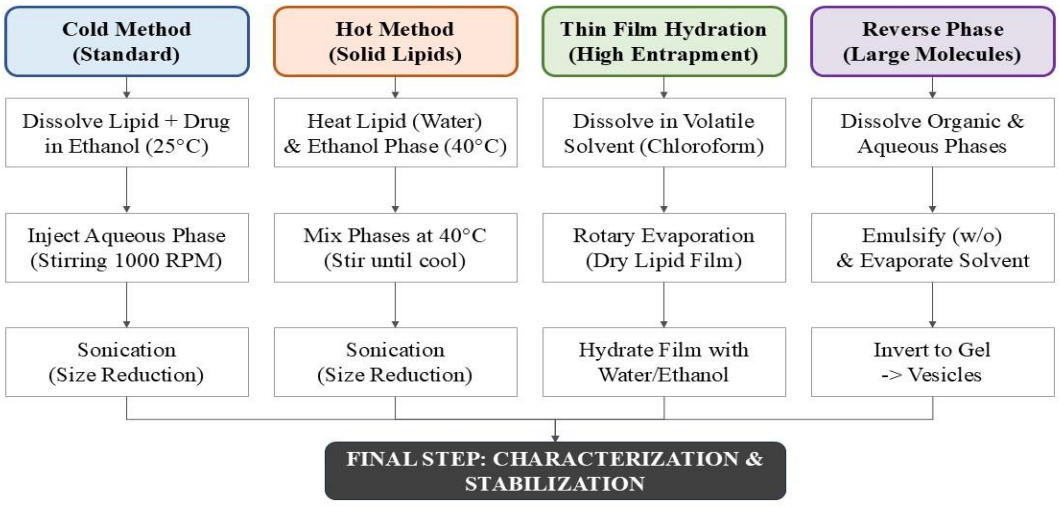

Fig3: Preparation Methods of Transethosomes.

Table 1: Summary of Transethosomal Formulations and Performance.

Drug	Optimized Variables	Key Parameters	Characterization	Performance
Sinapic acid.[16]	Sodium deoxycholate: Ethanol: lipid ratio	Size: 111.67 nm; PDI: 0.240; Zeta: -7.25 mV; EE: 74.36%	DSC: reduced crystallinity	2.86× penetration enhancement
Methotrexate.[17]	Soya lecithin: surfactant: Ethanol (Box-Behnken)	Size: 110.3 nm; PDI: 0.352; Zeta: -14.4 mV; EE: 49.36%	Spherical TEM; stable 90 days	1.55× flux vs. control; reduced paw edema
Rutin.[18]	Lipid: Ethanol ratio; sonication	Size: 160.45 nm; PDI: 0.235; Zeta: -22.89 mV; EE: 89.99%	Spherical TEM; pH 6.2	935 µg/cm² permeation; superior antibacterial
Fluconazole.[19]	Lecithin: Tween 80 (90:10)	Size: 300.2 nm; PDI: 0.203	High homogeneity	Enhanced antifungal delivery

TRANSLATIONAL HURDLES AND SAFETY CONSIDERATIONS

Despite their enhanced penetration characteristics, Transethosomes clinical translation remains impeded by significant physicochemical and dermatological issues. Future growth necessitates a thorough examination of these limits, as well as the engineering techniques used to overcome them.

The "Fluidity Paradox" and Physical Instability

The primary stability challenge stems from the system's engineered "ultra deformability" The high concentration of ethanol (30–40%) and edge activators (surfactants) significantly lowers the interfacial tension of the vesicle bilayer.

While this facilitates skin penetration, it simultaneously renders the vesicles thermodynamically unstable during storage.[20]

- **Ostwald Ripening:** In liquid suspension, Transethosomes exhibit a tendency toward Ostwald ripening, where smaller vesicles fuse to form larger, rigid structures (>300 nm). This size increase drastically reduces their ability to penetrate the stratum corneum, effectively nullifying their therapeutic advantage.[21,22]
- **Drug Leakage:** The fluid nature of the bilayer, while beneficial for entry, often fails to retain low-molecular-weight hydrophilic drugs. Recent stability studies indicate that up to 20% of encapsulated payload can leak into the external vehicle within 30 days if not properly stabilized.[23]

DERMATOLOGICAL SAFETY: THE ETHANOL CHALLENGE

The "ethanol effect," while crucial for fluidizing stratum corneum lipids, acts as a double-edged sword. Chronic application of high-ethanol vehicles can lead to the excessive extraction of physiological skin lipids (ceramides), potentially disrupting the skin barrier function.

- **Irritation Potential:** Recent *in vivo* studies have reported mild erythema and transient contact dermatitis at the application site when utilizing pure transethosomal suspensions, particularly in compromised skin conditions typical of elderly OA patients
- **Cytotoxicity:** Although generally biocompatible, the interaction between high concentrations of surfactants (e.g., Sodium Deoxycholate) and ethanol can induce dose-dependent cytotoxicity in keratinocytes if not properly buffered.

ENGINEERING SOLUTIONS: THE RISE OF "PRO-TRANSETHOSOMES" AND HYDROGELS

To mitigate these risks, recent research has pivoted toward solid-state engineering and matrix integration.

- **Lyophilization (Pro-Transethosomes):** Transforming liquid Transethosomes into a dry powder using cryoprotectants (e.g., Trehalose, Mannitol) has proven to prevent hydrolysis and fusion. These "Pro-Transethosomes" form a stable free-flowing powder that spontaneously forms vesicles upon hydration, significantly extending shelf-life.
- **Hydrogel Integration:** Incorporating Transethosomes into viscous **hydrogel matrices** (e.g., Carbopol 940, Chitosan) is now considered the gold standard for OA formulations.[10,24]

CONCLUSION

Osteoarthritis remains a challenging condition that significantly affects patient mobility and quality of life, highlighting the need for more effective and targeted treatment strategies. In this regard, Transethosomes have gained attention as a promising drug delivery system due to their ability to enhance skin penetration and improve localized drug action. By combining phospholipids, ethanol, and surfactants, Transethosomes offer improved flexibility, efficient drug encapsulation, and sustained release, making them suitable for delivering both hydrophilic and lipophilic drugs.

These properties provide a clear advantage over conventional formulations, particularly for transdermal management of osteoarthritis. However, despite these benefits, certain limitations such as stability issues, drug leakage, and potential skin irritation associated with high ethanol content must be carefully addressed. Recent advancements, including the development of pro transethosomes and hydrogel-based systems, show encouraging progress in overcoming these challenges.

Overall, Transethosomes represent a valuable and evolving platform in drug delivery. With continued research and optimization, they hold strong potential to improve therapeutic outcomes and support more patient friendly approaches in osteoarthritis treatment.

CONFLICT OF INTEREST

Nil.

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Nil.

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